Registries for Evaluating Patient Outcomes: A User's Guide

Second Edition

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Second Edition

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Preface

This project was performed under a contract from the Agency for Healthcare Research and Quality (AHRQ) in collaboration with the Centers for Medicare & Medicaid Services (CMS) through the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network of AHRQ's Effective Health Care (EHC) Program. The purpose of the project was to update and expand the 2007 "Registries for Evaluating Patient Outcomes" handbook. The 2007 handbook was developed as a reference for establishing, maintaining, and evaluating the success of registries created to collect data about patient outcomes. The purpose of the handbook revision was to incorporate information on new methodological or technological advances into the existing chapters and to add new chapters to address emerging topics in registry science.

Both the 2007 version and this revised version of the handbook were created with support from a large group of stakeholders. Following award of the initial project on September 29, 2005, we created a draft outline for the document that was posted for public comment on AHRQ's Effective Health Care Web site (www.effectivehealthcare.ahrq.gov) from January through March 2006. During that same period, we worked with AHRQ to create a process for selecting contributors and reviewers. We broadly solicited recommendations from a range of stakeholders, including government agencies, industry groups, medical professional societies, and other experts in the field; conducted a review of the pertinent literature; and contacted the initial list of contributors to confirm their interest and area of expertise and to seek further recommendations. Through that process and in collaboration with AHRQ and CMS, we arrived at a set of contributors and reviewers based on subject/content expertise, practical experience, and interest and availability, with balanced representation from key stakeholder groups for nearly all chapters. In addition, a request for submission of real-world case examples that could be used in the handbook to illustrate issues and challenges in implementing registries was posted on the Effective Health Care Web site. The primary selection criteria for these examples were their utility in illustrating a practical challenge and its resolution.

An initial meeting of contributors was convened in February 2006. A second meeting including contributors and chapter reviewers was held in June 2006, following creation of an initial draft document and focused review by the reviewers. The collaborative efforts of contributors, reviewers, and editors resulted in a draft document that was posted for public comment on the Effective Health Care Web site in October and November 2006. In all, 39 contributors and 35 individual reviewers participated in the creation of the first document, which was published online and in print format in May of 2007.

In August of 2008, the handbook update project was awarded. The project involved revising the existing chapters and case examples, creating new content to address four topics, and soliciting new case examples. From September to November 2008, we worked with AHRQ to select contributors and reviewers for the new handbook content. We followed a similar process to what was used in the creation of the original handbook to arrive at a set of contributors and reviewers with subject matter expertise and a broad range of perspectives. The contributors drafted white papers on "Use of Registries in Product Safety Assessment," "When to Stop a Registry," "Interfacing Registries and EHRs," and "Linking Registry Data." The white papers were reviewed and discussed at a meeting in April 2009. The papers

were then posted for public comment in August and September 2009. After revising the papers in response to public comments, the final papers were converted to chapters or sidebars and included in the expanded handbook.

During the same timeframe, we contacted the authors and reviewers from the 2007 version of the handbook. We asked authors and reviewers to update the existing chapters to address any new methodological, technological, or legal topics. The revised chapters were circulated for review and discussed at a meeting in July 2009. We also posted a new call for case examples on the Effective Health Care Web site in June 2009. The primary selection criteria for the new examples were their utility in illustrating issues and challenges related to the new topics addressed in the white papers. In addition, we contacted authors of the original case examples to obtain updated information on the registries.

For both the 2007 version and the new version of the handbook, the contributors and reviewers participated as individuals and not necessarily as representatives of their organizations. We are grateful to all those who contributed to both documents and who reviewed them and shared their comments.

To begin the discussion of registries, we would like to clarify some distinctions between registries and clinical trials. While this is further discussed in Chapter 1, from a high-level perspective, we offer the following distinctions: The clinical trial is an experiment in which an active intervention intended to change a human subject's outcome is implemented, generally through a randomization procedure that takes decisionmaking away from the practitioner. The research protocol describes inclusion and exclusion criteria that are used to select the patients who will participate as human subjects, focusing the experiment on a homogeneous group. Human subjects and clinical researchers agree to adhere to a strict schedule of visits and to conduct protocol-specific tests and measurements.

In contrast, registries use an observational study design that does not specify treatments (although a specific treatment may be an inclusion criterion) and observe without requiring any therapies intended to change patient outcomes. There are generally few inclusion and exclusion criteria in an effort to study a broad range of patients to make the results more generalizable. Patients are typically observed as they present for care and the data collected generally reflect whatever tests and measurements a provider customarily uses.

Patient registries represent a useful tool for a number of purposes. Their ideal use and their role in evidence development, design, operations, and evaluation resemble but differ from clinical trials in a number of substantive ways, and therefore they should not be evaluated with the same constructs. This handbook presents what the contributors and reviewers consider good registry practices. Many registries today may not meet even the basic practices described. On the whole, registry science is in an active state of development. This revised document is an important step in developing this field.

This book is divided into three sections: Creating, Operating, and Evaluating Registries. The first two sections provide basic information on key areas of registry development and operations, highlighting the spectrum of practices in each of these areas and their potential strengths and weaknesses. Section I, "Creating Registries," includes eight chapters. "Patient Registries" defines and characterizes types of registries, their purposes, and uses, and describes their place within the scope of this document. "Planning a Registry" focuses on the recommended steps in planning a registry, from determining if a registry is the right option, to describing goals and objectives, to determining when a registry may end.

"Registry Design" examines the specifics of designing a registry once the goals and objectives are decided. "Use of Registries in Product Safety Assessment" describes the utility and challenges of designing a registry to assess safety. "Data Elements for Registries" provides an approach to selecting data elements that is both scientific and practical. "Data Sources for Registries" addresses how existing data sources (administrative, pharmacy, other registries, etc.) may be used to enhance the value of patient registries. "Linking Registry Data" discusses the technical and legal issues surrounding the linkage of registry data with other data sources. "Principles of Registry Ethics, Data Ownership, and Privacy" reviews several key legal and ethical issues that should be considered in creating or operating a registry.

Section II, "Operating Registries," provides a practical guide to the day-to-day operational issues and decisions for producing and interpreting high-quality registries. "Patient and Provider Recruitment and Management" describes strategies for recruiting and retaining providers and patients. "Data Collection and Quality Assurance" reviews key areas of data collection, cleaning, storing, and quality assurance for registries. "Interfacing Registries and EHRs" describes the current state of electronic health record (EHR) integration technology and maps out potential options for developing interfaces between registries and EHRs. "Adverse Event Detection, Processing, and Reporting" examines relevant practical and regulatory issues. "Analysis and Interpretation of Registry Data to Evaluate Outcomes" addresses key considerations in analyzing and interpreting registry data.

Interspersed throughout the first two sections of the handbook are case examples. As discussed above, the choice of examples was limited to those submitted for consideration during the 2007 and 2009 public submission periods. The purpose of their inclusion is solely to illustrate specific point(s) in the text from real-world examples, regardless of whether the source of the example is within the scope of the handbook as described in Chapter 1. Inclusion of a case example in this handbook is not intended as an endorsement of the quality of the particular registry, nor do the case examples necessarily present registries that meet all the criteria described in Chapter 11 as basic elements of good practice. Rather, case examples are introduced to provide the reader with a richer description of the issue or question being addressed in the text. In some cases, we have no independent information on the registry other than what has been provided by the contributor.

Section III is "Evaluating Registries." This final chapter summarizes key points from the earlier chapters in a manner that can be used to review the structure, data, or interpretations of patient registries. It describes good registry practice in terms of "basic elements" and "potential enhancements." This information might be used by a person developing a registry, or by a reviewer or user of registry data or interpretations derived from registries.

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Executive Summary

Patient Registries

The purpose of this document is to serve as a guide to the design, implementation, analysis, interpretation, and evaluation of the quality of a registry for understanding patient outcomes. For the purpose of this handbook, a patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose(s). The registry database is the file (or files) derived from the registry. Although registries can serve many purposes, this handbook focuses on registries that are created for one or more of the following purposes: to describe the natural history of disease, to determine clinical effectiveness or cost effectiveness of health care products and services, to measure or monitor safety and harm, and/or to measure quality of care. Registries are classified according to how the populations are defined. For example, product registries include patients who have been exposed to biopharmaceutical products or medical devices. Health services registries consist of patients who have had a common procedure, clinical encounter, or hospitalization. Disease or condition registries are defined by patients having the same diagnosis, such as cystic fibrosis or heart failure.

Planning

There are several key steps in planning a patient registry, including articulating the purpose of the registry, determining whether the registry is an appropriate means for addressing the research question, identifying stakeholders, defining the scope and target population, assessing feasibility, and securing funding. The registry team and advisors should be selected based on expertise and experience. The plan for registry governance and oversight should clearly address such issues as overall direction and operations, scientific content, ethics, safety, data access, publications, and change management.

It is also helpful to plan for the entire lifespan of a registry, including how and when the registry will end and any plans for transitioning the registry at that time. A registry may be stopped because it has fulfilled its original purpose, is unable to fulfill its purpose, is no longer relevant, or is unable to maintain sufficient funding, staffing, or other support.

Registry Design

A patient registry should be designed with respect to its major purpose, with the understanding that different levels of rigor may be required for registries that are designed to address focused analytical questions to support decisionmaking, in contrast to those intended primarily for descriptive purposes. The key points to consider in designing a registry include formulating a research question; choosing a study design; translating questions of clinical interest into measurable exposures and outcomes; choosing patients for study, including deciding whether a comparison group is needed; determining where data can be found; and deciding how many patients need to be studied and for how long. Once these key design items have been determined, the registry design should be reviewed to evaluate potential sources of bias (systematic error); these should be addressed to the extent that is practical and achievable.

The specific research questions of interest will guide the registry design, identification of exposures and outcomes, and definitions of the target population (the population to which the findings are meant to apply). The registry population should be designed to approximate the characteristics of the target population as much as possible. The number of study subjects desired and length of observation (followup) should be planned in accordance with the overall purpose of the registry. The desired study size (in terms of subjects or person-years of observation) is determined by specifying the magnitude of an expected, clinically meaningful effect or the desired precision of effect estimates. Study size determinants are also affected by practicality, cost, and whether or not the registry is intended to support regulatory decisionmaking. Depending on the purpose of the registry, internal, external, or historical comparison groups strengthen the understanding of whether the observed effects are indeed real and, in fact, different from what would have occurred under other circumstances.

Registry study designs often restrict eligibility for entry to individuals with certain characteristics to assure that they will assemble enough information for analysis (e.g., age restriction) or use some form of sampling—random selection, systematic sampling, or a haphazard, nonrandom approach. The potential for bias refers to opportunities for systematic errors to influence the results. The information value of a registry is enhanced by its ability to provide an assessment of the potential for bias and to quantify how this bias could affect the study results.

Use of Registries for Product Safety Assessment

Whether as part of a post-marketing requirement or as a desire to supplement spontaneous reporting, prospective product and disease registries are also increasingly being considered as a resource for examining unresolved safety issues and/or as a tool for proactive risk assessment in the post-approval setting. Registries can be valuable tools for evaluating product safety, although they are only one of many approaches to safety assessments. When designing a registry for the purposes of safety, the size of the registry, the enrolled population, and duration of followup are all critical to ensure validity of the inferences made based on the data collected. Consideration in the design phase must also be given to other recognized aspects of product use in the real world (e.g., switching therapies during followup, use of multiple products in combination or in sequence, dose effects, delayed effects, and patient compliance). Registries designed for safety assessment purposes should also formulate a plan that ensures appropriate information will reach the right stakeholders (through reporting either to the manufacturer or directly to the regulator) in a timely manner. Stakeholders include patients, physicians, product manufacturers and authorization holders and payers, such as hospital, private, state, and national insurers. Registries not designed specifically for safety assessment purposes should, at a minimum, ensure that standard reporting mechanisms for adverse event information are described in the registry's standard operating procedures and are made clear to investigators.

Data Elements

The selection of data elements requires balancing such factors as their importance for the integrity of the registry and for the analysis of primary outcomes, their reliability, their contribution to the overall burden for respondents, and the incremental costs associated with their collection. Selection begins with identifying relevant domains. Specific data elements are then selected with consideration for established clinical data standards, common data definitions, and the use of patient identifiers. It is important to determine which elements are absolutely necessary and which are desirable but not essential. In choosing measurement scales for assessing patient-reported outcomes, it is preferable to use scales that have been

appropriately validated, when such tools exist. Once data elements have been selected, a data map should be created, and the data collection tools should be pilot tested. Testing allows assessment of respondent burden, accuracy, and completeness of questions, as well as potential areas for missing data. Inter-rater agreement for data collection instruments can also be assessed, especially in registries that rely on chart abstraction. Overall, the choice of data elements should be guided by parsimony, validity, and a focus on achieving the registry's purpose.

Data Sources

A single registry may integrate data from various sources. The form, structure, availability, and timeliness of the required data are important considerations. Data sources can be classified as primary or secondary. Primary data are collected for direct purposes of the registry. Secondary data are comprised of information that has been collected for purposes other than the registry, and they may not be uniformly structured or validated with the same rigor as primary data. Sufficient identifiers are necessary to guarantee an accurate match between secondary sources and registry patients. Furthermore, a solid understanding of the original purpose of the secondary data and how they were collected is advised, because the way that those data were collected and verified or validated will help shape their use in a registry. Common secondary sources of data linked to registries include medical records systems, institutional or organizational databases, administrative health insurance claims data, death and birth records, census databases, and related existing registry databases.

Linking Registry Data

Registry data may be linked to other data sources (e.g., administrative data sources, other registries) to examine questions that cannot be addressed using the registry data alone. Two equally weighted and important sets of questions must be addressed in the data linkage planning process: what is a feasible technical approach to linking the data, and is linkage legally feasible under the permissions, terms, and conditions that applied to the original compilations of each data set. Many statistical techniques (e.g., deterministic matching, probabilistic matching) for linking records exist; the choice of a technique should be guided by the types of data that are available. Linkage projects should include plans for managing common issues (e.g., records that only exist in one database, variations in units of measure). In addition, it is important to understand that linkage of de-identified data may result in accidental re-identification. Risks of re-identification vary depending on the variables used and should be managed with guidance from legal and statistical experts to minimize risk and ensure compliance with HIPAA, the Common Rule, and other legal and regulatory requirements.

Ethics, Data Ownership, and Privacy

Critical ethical and legal considerations should guide the development and use of patient registries. The Common Rule is the uniform set of regulations on the ethical conduct of human subjects research from the Federal agencies that fund such research. Institutions that conduct research agree to comply with the Common Rule for federally funded research and may opt to apply that rule to all human subjects activities conducted within their facilities or by their employees and agents, regardless of the source of funding. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) and its implementing regulations (collectively, the Privacy Rule) are the legal protections for the privacy of individually identifiable health information created and maintained by health care providers, health plans, and health care clearinghouses (called "covered entities"). The research purpose of a registry, the status of its developer, and the extent to which registry data are individually identifiable largely determine applicable

regulatory requirements. Other important ethical and legal concerns include transparency of activities, oversight, and data ownership.

Patient and Provider Recruitment and Management

Recruitment and retention of patients and providers (as registry sites) are essential to the success of a registry. Recruitment typically occurs at several levels, including facilities (hospital, practice, and pharmacy), providers, and patients. The motivating factors for participation at each level and the factors necessary to achieve retention differ according to the registry. Factors that motivate participation include the perceived relevance, importance, or scientific credibility of the registry, as well as the risks and burdens of participation and any incentives for participation. Because patient and provider recruitment and retention can affect how well a registry accurately represents the target population, well-planned strategies for enrollment and retention are critical. Goals for recruitment, retention, and followup should be explicitly laid out in the registry planning phase, and deviations during the conduct of the registry should be continuously evaluated for their risk of introducing bias.

Data Collection and Quality Assurance

The integrated system for collecting, cleaning, storing, monitoring, reviewing, and reporting on registry data determines the utility of those data for meeting the registry's goals. A broad range of data collection procedures and systems are available. Some are more suitable than others for particular purposes. Critical factors in the ultimate quality of the data include how data elements are structured and defined, how personnel are trained, and how data problems are handled (e.g., missing, out-of range, or logically inconsistent values). Registries may also be required to conform to guidelines or to the standards of specific end users of the data (e.g., 21 Code of Federal Regulations, Part 11). Quality assurance aims to affirm that the data were, in fact, collected in accordance with established procedures and that they meet the requisite standards of quality to accomplish the registry's intended purposes and the intended use of the data.

Requirements for quality assurance should be defined during the registry's inception and creation. Because certain requirements may have significant cost implications, a risk-based approach to developing a quality assurance plan is recommended. It should be based on identifying the most important or likely sources of error or potential lapses in procedures that may affect the quality of the registry in the context of its intended purpose.

Interfacing Registries and Electronic Health Records (EHRs)

Achieving electronic health record–registry interoperability will be increasingly important as adoption of EHRs and the use of patient registries for many purposes both grow significantly. Such interoperability should be based on open standards that enable any willing provider to interface with any applicable registry without requiring customization or permission by the EHR vendor. Interoperability for health information systems requires accurate and consistent data exchange and use of the information that has been exchanged. Syntactic interoperability (the ability to exchange data) and semantic interoperability (the ability to understand the exchanged data) are the core constructs of interoperability and must be present for EHRs and registries to share data successfully. Full interoperability is unlikely to be achieved for some time. The successive development, testing, and adoption of open standard building blocks (e.g. HITSP TP-50) is a pragmatic approach towards incrementally advancing interoperability while providing

real benefits today. Care must be taken to ensure that integration efforts comply with legal and regulatory requirements for the protection of patient privacy.

Adverse Event Detection, Processing, and Reporting

The U.S. Food and Drug Administration defines an adverse event (AE) as any untoward medical occurrence in a patient administered a pharmaceutical product, whether or not related to or considered to have a causal relationship with the treatment. AEs are categorized according to the seriousness and, for drugs, the expectedness of the event. Although AE reporting for all marketed products is dependent on the principle of "becoming aware," collection of adverse event data falls into two categories: those events that are intentionally solicited (meaning data that are part of the uniform collection of information in the registry) and those that are unsolicited (meaning that the AE is volunteered or noted in an unsolicited manner).

Determining whether the registry should use a case report form to collect AEs should be based on the scientific importance of the information for evaluating the specified outcomes of interest. Regardless of whether or not AEs constitute outcomes for the registry, it is important to develop a plan for detecting, processing, and reporting AEs for any registry that has direct patient interaction. If the registry receives sponsorship, in whole or in part, from a regulated industry (for drugs or devices), the sponsor has mandated reporting requirements, and the process for detecting and reporting AEs should be established and registry personnel trained on how to identify AEs and to whom they should be reported. Sponsors of registries designed specifically to meet requirements for surveillance of drug or device safety are encouraged to hold discussions with health authorities about the most appropriate process for reporting serious AEs.

Analysis and Interpretation

Analysis and interpretation of registry data begin with answering a series of core questions. Who was studied, and how were they chosen for study? How were the data collected, edited, and verified, and how were missing data handled? How were the analyses performed? Four populations are of interest in describing who was studied: the target population, the accessible population, the intended population, and the population actually studied (the "actual population"). The representativeness of the actual population to the target population is referred to as generalizability.

Analysis of registry outcomes first requires an analysis recruitment and retention, of the completeness of data collection and data quality. Considerations include an evaluation of losses to followup, completeness for most, if not all, important covariates and an understanding of how missing data were handled and reported. Analysis of a registry should provide information on the characteristics of the patient population, the exposures of interest, and the endpoints. Descriptive registry studies focus on describing frequency and patterns of various elements in a patient population, whereas analytical studies concentrate on associations between patients or treatment characteristics and health outcomes of interest. A statistical analysis plan describes the analytical plans and statistical techniques that will be used to evaluate the primary and secondary objectives specified in the study plan. Interpretation of registry data should be provided so that the conclusions can be understood in the appropriate context and so that any lessons from the registry can be applied to the target population and used to improve patient care and outcomes.

Evaluating Registries

Although registries can provide useful information, there are levels of rigor that enhance validity and make the information from some registries more useful for guiding decisions than the information from others. The term "quality" can be applied to registries to describe the confidence that the design, conduct, and analysis of the registry can be shown to protect against bias and errors in inference—that is, erroneous conclusions drawn from a registry. Although there are limitations in any assessment of quality, this handbook uses a quality component analysis to both evaluate high-level factors that may affect results and to differentiate between research quality (which pertains to the scientific process) and evidence quality (which pertains to the data/findings emanating from the research process). Quality components are classified as either "basic elements of good practice," which can be viewed as a checklist that should be considered for all patient registries, or as "potential enhancements to good practice," which may strengthen the information value in particular circumstances. The results of such an evaluation should be considered in the context of the disease area(s), the type of registry, and the purpose of the registry, and should also take into account feasibility and affordability.

Section I: Creating Registries

Chapter 1: Patient Registries

The purpose of this document is to serve as a guide for the design and use of patient registries for scientific, clinical, and health policy purposes. Properly designed and executed, patient registries can provide a real-world view of clinical practice, patient outcomes, safety, and comparative effectiveness. This handbook primarily focuses on practical design and operational issues, evaluation principles, and best practices. Where topics are well covered in other materials, references and/or links are provided. The goal of this document is to provide stakeholders in both the public and private sectors with information that they can use to guide the design and implementation of patient registries, the analysis and interpretation of data from patient registries, and the evaluation of the quality of a registry or one of its components. Where useful, case examples have been incorporated to illustrate particular points or challenges.

The term "registry"[1] is defined both as the act of recording or registering and as the record or entry itself. Therefore, "registries" can refer to both programs that collect and store data and the records that are so created.

The term "patient registry" is generally used to distinguish registries focused on health information from other record sets, but there is no consistent definition in current use. E.M. Brooke, in a 1974 publication of the World Health Organization, further delineated registries in health information systems as "a file of documents containing uniform information about individual persons, collected in a systematic and comprehensive way, in order to serve a predetermined purpose."[2]

The National Committee on Vital and Health Statistics[3] describes registries used for a broad range of purposes in public health and medicine as "an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons who have either a particular disease, a condition (e.g., a risk factor) that predisposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects."

This handbook focuses on patient registries that are used for evaluating patient outcomes. It is not intended to address several other types or uses for registries (although many of the principles may be applicable), such as geographically based population registries (not based on a disease, condition, or exposure); registries created for public health reporting (without tracking outcomes, e.g., vaccine registries); or listing registries that are used solely to identify patients with particular diseases in clinical practices but are not used for evaluating outcomes. This handbook is also not intended to address the wide range of studies that utilize secondary analyses of data collected for other purposes.

In the narrower context of patient registries used for evaluating patient outcomes, this handbook uses the following definitions:

A *patient registry* is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.

The *patient registry database* describes a file (or files) derived from the registry.

Based on these definitions, the handbook focuses on patient registries in which the following are true (although exceptions may apply):

The data are collected in a naturalistic manner, such that the management of patients is determined by the caregiver and patient together and not by the registry protocol.

The registry is designed to fulfill specific purposes, and these purposes are defined before collecting and analyzing the data. In other words, the data collection is purpose-driven rather than the purpose being data-driven (meaning limited to or derived from what is already available in an existing data set).

The registry captures data elements with specific and consistent data definitions.

The data are collected in a uniform manner for every patient. This consideration refers to both the types of data and the frequency of their collection.

The data collected include data derived from and reflective of the clinical status of the patient (e.g., history, examination, laboratory test, or patient-reported data). Registries include the types of data that clinicians would use for the diagnosis and management of patients.

At least one element of registry data collection is active, meaning that some data are collected specifically for the purpose of the registry (usually collected from the patient or clinician) rather than inferred from sources that are collected for another purpose (administrative, billing, pharmacy databases, etc.). This definition does not exclude situations where registry data collection is a specific, but not the exclusive, reason data are being collected, such as might be envisioned with future uses of electronic health records, as described in Chapter 10. This definition also does not exclude the incorporation of other data sources, as discussed in Chapter 6. Registries can be enriched by linkage with extant databases (e.g., to determine deaths and other outcomes or to assess pharmacy use or resource utilization), as discussed in Chapter 7. Other terms also used to refer to patient registries include clinical registries, clinical data registries, disease registries, and outcomes registries.[4,5]

Data from patient registries are generally used for studies that address the purpose for which the registry was created. Much like cohort studies, studies derived from patient registries generally follow patients over time. Unlike traditional cohort studies, registry-based studies are generally more flexible in that the scope and focus may adapt over time to address additional needs.

Current Uses for Patient Registries

A patient registry can be a powerful tool to observe the course of disease; to understand variations in treatment and outcomes; to examine factors that influence prognosis and quality of life; to describe care patterns, including appropriateness of care and disparities in the delivery of care; to assess effectiveness; to monitor safety and harm; and to measure quality of care. Through functionalities such as feedback of data, registries are also being used to study quality improvement.[6] Different stakeholders perceive and

may benefit from the value of registries in different ways. For example, for a clinician, registries can collect data about disease presentation and outcomes on large numbers of patients rapidly, thereby producing a real-world picture of disease, current treatment practices and outcomes. For a physician organization, a registry might provide data that can be used to assess the degree to which clinicians are managing a disease in accordance with evidence-based guidelines, focus attention on specific aspects of a particular disease that might otherwise be overlooked, or provide data for clinicians to compare themselves with their peers.[7] From a payer's perspective, registries can provide detailed information from large numbers of patients on how procedures, devices, or pharmaceuticals are actually used and on their effectiveness in different populations. This information may be useful for determining coverage policies.[8] For a drug or device manufacturer, a registry-based study might demonstrate the performance of a product in the real world, meet a postmarketing commitment or requirement,[9] develop hypotheses, or identify patient populations that will be useful for product development, clinical trials design, and patient recruitment. The U.S. Food and Drug Administration (FDA) has noted that "through the creation of registries, a sponsor can evaluate safety signals identified from spontaneous case reports, literature reports, or other sources, and evaluate the factors that affect the risk of adverse outcomes such as dose, timing of exposure, or patient characteristics."[10]

The use of patient registries varies by priority condition, with cancer and cardiovascular disease having a large number of registries and areas such as developmental delays or dementia, far fewer. Overall, the use of patient registries appears to be active and growing. For example, a review of clinicaltrials.gov in the area of cancer reveals over 200 large (more than 2,000 patients) observational studies that would meet the criteria for a patient registry. Of these studies, four have more than 100,000 patients, and 27 have more than 10,000. In some cases, the drivers for these registries have been federal stakeholders. For example, since 2005, the FDA Center for Devices and Radiological Health (CDRH) has called for some 120 post-approval studies, many of which use new or existing registries to study the real-world effectiveness of specific devices in community practice.[11]

Evaluating Patient Outcomes

Studies from patient registries and randomized controlled trials (RCTs) have important and complementary roles in evaluating patient outcomes.[12] Ideally, patient registries collect data in a comprehensive manner (with few excluded patients) and therefore produce outcome results that may be generalizable to a wide range of patients. They also evaluate care as it is actually provided, because care is not assigned, determined, or even recommended by a protocol. As a result, the outcomes reported may be more representative of what is achieved in real-world practice. Patient registries also offer the ability to evaluate patient outcomes when clinical trials are not practical (e.g., very rare diseases), and they may be the only option when clinical trials are not ethically acceptable. They are a powerful tool when RCTs are difficult to conduct, such as in surgery or when very long-term outcomes are desired.

RCTs are controlled experiments designed to test hypotheses that can ultimately be applied to real-world care. Because RCTs are often conducted under strict constraints, with detailed inclusion and exclusion criteria (and the need for subjects who are willing to be randomized), they are sometimes limited in their generalizability. If RCTs are not generalizable to the populations to which the information will be applied, they may not be sufficiently informative for decisionmaking. Conversely, patient registries that observe real-world clinical practice may collect all of the information needed to assess patient outcomes in a generalizable way, but interpreting this information correctly requires analytic methodology geared to

address the potential sources of bias that challenge observational studies. Interpreting patient registry data also requires checks of internal validity and sometimes the use of external data sources to validate key assumptions (such as comparing the key characteristics of registry participants with external sources in order to demonstrate the comparability of registry participants to the ultimate reference population). Patient registries, RCTs, other study designs, and other data sources should all be considered tools in the toolbox for evidence development, each with its own advantages and limitations.[13]

Hierarchies of evidence. One question that arises in a discussion of this type is where to place studies derived from patient registries within the hierarchies of evidence that are frequently used in developing guidelines or decisionmaking. While the definition of patient registry used in this handbook is intentionally broad, the parameters of quality described in Chapter 14 are intended to help the user evaluate and identify registries that are sufficiently rigorous observational studies for use as evidence in decisionmaking. Many registries are, or include, high quality studies of cohorts designed to address a specific problem and hypothesis. Still, even the most rigorously conducted registries, like prospective observational studies, are traditionally placed in a subordinate position to RCTs in some commonly used hierarchies, although equal to RCTs in others.[14,15,16] Debate continues in the evidence community regarding these traditional methods of grading levels of evidence, their underlying assumptions, their shortcomings in assessing certain types of evidence (e.g., benefit vs. harm), and their inter-scale consistency in evaluating the same evidence.[17,18,19]

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group has proposed a more robust approach that addresses some of the decisionmaking issues described in this handbook. As noted by the GRADE collaborators:

> [R]andomised trials are not always feasible and, in some instances, observational studies may provide better evidence, as is generally the case for rare adverse effects. Moreover, the results of randomised trials may not always be applicable–for example, if the participants are highly selected and motivated relative to the population of interest. It is therefore essential to consider study quality, the consistency of results across studies, and the directness of the evidence, as well as the appropriateness of the study design.[20]

As the methods for grading evidence for different purposes continue to evolve, this handbook can serve as a guide to help such evaluators understand study quality and identify well-designed registries. Beyond the evidence hierarchy debate, users of evidence understand the value of registries for providing complementary information that can extend the results of clinical trials to populations not studied in those trials; for demonstrating the real-world effects of treatments outside of the research setting and potentially in large subsets of affected patients; and for providing long-term followup when such data are not available from clinical trials.

Defining patient outcomes. The focus of this handbook is the use of registries to evaluate patient outcomes. An outcome may be thought of as an end result of a particular health care practice or intervention. According to the Agency for Healthcare Research and Quality (AHRQ), end results include effects that people experience and about which they care.[21] The National Cancer Institute further clarifies that "final" endpoints are those that matter to decision makers: patients, providers, private payers, government agencies, accrediting organizations, or society.[22,23] Examples of these outcomes include biomedical outcomes, such as survival and disease-free survival, health-related quality of life, satisfaction

with care, and economic burden.[24] Although final endpoints are ultimately what matter, it is sometimes more practical when creating registries to collect intermediate outcomes (such as whether processes or guidelines were followed) and clinical outcomes (such as whether a tumor regressed or recurred) that predict success in improving final endpoints.

In *Crossing the Quality Chasm*,[25] the Institute of Medicine (IOM) describes the six guiding aims of healthcare as safe, effective, efficient, patient-centered, timely, and equitable. While these aims are not outcomes per se, they generally describe the dimensions of results that matter to decision makers in the use of health care products and services: Is it safe? Does it produce greater benefit than harm? Is it clinically effective? Does it produce the desired effect in real-world practice? Does the right patient receive the right therapy or service at the right time? Is it cost effective or efficient? Does it produce the desired effect at a reasonable cost relative to other potential expenditures? Is it patient oriented, timely, and equitable? These last three aims focus on the delivery and quality of care. Most of the patient outcomes that registries evaluate reflect one or more of these guiding aims. For example, a patient presenting with an ischemic stroke to an emergency room has a finite window of opportunity to receive a thrombolytic drug, and the patient outcome, whether or not the patient achieves full recovery, is dependent not only on the product dissolving the clot but also the timeliness of its delivery.[26,27]

Purposes of Registries

As discussed throughout this handbook, registries should be designed and evaluated with respect to their intended purpose(s). Registry purposes can be broadly described in terms of patient outcomes. While there are a number of potential purposes for registries, this document primarily discusses four major purposes: describing the natural history of disease, determining clinical and/or cost effectiveness, assessing safety or harm, and measuring or improving quality of care. Other purposes of patient registries mentioned but not discussed in detail in this document are for public health surveillance and disease control. An extensive body of literature from the last half century of experience with cancer and other disease surveillance registries is available.

Natural history of disease. Registries may be established to evaluate the natural history of a disease, meaning its characteristics, management, and outcomes with and/or without treatment. The natural history may be variable across different groups or geographic regions, and it often changes over time. In many cases, the natural histories of diseases are not well described. Furthermore, the natural history of diseases may change after the introduction of certain therapies. As an example, patients with rare diseases, such as the lysosomal storage diseases, who did not previously survive to their twenties, may now be entering their fourth and fifth decades of life, and this uncharted natural history is being first described through a registry.[28]

Determining effectiveness. Registries may be developed to determine clinical effectiveness or cost effectiveness in real-world clinical practice. Multiple studies have demonstrated disparities between the results of clinical trials and results in actual clinical practice.[29,30] Furthermore, efficacy in a clinical trial for a well-defined population may not be generalizable to other populations or subgroups of interest. As an example, many important heart failure trials have focused on a predominantly white male population with a mean age of approximately 60 years, whereas actual heart failure patients are older, more diverse, and have a higher mortality rate than the patients in these trials.[31] Similarly, underrepresentation of older patients has been reported in clinical trials of 15 different types of cancer (e.g., studies with only 25

percent of patients age 65 years and over, while the expected rate is greater than 60 percent).[32] Conversely, data from registries have been used to fill these gaps for decision makers. For example, the FDA used the American Academy of Ophthalmology's intraocular lens registry to expand the label for intraocular lenses to older patients.[33] Registries may also be particularly useful for tracking effectiveness outcomes for a longer period than is typically feasible with clinical trials. For example, some growth hormone registries have tracked children well into adulthood.

In addition to clinical effectiveness, registries can be used to assess cost effectiveness. Registries can be designed to collect cost data and effectiveness data for use in modeling cost effectiveness.[34] Cost effectiveness is a means to describe the comparative value of a health care product or service in terms of its ability to achieve a desired outcome for a given unit of resources.[35] A cost-effectiveness analysis examines the incremental benefit of a particular intervention and the costs associated with achieving that benefit. Cost-effectiveness studies compare costs with clinical outcomes measured in units such as life expectancy or disease-free periods. Cost-utility studies compare costs with outcomes adjusted for quality of life (utility), such as quality-adjusted life years (QALYs). Utilities allow comparisons to be made across conditions because the measurement is not disease specific.[36] It should be noted that for both clinical and cost effectiveness, differences between treatments are indirect and must be inferred from data analysis, simulation modeling, or some mixture.

With improvement in methodologies for using observational research for comparative effectiveness research (CER), including better methods for managing bias and better understanding of the limitations,[37] across a number of stakeholders there is both increasing interest and investment in registries for CER. Reports from the Institute of Medicine (IOM) and the Congressional Budget Office (CBO) in 2007 have cited the importance of patient registries in developing comparative effectiveness evidence.[38,39] The Federal Coordinating Council for Comparative Effectiveness Research in its Report to the President and the Congress (June 30, 2009), defined CER as "the conduct and synthesis of research comparing benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in 'real world' settings." The report specifically identifies patient registries as a core component of CER data infrastructure.

While some registries are designed explicitly to examine questions of comparative effectiveness, many others are designed for different objectives yet still collect data that are useful for comparative effectiveness analyses. Registries that were not explicitly designed for CER may need to be augmented or linked to other data sources; for example, to obtain long-term outcomes data in the case of an in-hospital registry using linkage to claims data to evaluate blood pressure medications.[40]

Measuring or monitoring safety and harm. Registries may be created to assess safety vs. harm. Safety here refers to the concept of being free from danger or hazard. One goal of registries in this context may be to quantify risk or to attribute it properly. Broadly speaking, patient registries can serve as an active surveillance system for the occurrence of unexpected or harmful events for products and services. Such events may range from patient complaints about minor side effects to severe adverse events such as fatal drug reactions or patient falls in the hospital.

Patient registries offer multiple advantages for active surveillance. First, the current practice of spontaneous reporting of adverse events relies on a nonsystematic recognition of an adverse event by a clinician, and the active effort by the clinician to make a report to manufacturers and health authorities.

Second, these events are generally reported without a denominator (i.e., the exposed or treated population), and therefore an incidence rate is difficult to determine. Because patient registries can provide systematic data on adverse events and the incidence of these events, they are being used with increasing frequency in the areas of health care products and services. The role of registries in monitoring product safety is discussed in more detail in Chapter 4.

Measuring quality. Registries may be created to measure quality of care. The IOM defines quality as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge." Quality-focused registries are being used increasingly to assess differences between providers or patient populations based on performance measures that compare treatments provided or outcomes achieved with "gold standards" (e.g., evidence-based guidelines) or comparative benchmarks for specific health outcomes (e.g., risk-adjusted survival or infection rates). Such programs may be used to identify disparities in access to care, demonstrate opportunities for improvement, establish differentials for payment by third parties, or provide transparency through public reporting. There are multiple examples of such differences in treatment and outcomes of patients in a range of disease areas.[41,42,43,44,45,46]

Multiple purposes. While each of these purposes may drive the creation of a registry, many registries will be developed to serve more than one purpose.

Taxonomy for Patient Registries

Even limited to the definitions described above, the breadth of studies that might be included as patient registries is large. Patients in a registry are typically selected based on a particular disease, condition (e.g., a risk factor), or exposure. This handbook utilizes these common selection criteria to develop a taxonomy or classification based on how the populations for registries are defined. Three general categories with multiple subcategories and combinations account for the majority of registries that are developed for evaluating patient outcomes. These categories include observational studies in which the patient has a particular disease or condition, or has had an exposure to a product or service, or various combinations thereof.

Product Registries

In the case of a product registry, the patient is exposed to a health care product, such as a drug or a device. The exposure may be brief, as in a single dose of a pharmaceutical product, or extended, as in an implanted device or chronic usage of a medication.

Device registries may include all, or a subset, of patients who receive the device. A registry for all patients who receive an implantable cardioverter defibrillator, a registry of patients with hip prostheses, or a registry of patients who wear contact lenses are all examples of device registries. Biopharmaceutical product registries similarly have several archetypes, which may include all, or subsets, of patients who receive the biopharmaceutical product. E.g., the British Society for Rheumatology established a national registry of patients on biologic therapy.[47] Again, the duration of exposure may range from a single event to a lifetime of use. Eligibility for the registry includes the requirement that the patient received the product or class of products (e.g., COX-2 inhibitors). In some cases, such registries are mandated by public health authorities to ensure safe use of medications. Examples include registries for thalidomide, clozapine, and isotretinoin.

Pregnancy registries represent a separate class of biopharmaceutical product registries that focus on possible exposures during pregnancy and the neonatal consequences. The FDA has a specific guidance focused on pregnancy exposure registries, which is available at http://www.fda.gov/CbER/gdlns/pregexp.htm. This guidance uses the term "pregnancy exposure registry" to refer to "a prospective observational study that actively collects information on medical product exposure during pregnancy and associated pregnancy outcomes."

Health Services Registries

In the context of evaluating patient outcomes, another type of exposure that can be used to define registries is exposure to a health care service. Health care services that may be utilized to define inclusion in a registry include individual clinical encounter(s), such as office visits or hospitalizations, procedures, or full episodes of care. Examples include registries enrolling patients undergoing a procedure (e.g., carotid endarterectomy, appendectomy, or primary coronary intervention) or admitted to a hospital for a particular diagnosis (e.g., community-acquired pneumonia). In these registries, one purpose of the registry is to evaluate the health care service with respect to the outcomes. Health care service registries are sometimes used to evaluate the processes and outcomes of care for quality measurement purposes (e.g., Get With The Guidelines® of the American Heart Association, National Surgical Quality Improvement Program of the Department of Veterans Affairs).

Disease or Condition Registries

Disease or condition registries use the state of a particular disease or condition as the inclusion criterion. In disease or condition registries, the patient may always have the disease (e.g., a rare disease, such as cystic fibrosis or Pompe disease, or a chronic illness, such as heart failure, diabetes, or end-stage renal disease) or may have the disease or condition for a more limited period of time (e.g., infectious diseases, some cancers, obesity). These registries typically enroll the patient at the time of a routine health care service, although patients also can be enrolled through voluntary self-identification processes that do not depend on utilization of health care services (such as Internet recruiting of volunteers). In other disease registries, the patient has an underlying disease or condition, such as atherosclerotic disease, but is enrolled only at the time of an acute event or exacerbation, such as hospitalization for a myocardial infarction or ischemic stroke.

Combinations

Complicating this classification approach is the reality that these categories can be overlapping in many registries. For example, a patient with ischemic heart disease may have an acute myocardial infarction and undergo a primary coronary intervention with placement of a drug-eluting stent and postintervention management with clopidogrel. This patient could be enrolled in an ischemic heart disease registry tracking all patients with this disease over time, a myocardial infarction registry that is collecting data on patients who present to hospitals with acute myocardial infarction (cross-sectional data collection), a primary coronary intervention registry that includes management with and without devices, a coronary artery stent registry limited to ischemic heart disease patients, or a clopidogrel product registry that includes patients undergoing primary coronary interventions.

Duration of Observation

The duration of the observational period for a registry is also a useful descriptor. Observation periods may be limited to a single episode of care (e.g., a hospital discharge registry for diverticulitis), or they

may extend for as long as the lifetime of a patient with a chronic disease (e.g., cystic fibrosis or Pompe disease) or patients receiving a novel therapy (e.g., gene therapy). The period of observation or followup depends on the outcomes of interest.

From Registry Purpose to Design

As will be discussed extensively in this document, the purpose of the registry defines the registry focus (e.g., product vs. disease) and therefore the registry type. A registry created for the purpose of evaluating outcomes of patients receiving a particular coronary artery stent might be designed as a single product registry if, for example, the purpose is to systematically collect adverse event information on the first 10,000 patients receiving the product. However, the registry might alternatively be designed as a health care service registry for primary coronary intervention if a purpose is to collect comparative effectiveness or safety data on other treatments or products within the same registry.

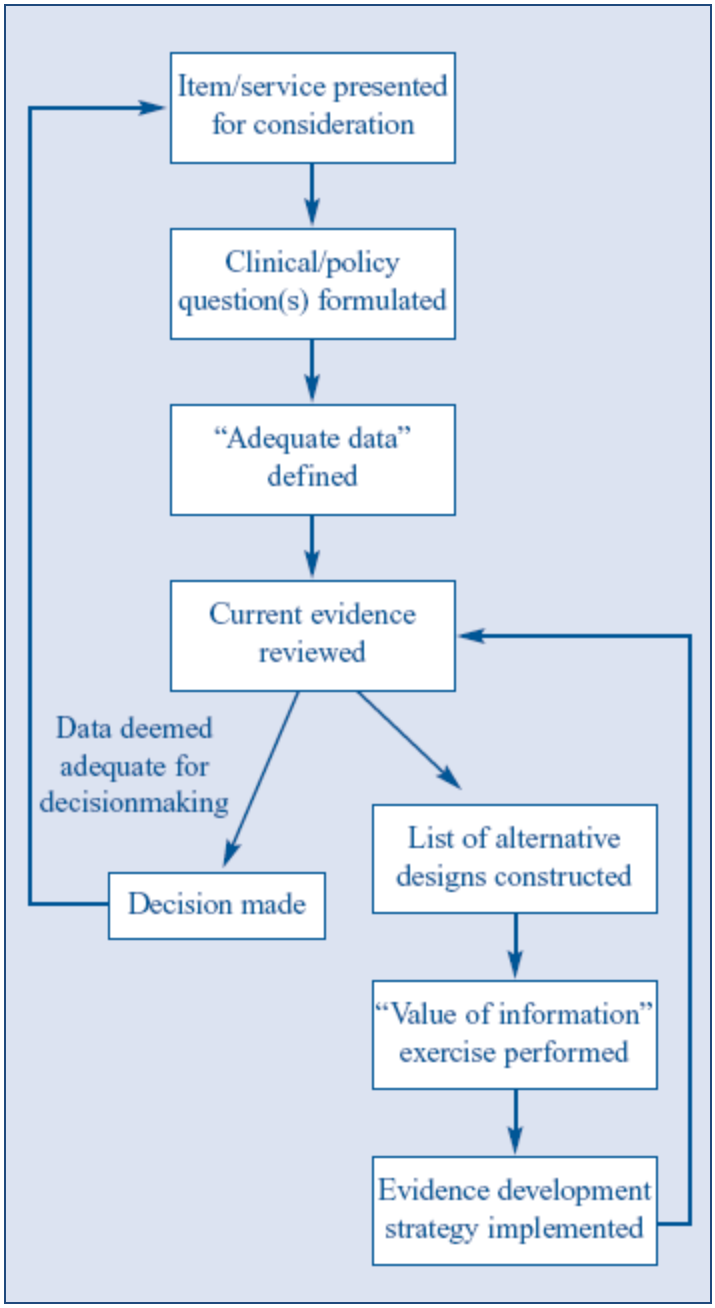
Patient Registries and Policy Purposes

In addition to the growth of patient registries for scientific and clinical purposes, registries are receiving increased attention for their potential role in policymaking or decision-making.[48,49] As stated earlier, registries may offer a view of real-world health care that is typically inaccessible from clinical trials or other data sources and may provide information on the generalizability of the data from clinical trials to populations not studied in those trials.

The utility of registry data for decisionmaking is related to three factors: the stakeholders, the primary scientific question, and the context. The stakeholders are those associated with the disease or procedure that may be affected from a patient, provider, payer, regulator, or other perspective. The primary scientific question for a registry may relate to effectiveness, safety, or practice patterns. The context includes the scientific context (e.g., previous randomized trials and modeling efforts that help to more precisely define the primary scientific question), as well as the political, regulatory, funding, and other issues that provide the practical parameters around which the registry is developed. In identifying the value of information from registries, it is essential to look at the data with specific reference to the purpose and focus of the registry and in that context.

From a policy perspective, there are several scenarios in which the decision to develop a registry may arise. One possible scenario is as follows. An item or service is considered for use. Stakeholders in the decision collaboratively define “adequate data in support of the decision at hand.” Here, "adequate data" refers to information of sufficient relevance and quality to permit an informed decision. An evidence development strategy is selected from one of many potential strategies (RCT, practical clinical trial, registry, etc.) based on the quality of the evidence provided by each design, as well as the burden of data collection and the cost that is imposed. This tradeoff of the quality of evidence vs. cost of data collection for each possible design is termed the "value of information" exercise (Figure 1). Registries should be preferred in those circumstances where they provide sufficiently high quality information for decisionmaking at a sufficiently low cost (relative to other "acceptable" designs).

Figure 1. Deciding When to Develop a Registry: The "Value of Information" Exercise



One set of policy determinations that may be informed by a patient registry centers on the area of payment for items or services. For example, in the Centers for Medicare & Medicaid Services (CMS) Guidance on National Coverage Determinations With Data Collection as a Condition of Coverage, CMS describes several examples of how data collected in a registry might be used in the context of coverage determinations. As described in the Guidance:

> [T]he purpose of CED [Coverage with Evidence Development] is to generate data on the utilization and impact of the item or service evaluated in the NCD [National Coverage Determination], so that Medicare can a) document the appropriateness of use of that item or

> service in Medicare beneficiaries under current coverage; b) consider future changes in coverage for the item or service; c) generate clinical information that will improve the evidence base on which providers base their recommendations to Medicare beneficiaries regarding the item or service.[50]

The Guidance provides insight into when registry data may be useful to policymakers. These purposes range from demonstrating that a particular item or service was provided appropriately, to patients meeting specific characteristics, to collecting new information that is not available from existing clinical trials. CED based on registries may be especially relevant when current data do not address relevant outcomes for beneficiaries, off-label or unanticipated uses, important patient subgroups, operator experience or other qualifications. They may also be important when an existing treatment is being reconsidered (an RCT may not be possible under such circumstances). Registry based studies are also being used increasingly in fulfillment of postmarketing commitments and requirements.

In many countries, policy determinations on payment rely on cost-effectiveness and cost-utility data and therefore can be informed by registries as well as clinical trials.[51] These data are used and reviewed in a variety of ways. In some countries, there may be a threshold above which a payer is willing to pay for an improvement in patient outcomes.[52] In these scenarios—particularly for rare diseases, when it can be difficult to gather clinical effectiveness data together with quality-of-life data in a utility format—the establishment of disease-specific data registries has been recommended to facilitate the process of technology assessment and improving patient care.[53] In fact, the use of new or existing registries to assess health technology or risk-sharing arrangements is growing in such countries as the United Kingdom, France, Germany, and Australia, and in conditions ranging from bariatric surgery to stroke care.[54,55,56,57,58,59]

Consider the clinical question of carotid endarterectomy surgery for patients with a high degree of stenosis of the carotid artery. Randomized trials, using highly selected patients and surgeons, indicate a benefit of surgery over medical management in the prevention of stroke. However, that benefit may be exquisitely sensitive to the surgical complication rates (i.e., a relatively small increase in the rate of surgical complications is enough to make medical management the preferred strategy instead), and the studies of surgical performance in a variety of hospitals may suggest substantial variation in surgical mortality and morbidity for this procedure. In such a case, a registry to evaluate treatment outcomes, adjusted by hospital and surgeon, might be considered to support a policy decision as to when the procedure should be reimbursed (e.g., only when performed in medical centers resembling those in the various randomized trials, or only by surgeons or facilities with an acceptably low rate of complications).[60]

Global Registries

As many stakeholders have international interests in diseases, conditions, and health care products and services, it is not surprising that interest in patient registries is global. While some of the specific legal and regulatory discussions in this handbook are intended for and limited to the United States, most of the concepts and specifics are more broadly applicable to similar activities worldwide. Chapters 8 and 12 are perhaps the most limited in their applicability outside the United States. In addition, there may be differences or additions to be considered in data element selection (Chapter 5) stemming from: differences ranging from medical training to use of local remedies; the types of data sources that are

available outside the United States (Chapter 6); the issues surrounding physician and patient recruitment and retention in different health systems and cultures (Chapter 9); and specific data collection and management options and complexities (Chapter 10), ranging from available technologies to languages.

Summary

A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves predetermined scientific, clinical, or policy purpose(s). Studies derived from well-designed and well-performed patient registries can provide a real-world view of clinical practice, patient outcomes, safety, and comparative effectiveness and cost-effectiveness, and serve a number of evidence development and decisionmaking purposes. In the chapters that follow, this handbook presents practical design and operational issues, evaluation principles, and good registry practices.

Chapter 2: Planning a Registry

There is tremendous variability in size, scope, and resource requirements for registries. Registries may be large or small in their numbers of patients or participating sites. They may target rare or common conditions and exposures. They may require the collection of limited or extensive amounts of data, operate for short or long periods of time, and may be funded generously or with limited financial support. In addition, the scope and focus of a registry may be adapted over time to reflect updated information, to reach broader or different populations, to assimilate additional data, to focus on or expand to different geographical regions, or to address new research questions. While this degree of flexibility confers enormous potential, registries require good planning in order to be successful.

When planning a registry, it is desirable to follow these initial steps: 1) articulate the purpose of the registry; 2) determine if a registry is an appropriate means to achieve the purpose; 3) identify key stakeholders; and 4) assess the feasibility of registry.

Once a decision is made to proceed, the next considerations in planning are to 5) build a registry team; 6) establish a governance and oversight plan; 7) define the scope and rigor needed; 8) define the data set, patient outcomes, and target population; and 9) develop a project plan. Registry planners should also 10) determine what will happen when the registry ends. Of course, the planning for a registry is often not a linear process. Many of the steps described in this chapter occur in parallel.

The *Guidelines for Good Pharmacoepidemiology Practice* from the International Society of Pharmacoepidemiology is a useful resource for registry planners, as are the STROBE guidelines for reporting observational studies.[61, 62] The *Updated Guidelines for Evaluating Public Health Surveillance Systems* may also be useful to planners, especially the appendices, which provide various checklists.[63] *A Guide to the Project Management Body of Knowledge (PMBOK® Guide)* may also be a useful resource to registry planners.[64]

Articulate the Purpose

One of the first steps in planning a registry is articulating the purpose. Having a clearly defined goal and/or purpose and supporting rationale makes it easier to evaluate whether a registry is the right approach for capturing the information of interest.[65,66] In addition, a clearly defined purpose helps clarify the need for certain data. Conversely, having a clear sense of how the data may be used will help refine the stated purpose. Attempts to be all-inclusive increase the likelihood of including data or procedures that add costs but not value, resulting in overly burdensome data collection that can reduce quality and erode compliance.

A registry may have a singular purpose, or it may serve several purposes.[67] In either case, the overall purpose should be translated into specific objectives or questions to be addressed through the registry. This process needs to take into account the interests of those collaborating in the registry and the key audiences to be reached.[68] Clear objectives are essential to define the structure and process of data

collection and to ensure that the registry effectively addresses the important questions through the appropriate outcomes analyses. Specific objectives also help the registry to avoid collecting large amounts of data of limited value. The time and resources needed to collect and process data from a registry can be substantial.[69] The identification of a core data set is essential. The benefits of any data element included in the registry must outweigh the costs of including it.

Registry planners can begin to establish specific objectives by considering what key questions the registry needs to answer. Critical consideration needs to be given to defining the key questions in order to evaluate how best to proceed, as these questions will help to establish the type of registry (e.g., single focus or comparative), the data elements to be captured, and the types of analysis that will be planned. Examples of key, or driving, questions are listed below:

- What is the natural course of a disease and how does geographic location affect the course?
- Does a treatment lead to long-term benefits or harm, including delayed complications?
- How is disease progression affected by available therapies?
- What are significant predictors of poor outcomes?
- What is the safety profile of a specific therapy?
- Is a specific product or therapy teratogenic?
- How do clinical practices vary, and what are the best predictors of treatment practices?
- Are there disparities in the delivery and/or outcomes of care?
- What characteristics or practices enhance compliance and adherence?
- Do quality improvement programs affect patient outcomes, and, if so, how?
- What process and outcomes metrics should be incorporated to track quality of patient care?
- Should a particular procedure or product be a covered benefit in a particular population?
- Was an intervention program or risk management activity successful?
- What are the resources used/economic parameters of actual use in typical patients?

Two of the case examples in this chapter provide examples of how key questions have shaped registries. (See Case Examples 1, 2, and 3.)

Determine if a Registry is an Appropriate Means to Achieve the Purpose

Two key questions to consider are whether a registry (or other study) is needed to address the purpose; and, if the answer is yes, whether a registry is an appropriate means of accomplishing the scientific objectives. Every registry developer should consider early in the planning process, "Do these data already exist and, if so, are they of sufficient quality to answer the research question and are they accessible, or does an entirely new data collection effort need to be initiated?" For example, could the necessary data be extracted from electronic medical records or administrative health insurance claims data? In such cases, registries might avoid re-collecting data that have already been collected elsewhere and are accessible. Thought should be given to adapting the registry (based on extant data) and/or linking to other relevant data sources (including "piggybacking" onto other registries). When the required data have not been sufficiently collected or are not accessible for the desired purpose, it is appropriate to consider creating a new registry.

The next step is to consider whether the purpose would be best met by a clinical trial or a registry, and to consider that decision in the context of the state of current knowledge, gaps in evidence, how broad the

target population of interest is, how complex the current treatment patterns are, how long an observational period would be needed to achieve the objective, the scope and variety of treatments used, and the approximate amount of funding available to address these objectives, and the likelihood that a clinical trial could be conducted for the population of interest in a suitable time frame. While clinical trials are extremely useful tools for studying treatment effectiveness and safety in narrowly focused populations where patients have high adherence to treatment protocols, clinical trials are quite rigid by design, are not suited to adaptation over time, and are relatively expensive and, by definition, cannot measure events under conditions of usual practice. If it appears that a more comprehensive, flexible research tool is needed, then a registry should be considered.[70,71] A careful evaluation of the possibilities for data collection and registry design, the degree of certainty required, and the timeframe in which this certainty is expected can help in selecting an appropriate study design.

It is important to note that, historically, there has been a lack of consensus standards for conducting and reporting methods and results for registries. Therefore, registries have tended to be more variable in implementation and have been more difficult to assess for quality than randomized controlled trials. Advances in epidemiological and biostatistical methods have broadened the scope of questions that can be addressed through observational studies such as a registry. Stratification, propensity score matching, and risk adjustment are increasingly useful approaches for addressing confounding issues and for creating comparably homogeneous subgroups for analysis within registry data sets, and advances in bias analysis are being used to help interpret results from observational studies like registries (see Chapters 3 and 13).[72,73,74] These techniques may allow registries to be used to support investigations of comparative safety and effectiveness. Following good registry practices, as described in this handbook, can strengthen scientific rigor (see Chapters 10 and 14).

Identify Key Stakeholders

It is important to consider to whom the research questions matter, as a means to identifying potential stakeholders. It is useful to identify these stakeholders at an early stage of the registry planning process, as they may have important input into the type and scope of data to be collected, they may ultimately be users of the data, and/or they may have a key role in disseminating the results of the registry.

One or more parties could be considered stakeholders of the registry. These parties could be as specific as a regulatory agency that will be monitoring postmarketing studies or as broad as the general population, or simply those patients with the condition(s) of interest. Often, a stakeholder's input directly influences whether development of a registry can proceed, and it can have a strong influence on how a registry is conducted. A regulatory agency looking for management of a therapeutic with a known toxicity profile may require a different design than a manufacturer with general questions about how a product is being used. As regulators in the US and abroad increasingly look for registries to provide continuing reports on disease progression and on treatment safety and effectiveness, it is important to consider their potential needs at an early stage in development, possibly before beginning Phase III clinical trials.

Typically, there are primary and secondary stakeholders for any registry. A primary stakeholder is usually responsible for creating and funding the registry. The party that requires the data, such as a regulatory authority, may also be considered a primary stakeholder. A secondary stakeholder is a party that would benefit from knowledge of the data or that would be impacted by the results, but is not critical

in establishing the registry. Treating physicians and their patients could be considered secondary stakeholders. A partial list of possible stakeholders, both primary and secondary, follows:

- Public health or regulatory authorities
- Product manufacturers
- Health care service providers
- Payer or commissioning authorities
- Patients and/or advocacy groups
- Treating physician groups
- Academic institutions or consortia
- Professional societies

Although interactions with potential stakeholders will vary, the registry will be best supported by defined interactions and communications with these parties. Defining these interactions during the planning stage will ensure that adequate dialogue occurs and appropriate input is received to support the overall value of the registry. Interactions throughout the entire duration of the registry can also assure stakeholders that the registry is aligned with the purposes and goals that were set out during the planning stages and that the registry complies with all required guidances, rules, and/or regulations.

Assess the Feasibility

A key element in determining the feasibility of developing a new registry relates to funding. Registries that meet the attributes described in this handbook will most likely require significant funding. The degree of expense incurred will be determined by the scope of the registry and the rigor of data collection and any audits that may be required. The larger the numbers of sites, patients, and scope of data collected, and the greater the need for representation from a wide variety of patient characteristics, the greater the expense. In addition, the method of data collection will contribute to expense. Historically, electronic data collection has been more expensive to implement, but generally less expensive to maintain, compared with fax and scanned or mailed forms;[75] however, the cost difference for start up has been lessening. Funding will be affected by whether other relevant data sources and/or infrastructures exist that capture some of the information of interest; whether the registry adapts to new issues over time; and whether multiple funding sources participate. Funding needs should also be examined in terms of the projected life of the registry and/or its long-term sustainability.

There are many potential funding sources for registries. Funding sources are likely to want to share in planning and to provide input for the many choices that will need to be made in the implementation plans. Funding sources may negotiate to receive access to de-identified data as a condition for their participation. Funding models for registries may vary significantly, and there is no preferred approach. Rather, the funding model for a registry should be dictated by the needs of the registry. Potential sources of funding include:

- Government: Federal agencies, such as NIH, CDC, and state agencies, may be interested in a registry to determine long-term outcomes of agents, devices, or groups of drugs. While the pharmaceutical industry or device manufacturers collect most long-term data on drug and device safety, many research questions arise that could potentially be suitable for government funding in the context of sponsored Phase IV safety studies mandated by FDA. To determine if there is

interest in funding a registry, look for Requests for Proposals (RFPs) on the Web site of the agency. An RFP posting or direct communication with the appropriate agency staff may provide a great deal of specific information as to how a submission will be judged and what specific criteria would be needed in order for a proposal to be favorably ranked. Even if an RFP is not posted, contacting the appropriate agency staff may uncover potential interest in a registry to fill an unmet need.

- Product manufacturers: Product manufacturers may be interested in: studying the natural history of the disease for which they have (or are developing) a product; demonstrating the effectiveness and/or safety of existing products in real-world use, through REMS programs, as part of postmarketing commitments or requirements, or through studies; or assisting providers in evaluating or improving quality of care.
- Foundations: Non-profit disease foundations may be interested in a registry to track the natural history of the disease of interest as well as the impact of therapeutic interventions. Registries may be used to track practice patterns and outcomes for quality improvement initiatives. Ongoing registries can sometimes serve the additional purpose of assisting in recruitment for clinical trials.[76]
- Private funding: Private philanthropic individuals or charitable foundations and trusts may have an interest in furthering research to better understand the effects of a particular intervention or sets of interventions on a disease process.
- Health plan providers: Under certain circumstances, health plan providers may be interested in funding a registry as practical clinical research is increasingly viewed as a useful tool for providing evidence for health coverage and health care decisions.[77]
- Professional societies: Health care professional associations are increasingly participating in developing or partnering with registries for scientific and quality measurement or improvement purposes.
- Professional society/pharmaceutical industry "hybrid": Situations may exist in which a product manufacturer funds a registry that would be designed and implemented by a professional society to gain insight into a set of research questions.
- Multiple sponsors: Registries may meet the goals of multiple stakeholders, and such stakeholders may have an interest in sharing the funding. Registries for isotretinoin and antiretrovirals in pregnancy are examples. While multiple sponsorship can decrease the costs for each funding source, their varied interests and needs almost always increase the complexity and overall cost of the registry.

While true public-private partnerships for registries currently exist (e.g., state-level immunization registries, bioterrorism surveillance),[78,79,80] there is great potential for growth in this approach. With increasing interest in registries from the both government and private sources for improved safety monitoring, for comparative effectiveness goals, and for streamlining the costs of the drug development process[81,82,83,84,85,86] there have been several legislative actions which have stated or suggested the role of public-private partnerships for activities such as registry development.[87] A public-private partnership is a service or business venture that is funded and operated through a partnership (contractual agreement) between a public agency (federal, state, or local) and a private sector entity or entities (see Case Example 4).[88] There are many reasons for multiple stakeholders, including government agencies, providers, and

industry to be interested in working together on particular registries in certain conditions. Thus, it is anticipated that shared funding mechanisms are likely to become more common.

Build a Registry Team

Several different kinds of knowledge, expertise, and skills are needed to plan and implement a registry. In a small registry run by a single individual, consultants may be able to provide the critical levels of expertise needed to plan all components of the registry. In a large registry, a variety of individuals may work together as a team to contribute the necessary expertise. Depending on the size, scope, and purpose of the registry, few, some, or all of the individuals representing the components of expertise described below may be included at the time of the planning process. Whatever number of individuals is eventually assembled, it is important to build a group that can work together as a collegial team to accomplish the goals of the registry. Additionally, the team participants must understand the data sources. By understanding the goals and data sources, the registry team will enable the data to be utilized in the most appropriate context for the most appropriate interpretation. The different kinds of expertise and experience that are useful include the following:

- Project management: Project management will be needed to coordinate the components of the registry; to manage timelines, milestones, deliverables, and budgets; and to ensure communication with sites, stakeholders, oversight committees, and funding sources. Ongoing oversight of the entire process will require a team approach. (See the next section.)
- Subject matter: A registry must be designed so that it contains the appropriate data to meet its goals as well as the needs of its stakeholders. For example, experts in the treatment of the clinical disease to be studied who are also familiar with the potential toxicities of the treatment(s) to be studied are critical to the success of the registry. Clinical experts must be able to apply all of the latest published clinical, toxicity, and outcome data to components of the registry and determine which elements are necessary, desirable, or superfluous.
- Registry science: Epidemiology and biostatistics expertise specific to the subtleties of patient registries and observational research are very important in the design, implementation, and analysis of registry data. Epidemiologists can provide the study design and can work in collaboration with biostatisticians to develop a mutual understanding of the research objectives and data needed. Health outcomes and economics researchers can also lend valuable expertise to the registry team. These scientists should work with the subject matter experts to ensure that appropriate analytic methods are being used to address the clinical issues relevant to achieving the goals of the registry.
- Data collection and database management: The decision to include various data elements can be made in consultation with experts in this field to place "critical fields" in a prominent and logical position on the data form for both paper-based and electronic data collection tools. A final determination of what is usable and workable for data collection tools should be approved by all members of the team. These experts may also need to write specific programs so that the data received from the registry are grouped, stored, and identified. They may generate reports for individuals who track registry participation, and they may provide data downloads periodically to registry analysts. This team will also be responsible for implementing and maintaining firewalls to protect the data according to accepted levels of security for similar collections of sensitive data.

- Legal/patient privacy: In the present legal climate, it is critical that either information that identifies individual patients be excluded or specific consent be sought to include information on the identity of a patient. The complexities of this topic are dealt with in detail in Chapter 8. Legal and privacy expertise is needed to protect the patients and the owners of the database by ensuring that the registry complies with all national and local laws applicable to patient information.
- Quality assurance: As discussed in Chapter 10, quality assurance of procedures and data is another important component of registry success. Expertise in quality assurance will help in planning a good registry. The goals for quality assurance should be established for each registry, and the efforts made and the results achieved should be described.

Establish a Governance and Oversight Plan

Governance refers to guidance and high-level decisionmaking, including concept, funding, execution, and dissemination of information. A successful demonstration of proper governance and oversight is achieving transparency in operations, decisionmaking, and reporting of results.

The composition and relative mix of stakeholders and experts relate largely to the purpose of the registry. For example, if the purpose of the registry is to determine a comparative effectiveness or reimbursement policy, those impacted by the policy should not solely govern the registry. Broad stakeholder involvement is most desirable in governance boards when there are many stakeholders. Depending on the size of the registry, governance may be assumed by various oversight committees made up of interested individuals who are part of the design team (internal governance) or who remain external to the day-to-day operations of the registry (external governance). Differences in the nature of the study questions, the overall resources being consumed by the registry, the soundness of the underlying data sources, and many other factors will influence the degree of involvement and role of oversight groups. In other words, the purpose of the committee functions described below is to lay out the roles that need to be assumed by the governance structure of many registries, but these should be individualized for a particular registry. It is also possible, if methods are clear and transparent, that oversight requirements may be minimal.

Registries fulfill governance roles in a variety of ways. Many of the roles, for example, could be assumed by a single committee (e.g., a steering committee) in some registries. Whatever model is adopted, it must accommodate all of the working constituencies and provide a mechanism for these individuals to work together to achieve the goals of the registry.

All aspects of governance should be codified in a written format that can be reviewed, shared, and refined over time. In addition, governance is a dynamic process, subject to change in policy as evidence emerges that is likely to lead to improvements in the process.

Governance and oversight functions that may be considered include:

- Executive or steering: This function assumes responsibility for the major financial, administrative, legal/ethical, and scientific decisions that determine the direction of the registry. These decisions are made with appropriate input from legal, scientific, and administrative experts. Depending on their capabilities and the size and resources of the registry, the group serving the steering function may also assume some of the functions described below.

- Scientific: This function may include experts ranging from database content, to general clinical research, to epidemiology and biostatistics. This function may determine the overall direction of database inquiries and recommend specific analyses to the executive or steering group. It is strongly desirable that the reports that emerge from a registry be scientifically based analyses that are independent and transparent.[89] To enhance credibility and in the interest of full disclosure, the role of all stakeholders in the publication process should be specified and any potential conflicts of interest identified.
- Liaison: In large registries, a function may be specified to focus on maintaining relationships with the funding source, health care providers, and patients who utilize the database. The group serving this function may develop monitoring and satisfaction tools to assure that the day-to-day operations of the registry remain healthy.
- Adjudication: Adjudication is used to review and confirm cases (outcomes) that may be difficult to classify. Individuals performing this function are generally blinded to the exposure (product or process) under study so that the confirmation of outcomes is made without knowledge of exposure.
- External Review: External Review Committees, Advisory Boards, or Data Safety Monitoring Boards (DSMBs) can be useful for providing independent oversight throughout the course of the registry. The majority of registries will not require a DSMB, since a DSMB is commonly used in situations where data are randomized and treatment status is blinded. However, there may be situations in which the registry is responsible for the primary accumulation of safety data on a particular intervention; in such situations, an external committee or DSMB would be useful for conducting periodic reviews (e.g., annually).
- Data access, use, and publications: A process by which registry investigators access and perform analyses of registry data for the purpose of submitting abstracts to scientific meetings and developing manuscripts for peer reviewed journal submission should be addressed by this function. Authorship (including registry sponsors) in scientific publications should satisfy the conditions of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.[90] The rules governing authorship may be affected by the funding source, as in the case of NIH or foundation funding, or by the biomedical journal. (See Case Examples 2 and 5.) Other investigators may request permission to access the data. For example, a Ph.D. candidate at an institution might seek registry-wide aggregate data for the purposes of evaluating a new scientific question. A process for reviewing and responding to such requests from other investigators should be considered in some registries that may generate broad external interest if the registry stakeholders and participants are agreeable to such use.

Consider the Scope and Rigor Needed

Scope of Data

The scope of a registry may be viewed in terms of size, setting, duration, geography, and financing. The purpose and objectives of the registry should frame the scope, but other factors (aside from feasibility) may ultimately shape it. For example, the scope may be affected by:

- Regulatory requirements, such as those imposed by the U.S. Food and Drug Administration (FDA) as a condition of product marketing.

- Reimbursement decisions, such as national coverage decisions by the Centers for Medicare & Medicaid Services or "Prior Authorization" requirements used by health insurers in some situations.
- National research interests, such as those driven by the National Institutes of Health (NIH).
- Public health policy, such as policy of the Centers for Disease Control and Prevention (CDC) and immunization policy.

The scope is also affected by the degree of uncertainty that is acceptable to the primary stakeholders, with that uncertainty being principally driven by the quantity, quality, and detail of the data collection balanced against its considered importance and value. Therefore, it is critical to understand the potential questions that may or may not be answerable because of the quantity and quality of the data. It should also be noted that the broader the audience of stakeholders, the broader the list of questions that may need to be included. This increased breadth can result in an increase in the number of patients that need to be enrolled and/or data points that need to be collected in order to meet the objective of the registry with an acceptable level of precision.

Some of the specific variables that can characterize the scope of a registry include:

- Size: This may refer to the number and complexity of data points or to the enrollment of investigators and patients. A registry with a large number of complex data points may allow for detailed and thoughtful analyses but may be so burdensome as to discourage investigator and patient enrollments. In turn, a small registry with few patients and data points may be easier to execute, but the data could lack depth and be less meaningful.[91] Size also determines the precision with which measures of risk or risk difference can be calculated.
- Setting: This refers to the specific setting through which the registry will recruit investigators and patients as well as collect data (e.g., hospital, doctor's office, pharmacy, home).
- Duration: The planning of a registry must reflect the length of time that the registry is expected to collect the data in order to achieve its purpose and provide analysis of the data collected. An example of a relevant factor is whether a product is nearing the end of the life of its patent.
- Geography: The setup, management, and analysis of a locally run registry represent a very different scope than the setup, management, and analysis of a global registry. A global registry poses challenges (e.g., language, cultural, time zone, regulatory) that must be taken into consideration in the planning process.
- Cost: The scope of a registry will determine the cost of creating, managing, and analyzing the registry. Budgetary constraints must be carefully considered before moving from conception to reality. Additionally, the value of the information weighs in on the financial decisions. The cost of the registry should be less than (or at a minimum, equal to) the projected value gained through the information generated. Certain choices in planning, such as building on existing infrastructure and/or linking to data sources relevant to the purposes of the registry, may increase the net return.
- Richness of clinical data needed: In some situations, the outcome may be relatively simple to characterize (e.g., death). In other cases, the focus of interest may be a complex set of symptoms and measurements (e.g., for Churg-Strauss Syndrome) or may require specialized diagnostic testing or tissue sampling (e.g., sentinel node in melanoma). Some outcomes may require assessment by an independent third party. (See "Scientific Rigor," below.)

When Data Need to be Available for Analysis

Meaningful data on disease progression or other long-term patient outcomes may not be available through a registry for many years, whereas safety data could be analyzed on a rolling basis. Therefore, the type of data on patient outcomes and when they will be available for analysis should be addressed from the perspective of the intended uses of the data in **both** the short term and long term. For industry-sponsored registries, if planning begins at an early stage, it may be possible to consider whether to align registry questions with those from the clinical trial (where appropriate) so that some data can carry over for more comprehensive longitudinal analyses.

Scientific Rigor

The content of the data to be collected should be driven by the scientific analyses that are planned for the registry, which, in turn, are determined by the specific objectives of the registry. A registry that is designed primarily for monitoring safety will inevitably contain different data elements from one that is designed primarily for monitoring effectiveness. Similarly, the extent to which data need to be validated will depend on the purpose of the registry and the complexity of the clinical information being sought. For some outcomes, clinical diagnosis may be sufficient; for others, supporting documents from hospitalizations, referrals or biopsies may be needed; and for others, formal adjudication by a committee may be required. Generally, registries that are undertaken for regulatory decisionmaking will require increased attention toward diagnostic confirmation (i.e., enhanced scientific rigor).

Define the Core Data Set, Patient Outcomes and Target Population

Core Data Set

Elements of data to be included must have potential value in the context of the current scientific and clinical climate and must be chosen by a team of experts, preferably with input from experts in biostatistics and epidemiology. Each data element should relate to the purpose and specific objectives of the registry. Ideally, each data element should address the central questions for which the registry was designed. It is useful to consider the generalizability of the information collected, as appropriate. For example, when seeking information on cost-effectiveness, it is preferable to collect data on resource utilization rather than actual costs of this utilization, since the broader descriptor can be more easily generalized to other settings and cost structures. While a certain number of speculative fields may be desired to generate and explore hypotheses, these must be balanced against the risk of overburdening sites with capturing superfluous data. A plan for quality assurance should be considered in tandem with developing the core data set.

The core data set variables ("need to know") define the information set needed to address the critical questions for which the registry was created. At a minimum, when calculating the resource needs and overall design of the registry, registry planners must account for these fields. If additional noncore variables ("nice to know") are included, such as more descriptive or exploratory variables, it is important that such data elements align with the goals of the registry and take into account the burden of data collection and entry at the site level. A parsimonious use of "nice to know" variables is important for several reasons.

First, when data elements change, there is a cascade effect to all dependent components of the registry process and outputs. For example, the addition of new data elements may require changes to the data

collection system, retraining of site personnel on data definitions and collection practices, adjustments to the registry protocol, and amendment submissions to institutional review boards. Such changes often require additional financial resources. Ideally, the registry would both limit the total number of data elements and include, at the outset, data elements that might change from "nice to know" to "need to know" during the course of the registry. In practice, this is a difficult balance to achieve, so most registries should plan adequate resources to be used for change management.

Second, a registry should avoid attempting to accomplish too many goals, or its burden will outweigh its usefulness to the clinical sites and researchers. Examples exist, however, of registries that serve multiple purposes successfully without overburdening clinicians. (See Case Example 2.)

Third, even "need-to-know" variables can sometimes be difficult to collect reliably (e.g., use of illegal substances) or without substantial burden (e.g., unusual laboratory tests). Even with a limited core data set, feasibility must still be considered. (See Chapter 5.)

Fourth, it is useful to consider what data are already available and/or collected and what data need to be additionally collected. When determining data elements that will be additionally collected, it is imperative to consider whether the information desired is consistent with general practice or whether it might be considered "interventional" rather than observational. The distinction between "interventional" and "observational" is challenging to many. According to Chapter 1.7.1 of Volume 9A of the Rules Governing Medicinal Products in the European Union,[92] registries may "collect a battery of information using standardized questionnaires in a prospective fashion: and that questionnaires, by themselves, are not considered interventional." These rules also state that

- "the assignment of a patient to a particular strategy is not decided in advance by a [trial] protocol but falls within the current practice…", and
- "no additional diagnostic or monitoring procedures shall be applied to patients."

This last bullet is sometimes challenging to interpret since registries sometimes perform diagnostic tests that are consistent with general practice but may be performed more frequently than would be used in general practice.

Finally, it is important to consider patient privacy, national and international rules concerning ethics, and regulatory requirements to assure that the registry data requirements do not jeopardize patient privacy nor do they put institutional/ethics reviews and approvals at risk.

Patient Outcomes

The outcomes of greatest importance should be identified early in the concept phase of the registry. Delineating these outcomes (e.g., primary or secondary endpoints) will force registry designers to establish priorities. Prioritization of interests in the planning phase will help focus the work of the registry and will guide study size requirements. (See Chapter 3.) Identifying the patient outcomes of the greatest importance will also help to guide the selection of the data set. Avoiding the temptation to collect "nice to know" data that are likely of marginal value is of paramount importance, yet some registries that accomplish their purposes do, in fact, need to collect large amounts of data. Possessing adequate data in order to properly address potential confounders during analyses is one reason that extensive data collection is sometimes required.[93]

Methods to ascertain the principal outcomes should be clearly established. The diagnostic requirements, level of data detail, and level of data validation and/or adjudication should also be addressed. As noted below in the context of identifying a target population, relying on established guidelines and standards to aid in defining outcomes of interest has many benefits and should be considered.

The issues of ascertainment noted here are important to consider because they will have a bearing on some attributes by which registries may be evaluated.[94] These attributes include sensitivity (the extent to which the methods identify all outcomes of interest) and external validity (generalizability to similar populations), among others.

The Target Population

The target population is the population to which the findings of the registry are meant to apply. It must be defined for two basic reasons. First, the target population serves as the foundation for planning the registry. Second, it also represents a major constituency that will be impacted by the results of the registry.

One of the goals for registry data may be to enable generalization of conclusions from clinical research on narrowly defined populations to broader ones, and therefore, the inclusion criteria for most (although not all) registries are relatively broad. As an example, screening criteria for a registry may allow inclusion of elderly patients, patients with multiple comorbidities, patients on multiple therapies, patients who switch treatments during the period of observation, or patients who are using products "off label." The definition of the target population will depend on many factors (e.g., scope and cost), but ultimately will be driven by the purpose of the registry.

As with defining patient outcomes, target population criteria and/or definitions should be consistent with established guidelines and standards within the therapeutic area. Achieving this goal enhances the potential utility of the registry by leveraging other data sources (historical or concurrent) with different information on the same target population, and enhancing statistical power if similar information is collected on the target population.

In establishing target population criteria, consideration should be given to the feasibility of access to that population. One should try to distinguish the ideal from the real. Some questions to consider in this regard are:

- How common is the exposure or disease of interest?
- Can eligible persons be readily identified?
- Are other sources competing for the same patients?
- Is care centralized or dispersed (e.g., in a referral or tertiary care facility)?
- How mobile is the target population?

Ultimately, methods to ascertain members of the target population should be carefully considered (e.g., use of screening logs that identify all potential patients and indicate whether they participate and, if not, why not), as should the use of sources outside the registry (e.g., patient groups). Greater accessibility to the target population will reap benefits in terms of enhanced representativeness and statistical power.

Lastly, thought should be given to comparison (control) groups either internal or external to the registry. Again, much of this consideration will be driven by the purpose and specific objectives of the registry. For example, a lack of need for controls exists in natural history registries, but controls are especially desirable for registries created to evaluate comparative effectiveness or safety.

Develop a Project Plan

Developing an overall project plan is critically important so that the registry team has a roadmap to guide their collective efforts. Depending on the complexity of the registry project, the project plan may include some or all of the following elements:

- Scope management plan to control the scope of the project. It should provide the approach to making changes to the scope through a clearly defined change control system;
- Detailed timeline and schedule management plan to ensure that the project and its deliverables are completed on time;
- Cost management plan for keeping project costs within the budget. Cost management plan may provide estimates on cost of labor, purchases and acquisitions, compliance with regulatory requirements, etc. This plan should be aligned with the change control system so that all changes to the scope will be reflected in the cost component of the registry project;
- Quality management plan to describe the procedures to be used to test project concepts, ideas, and decisions in the process of building a registry. Having a quality management plan in place can help in detecting design errors early, formulating necessary changes to the scope, and ensuring that the final product meets stakeholders' expectations;
- Staffing management plan to determine what skills will be needed and when to meet the project goals (see above, Building a Registry Team);
- Communication plan that includes who is responsible for communicating information and to whom. Considerations include different categories of information, frequency of communications, and methods of communication. It also should provide steps to escalate issues that cannot be resolved on a lower staff level;
- Procurement plan for external components or equipment and/or outsourced software development for the planned registry, if pertinent. Such a plan should describe how the procurement process will be managed within the organization. Decisions to procure products or services may have a direct impact on other components of the project plan, including the staffing plan and timeline;
- Risk management plan to identify and mitigate risks. Many project risks are predictable events and therefore they can, and should, be assessed in the very early stages of registry planning. It is important to prioritize project risks by their potential impact on the specific objectives and to develop an adequate risk response plan for the most significant risks. Some predictable risks include:
    - disagreement between stakeholders over the scope of specific tasks;
    - inaccurate cost estimates;
    - delays in the timeline.

Determine What Will Happen When the Registry Ends

Most registries have a finite lifespan. A registry that tests the safety of a product used during pregnancy will have a different lifespan from one that examines the effectiveness of new interventions in a chronic

disease. Sponsors and registry participants should have an understanding of the proposed lifespan of the registry at the time of its inception, or at least have developed some contingency plans, such as "if/then" alternatives.

The determination of who owns the data at the end of the natural lifespan of the registry and where the data are to be stored should also be defined at the time of registry inception. Possibilities include the principal investigator, the sponsor, or funding source, or a related professional society. Chapter 8 discusses issues of ownership.

Registries that generate continuing societal value, such as quality improvement programs and safety programs, might consider transitions that continue the registry functions after the original funding sources have expired.

For a more detailed discussion, see the "When Should a Patient Registry End?" sidebar below and Case Example 6.

When Should a Patient Registry End?

Once a registry is in place, how long should it continue? What are reasonable decision criteria for stopping data collection? This section considers the issues relating to stopping a patient registry study and suggests some guidelines. Although the specific answers to the above questions will vary from study to study, the types of considerations may be more general. The discussion here is focused on registries intended to assess specific safety or effectiveness outcomes rather than those intended to assess health care operations, such as continuous quality improvement.

Stopping an Experiment

The principles regarding rules for stopping a study mostly stem from the need to consider stopping an experiment. Because experiments differ from registries in crucial ways, it is important to distinguish between the issues involved in stopping an experimental study and in stopping a non-experimental study. In an experiment, the patient's treatment is determined by the study protocol, which typically involves random assignment to a treatment regimen. In a non-experimental study, patients are treated according to the treatment protocol devised by their own physician, typically uninfluenced by the study. In a randomized trial of a new therapeutic agent or a field trial for a vaccine, the size of the study population is ordinarily set in the study protocol, based on assumptions about the expected or hypothesized results and the study size needed to reach a reasonable scientific conclusion. Ordinarily this planned study size is based on power calculations, which require as input: the criteria for statistical significance, the effect size anticipated, the baseline occurrence rate of the study outcome, and the relative size of the study arms. Because of inherent problems in relying on statistical significance for inference, the study size may (preferably) be planned around estimation of effect and the desired level of precision. In a study intended to provide some reassurance about the safety of an agent, the study size may be planned to provide a specific probability that the upper confidence bound of a conventional confidence interval measuring an adverse effect would be less than some specified value, given a postulated value for the effect itself (such as no effect). In the latter situation, if no effect is anticipated, a power calculation is not only unreasonable, but is not even possible, whereas planning a study on the basis of precision of estimation is always possible and always reasonable.

Stopping an experiment earlier than planned is an important decision that is typically made by an advisory group, such as a Data Safety and Monitoring Committee, which is constituted to monitor study results and make decisions about early stopping. In a biomedical experiment, the investigator has a greater ethical obligation than in a non-experimental study to safeguard the well-being of study participants. This is due to the fact that the investigator is administering an intervention to study participants that is expected to affect the probability that study participants will experience one or more

specific health outcomes. A widely accepted (but, unfortunately, not universally accepted) ethical precept regarding human biomedical experimentation is equipoise. Equipoise requires that at the outset of the study, the investigator has a neutral outlook regarding which of the study groups would fare better. A strict interpretation of equipoise requires each of the study investigators to be in a state of equipoise. An alternative view, referred to as "clinical equipoise," is that equipoise can be achieved at the group level, with the enthusiasm of some investigators for the prospects of the study intervention, balanced by the skepticism of others. Whichever interpretation of equipoise is adopted, most investigators agree that if equipoise becomes untenable as study results accumulate, the study should be stopped to avoid depriving some study participants of a potential benefit, relative to what other participants receive.

For an advisory board to decide to stop a study early there must be solid evidence of a difference between the groups before the planned study endpoint is reached. Such stopping decisions are usually based on ethical concerns, as scientific considerations would seldom dictate an early stop to a study that had been planned to reach a specific size. Advisory boards must base stopping decisions on analyses of accumulating study data, which are usually formally presented at regular meetings of the review board. Statistical concerns have been raised about biases that can arise from repeated analyses of accumulating data. To offset these concerns, many experiments are planned with only a limited number of interim analyses, and the interpretation of study results takes into account the number of interim analyses.

Stopping a Fixed Length Non-Experimental Study

Like experiments, most non-experimental studies also have a fixed time for their conduct and a planned size that reflects goals analogous to those in experimental studies. Nevertheless, the ethical concerns that motivate stopping an experiment before its planned completion do not have a direct counterpart in non-experimental studies. Non-experimental studies do have ethical concerns, but they relate, for example, to data privacy, intrusive questioning, or excessive inducements for participation, rather than to concerns about intervention in the lives of the participants. Although it is theoretically reasonable that an investigator could choose to stop a non-experimental study for ethical reasons, those reasons would presumably relate to ethical problems that were discovered in the course of the study, but were presumably unrecognized at the outset, rather than to an early conclusion regarding the study goal. The investigator in a non-experimental study could learn, from an interim analysis, that the association between the exposure and the outcome under study was much stronger than anticipated. Unlike the experimental setting, however, the investigator in a non-experimental study is not administering the exposure to any of the study subjects, and thus has no responsibility to the study subjects regarding their exposure.

The discovery of an ethical problem during the conduct of a non-experimental study is therefore possible, but extremely rare. Because the findings from an interim analysis should not lead to discontinuation of a non-experimental study, there is consequently little motivation to conduct interim analyses for non-experimental studies that have been

planned with a fixed size and period of execution. If there is some considerable time value to the findings, such as to inform regulatory action, it might be worthwhile to conduct an interim analysis in a non-experimental study to get an early appraisal of study findings. Unless there is an appropriate outlet for releasing interim findings, however, it is possible that early findings will not circulate beyond the circle of investigators. In most circumstances, such analyses are hard to justify in light of the fact that they are based on less data than was judged appropriate when the study was planned, and thus the originally planned analysis based on all the collected data will still need to be conducted. Unless there is a clear public health case to publicize interim results, journal policies that require that published data have not been previously published may inhibit any release of preliminary findings to news media or to journals in the form of preliminary findings.

Stopping an Open-Ended Study

Although patient registries may be undertaken with a fixed length or size, or both, based on study goals relating to specific safety or efficacy hypotheses, many such studies are begun as open-ended enterprises, without a planned stopping point. For example, patient registries may be undertaken to monitor the safety of patients receiving a novel therapy, without specific hypotheses. The Antiepileptic Drug Pregnancy Registry, established in 1997, is an example of an open-ended registry that focuses on a set of specific endpoints (congenital malformations) among a subset of patients (pregnant women) taking a class of medications (antiepileptic drugs). It has no fixed stopping point.

Measuring the frequency of rare endpoints demands large study sizes. Therefore, a monitoring system that includes rare endpoints may have to run for a long while before the accumulated data will be informative for low frequency events. On the other hand, the lower the frequency of an adverse event, even one with serious consequences, the smaller the public health problem that a relative excess of such events would represent.

Traditional surveillance systems are intended to continue indefinitely because they are intended to monitor changes in event frequency over time. Thus, surveillance systems for epidemic infectious diseases provide early warning about outbreaks and help direct efforts to contain such outbreaks. In contrast, a patient registry is not a true surveillance system, since most are not intended to provide an early warning of a change in outcome frequency. Rather, most patient registries are intended to compile data on outcomes associated with novel treatments, to supplement the sparse data usually available at the time that these treatments are considered for approval by regulatory agencies. For example, a patient registry might be mandated by the regulatory agency as a condition of approval, to supplement safety information that was submitted during the application process. How long should such a registry continue?

Although it is not possible to supply a general answer to this question, there is little reason to support a registry continuing indefinitely, unless there is a suspicion that the treatments or treatment effects will change over time. Otherwise, the time should come when the number of patients studied suffices to answer the questions that motivated the registry. The Acyclovir Pregnancy Registry, which began in 1984, was stopped in 1999.

Its advisory committee concluded that "The [Acyclovir Pregnancy] Registry findings to date do not show an increase in the number of birth defects identified among the prospective reports [of exposures to acyclovir] when compared with those expected in the general population. In addition, there is no pattern of defects among prospective or retrospective acyclovir reports. These findings should provide some assurance in counseling women following prenatal exposure [to acyclovir]." The consensus was that additional information would not add materially to the information that had already been collected, and thus the registry was closed down.

To avoid uncertainty about the fate of an open-ended study, it would be sensible to formulate a specific goal that permits a satisfactory conclusion to data collection. Such a goal might be, for example, the observation of a minimum number of specific adverse events of some type. Even better would be to plan to continue data collection until the upper bound of a confidence interval for the rate or risk of the key outcome falls below some threshold, or the lower bound falls above a threshold. Analogous stopping guidelines could be formulated for registry studies that are designed with a built-in comparison group.

Stopping Decisions and Registry Goals

Ideally, stopping decisions ought to evaluate data from a registry against its stated goals. Thus, the registry protocol or charter should include one or more specific and measurable endpoints against which to judge whether the project should continue or stop. Without that guidance, any decision to discontinue a registry may appear arbitrary and will be more readily subject to political considerations. In cases where there are no measurable endpoints to use in making the decision, it is important that any final reports or publications linked to the registry include a clear discussion of the reasons for stopping it.

Registry goals will vary according to the motivation for undertaking the project and the source of funding. Product-specific registries may be created as post-approval regulatory commitments. For products about which there are limited pre-approval safety data, the wish for additional comfort about the product's safety profile can be translated into a measurable goal. Such a goal might be to exclude the occurrence of life threatening or fatal drug-related events at a certain frequency. For example, the goal could be to establish a specified level of confidence that unexplained hepatic necrosis in the three months following drug exposure occurs in less than one patient in 1,000. Alternatively, the goal might be to provide a more precise estimate of the frequency of a previously identified risk, such as anaphylaxis. Ideally, this goal should be formulated in specific numeric terms. With specific goals, the registry can have a planned target and will not be open ended.

If a registry study does not have a single or very limited set of primary objectives, a stopping point will be more challenging to plan and to justify. Even so, with measurable goals for some endpoints, it will be possible to determine whether the registry has achieved a core purpose and may lead to a reasonable stopping point. Conversely, a registry that fails to meet measurable goals and appears to be unable to meet them in a

reasonable time is also a candidate to be stopped. For example, if the registry faces unexpectedly low patient accrual, it should be stopped, as was done with the Observational Familial Adenomatous Polyposis Registry Study in Patients Receiving Celecoxib. This study enrolled only 72 patients in four years, out of a planned 200 during five years. Another reason to consider stopping is incomplete or poor quality information. Poor quality data is of particular concern when it regards sensitive or illegal behavior, such as self-reported information on sexual practices. Decisions about stopping a registry because of low enrollment or inadequate information are made simpler with clearly stated goals regarding both features of the study. The criteria for useful quantity and quality of information should be specified at the outset. How well the study meets the criteria can be assessed periodically during data collection.

A registry may outlive the question it was created to answer. For example, if use of the product is superseded by another treatment, the questions that drove the creation of the registry may no longer be relevant, in which case it may best be retired. For medical devices, for example, newer technology is continuously replacing the old, although safety issues for older technology may motivate continuing a registry of an outmoded technology. A related issue arises when the question of interest evolves as data collection proceeds. Stopping or continuing the registry depends on whether it can address the changing goal or goals. That, in turn, depends on whether the governance of the registry provides adequate flexibility to refocus the registry in a new direction.

The decision to stop a registry may also depend on mundane considerations such as cost or staffing. For long-running registries, eventually the value of new information may face diminishing returns. Some registries have central core staff, deeply committed to the registry, who serve as its historical memory. Departure of such individuals can cripple the registry's function and a decision to stop may be appropriate. Similarly, a cohort of engaged investigators may disperse over time or lose interest in the registry. Funding sources may dry up making it impossible for the registry to function at a level that justifies its continued existence.

A thorny question is how a registry can continue with altered ownership or governance. Suppose a registry is formed with multiple stakeholders and one or more withdraws for the reasons described above. For example, when the implantable cardioverter defibrillator (ICD) registry was formed, it came about in response to a Centers for Medicare and Medicaid Services (CMS) Coverage under Evidence Development decision. The Heart Rhythm Society and the American College of Cardiology developed the registry with funding from industry to help institutions meet the need for registry participation for payment purposes and layered quality improvement and research goals onto that mandate. The resulting registry was rapidly integrated into more than 2,000 institutions in the U.S. Recently CMS has determined that the current ICD registry is no longer needed for its purposes, so the registry must determine if it will continue on as a quality improvement program and whether to add other stakeholders and funding sources or participation drivers (such as manufacturers, insurers, or other government agencies such as the Food and Drug Administration).

What Happens When a Registry Stops?

Stopping a registry might mean ceasing all information collection and issuing a final report. An intermediate decision that falls short of a full stop might involve ceasing to accrue new patients while continuing to collect information on existing participants. This step may be useful if the registry goals are in the process of changing. If a registry is to be stopped, the archiving rules should be checked and followed, so that those who need to consult the data for questions not fully addressed in reports or publications can be answered later, provided that the charter of the registry allows it. Following German reunification in 1990, it was determined that the East German National Cancer Registry, which had received detailed reports on 2 million cancer cases from 1954- 1990, was in violation of West German privacy laws and the data were quarantined. In the more usual case, orderly archiving of the data in anticipation of later access should be part of the close-down procedure, in a manner consistent with the charter under which the data were collected.

A slightly different scenario is when the registry has a single sponsor whose purposes have been achieved or determined to be unachievable and the sponsor decides to end the registry. Is there an obligation to patients or participating providers to continue the registry because some value (e.g. quality improvement, data for other comparisons) can still be derived? It is difficult to argue that the sponsor has an ongoing financial responsibility once the registry has achieved or failed to achieve its primary purpose, especially if this has been spelled out in the protocol and informed consent. Yet, one can argue that to the extent that it is feasible and affordable to engage other stakeholders in discussions of potential transitioning of the registry to other owners, this approach should be encouraged. Nontrivial issues of data ownership, property, confidentiality, and patient privacy would need to be satisfactorily addressed to make such transitions possible and therefore, it is always best to consider this possibility early on in registry planning. Both the National Registry of Myocardial Infarction (NRMI), sponsored by Genentech, Inc. and the OPTIMIZE-HF registry, sponsored by GlaxoSmithKline, successfully completed transitions to other organizations (American College of Cardiology and American Heart Association, respectively) when those registries were concluded, providing their participating hospitals in each case with the ability to continue the quality improvement efforts begun under those registries.

There is no clear ethical obligation to participants to continue a registry that has outlived its scientific usefulness. In fact, the prospect of altering the purpose of a registry would be complicated, unless the original registry operators were interested in doing so. For instance, if a registry is to be transferred, then it should be a restricted transfer (presumably a gift) to ensure the permissions, terms, and conditions under which it was compiled continue to be satisfied. The participants should be notified and should determine if they will continue participation and allow their data to be used for this new purpose.

There are a few potential reasons to consider preserving registry data once the registry developers have determined that it should end. One reason is that the data may be

capable of producing a recognized public health benefit that will continue if the registry does. Another situation may be that the registry has historical importance, such as a registry that tracks the outbreak of a novel infectious disease that may provide insight into the transmission of the disease, if not now, then sometime in the future. Longitudinal collections of data may also be useful for hypothesis generation.

In creating a registry, the investigators should plan what will happen to data when the registry ends. If a public health benefit might be realized from registry data, then archiving of registry data is a potential answer. Decisions must be made by the registry owners in careful consideration of other stakeholders and potential costs.

Conclusion

Experimental studies, such as clinical trials or field trials, come with a high ethical burden of responsibility, which includes periodically re-evaluating the ethical basis for continuing the trial in the light of interim results. Consequently, trials require interim analyses and data safety monitoring boards, which decide whether the study should be stopped for ethical reasons. In non-experimental studies, there is much less motivation to conduct interim analyses, because there is no ethical motivation to do so. There is also no reason to appoint a data safety monitoring board, although any study could appoint an external advisory board. If non-experimental studies are planned to be of fixed length or fixed study size, they can be conducted as planned without interim analyses, unless the time value of an early, interim analysis is important enough to compensate for the added cost of conducting it and the tentativeness of the findings, which are based on only a subset of the planned study data.

If a patient registry is undertaken as an open-ended project, without a fixed endpoint, it need not continue forever. Unlike true surveillance efforts, patient registries of novel therapies are not intended to monitor for changes in occurrence rates over time. Rather, they are conducted to assemble enough data to evaluate associations that could not be evaluated with the limited data available at the time of new drug approval. Therefore, reasonable goals should be set for the amount of information to be collected in such registries, based on specific endpoints of interest. These goals can, and should, be cast in specific terms regarding data quality, study enrollment, and precision of the estimates of specific measures that the registry is intended to describe.

Case Example 1: Using registries to understand rare diseases

Description:	The International Collaborative Gaucher Group (ICGG) Gaucher Registry aims to enhance understanding of the variability, progression, and natural history of Gaucher disease, with the ultimate goals of better guiding and assessing therapeutic intervention and providing recommendations on patient care to the medical community.
Sponsor:	Genzyme Corporation
Year Started:	1991
Year Ended:	Ongoing
No. of Sites	772
No. of Patients:	Over 5,500, with open-ended followup

Challenge

Rare diseases pose special research challenges. The small number of affected patients often results in limited clinical experience within individual centers. Therefore, the clinical description of rare diseases may be incomplete or skewed. The medical literature often consists of individual case reports or small case series, limiting understanding of the natural history of the disease. Furthermore, randomized controlled trials with adequate sample size and length of followup to assess treatment outcomes may be extremely difficult or not feasible. The challenge is even greater for rare diseases that are chronic in nature, where long-term followup is especially important. As a result, rare diseases are often incompletely characterized and lack published data on long-term treatment outcomes.

Gaucher disease, a rare enzyme deficiency affecting fewer than 10,000 known patients worldwide, illustrates many of the challenges facing researchers of rare diseases. Physicians who encounter patients with Gaucher disease typically have one or two patients in their practice; only a few physicians around the world have more than 10 to 20 patients in their care. Understanding Gaucher disease is further complicated by the fact that it is a highly heterogeneous and rare disorder, and a patient cohort from a single center may represent a subset of the entire spectrum of disease phenotypes.

The rarity and chronic nature of Gaucher disease also pose challenges in conducting clinical research. The clinical trial that led to U. S. Food and Drug Administration approval of enzyme replacement therapy (ERT) for Gaucher disease (Ceredase®, alglucerase injection) in 1991 was a single-arm, open-label study involving only 12 patients followed for 9-12 months. In 1994, a recombinant form of enzyme replacement therapy was approved (Cerezyme®, imiglucerase for injection), based on a randomized two-arm clinical trial comparing Ceredase and Cerezyme in 30 patients (15 in each arm) followed for 9 months.

Proposed Solution

With planning initiated in 1991, the registry is an international, longitudinal disease registry, open voluntarily to all physicians caring for patients with all subtypes of Gaucher disease, regardless of treatment status or treatment type. Data on patient demographics; clinical characteristics; treatment regimen; and laboratory, radiologic, and quality-of-life outcomes are entered and analyzed to address the research challenges of this rare disease. Responsibility for the use, integrity, and objectivity of the data and analyses is invested in the ICGG board, which is comprised of physician-investigators who are not employees of the sponsor.

Results

With an aggregated, international database, analysis of data from the registry has provided a much more complete clinical description of Gaucher disease and its natural history, with longitudinal data on more than 5,500 patients from over 700 centers in more than 60 countries. The registry has an open-ended followup period, with the length of followup currently ranging from zero to 18 years. The registry has collected over 25,000 patient-years of followup over the past 18 years.

With these extensive followup data, analysis of the registry has increased knowledge of longer term treatment outcomes for enzyme replacement therapy. In 2002, the ICGG published the clinical outcomes of 1,028 patients treated with ERT with up to 5 years of followup. A clinical trial of this size and duration would not be feasible for such a rare disease. As the registry database continues to grow in size and duration, further analyses of clinically significant long-term treatment outcomes are being conducted.

A rare disease registry can also help foster the formation of an international community of expert physicians who can collaboratively develop recommendations on the clinical management of patients. The collective clinical experience of the ICGG led to the development of recommendations for evaluation and monitoring of patients with Gaucher disease. The analysis of registry data on treatment outcomes has facilitated the establishment of therapeutic goals for patients with type 1 Gaucher disease. Together, these publications have formed the foundation for a consensus- and evidence-based disease management approach, something usually only possible for much more common diseases.

Key Point

For rare or ultra-rare diseases such as Gaucher disease, an international, longitudinal disease registry may be the best or only feasible way to comprehensively increase knowledge about the clinical characteristics and natural history of the disease and assess the long-term outcomes of treatment.

For More Information

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Case Example 2: Creating a registry to fulfill multiple purposes and using a publications committee to review data requests

Description:	The National Registry of Myocardial Infarction (NRMI) collected, analyzed, and disseminated data on patients experiencing acute myocardial infarction. Its goal was improvement of patient care at individual hospitals through the hospital team's evaluation of data and assessment of care delivery systems.
Sponsor:	Genentech, Inc.
Year Started:	1990
Year Ended:	2006
No. of Sites	451 hospitals (NRMI 5). Over 2,150 hospitals participated over 16 years.
No. of Patients:	2,515,106

Challenge

Over the past 20 years, there have been significant changes in the treatment of acute myocardial infarction (AMI) patients. Evidence from large clinical trials has led to the introduction of new guidelines and therapies for treating AMI patients, including fibrinolytic therapy and percutaneous coronary intervention. While these treatments can improve both morbidity and mortality for AMI patients, they are time sensitive and must be administered very soon after hospital arrival in order to be most effective.

After the release of its first fibrinolytic therapy product in 1987, the sponsor's field representatives learned from their discussions with emergency department physicians, cardiologists, and hospital staff that most clinicians believed they were treating patients quickly, although there was no documentation or benchmarking to confirm this assumption or to identify and correct delays. At that time, many emergency departments did not have readily available diagnostic tools (such as angiography labs) and hospitals with AMI-specific decision pathways and treatment protocols were the exception rather than the rule.

In addition, since fibrinolytic therapy was being widely used for the first time, the sponsor wanted to gather safety information related to its use in real world situations and in a broader range of patients than those treated in the controlled environment of a clinical trial.

Proposed Solution

The sponsor decided to create the registry to fulfill the multiple purposes of identifying treatment patterns, promoting time-to-treatment and other quality improvements, and gathering real-world safety data. The scope of the data collection necessary to meet these needs could have made such a registry impracticable, so the project team faced the sizable challenge of balancing the data needs with the feasibility of the registry.

The sponsor formed a Scientific Advisory Board with members representing the various clinical stakeholders (emergency department, cardiology, nursing, research, etc.). The Scientific Advisory Board developed the data set for the registry, keeping a few guiding principles in mind. These principles emphasized maintaining balance between the clinical research and the feasibility of the registry. The first principle was to determine whether the proposed data element was necessary by asking several key questions: How will the data element be used in generating hospital feedback reports or research analyses? Is the data element already collected? If not, should it be collected? If it should be collected,

is it feasible to collect those data? The second principle focused on using existing data standards whenever possible. If a data standard did not exist, the team tried to collect the data in the simplest possible way. The third principle emphasized data consistency and making the registry user-friendly by continually refining data element definitions until they were as clear as possible.

In 1990, the sponsor launched the registry. During the 16 years that the registry was conducted, it demonstrated that the advisory board's efforts to create a feasible multipurpose registry were successful. The registry collected data on the clinical presentation, treatment, and outcomes of over 2.5 million patients with AMI from more than 2,150 participating sites.

The success of the registry presented a new challenge for the registry team. The sponsor received a large volume of requests to analyze the registry data, often for research topics that fell outside of the standardized reports developed for the registry. As a guiding principle, the registry team was committed to making the data available for research projects, but it had limited resources. To support these requests, the team developed a process that would allow outside researchers to access the registry data without overburdening the registry team.

The registry team created a publication process to determine when another group could use the data for research. The team set high-level criteria for all data requests: the analysis had to be feasible given the data in the registry, and the request could not represent a duplication of another research effort.

The registry team involved its Scientific Advisory Board, made up of cardiologists, emergency department physicians, nurses, research scientists, pharmacists, and reviewers with specialties in biostatistics and statistical programming, in creating a publication Review Committee. The Review Committee evaluated all research proposals to determine originality, interest to peers, feasibility, appropriateness, and priority. The Review Committee limited its review of research proposals to a set number of reviews per year, and scheduled the reviews and deadlines around the abstract deadlines for the major cardiology conferences. Research analyses had to be intended to result in peer-reviewed presentations and publications. Researchers were asked to submit proposals that included well-defined questions and an analysis plan. If the proposal was accepted, the researchers discussed any further details with the biostatisticians and statistical programmers who performed the analyses (and who were employed at an independent clinical research organization). The results were sent directly to the researchers.

The Scientific Advisory Board and Review Committee remained involved in the process after a data request had been granted. All authors submitted their abstracts to the Review Committee before sending them to conferences. The Review Committee offered constructive criticism to help the authors improve their abstracts. The Review Committee also reviewed manuscripts before journal submission to help identify any issues or concerns that the authors should address.

Results

This publication process enabled the wealth of data collected in this registry to be used in over 150 scientific abstracts and 100 peer-reviewed articles, addressing each of the purposes of the registry as well as other research topics. By involving the Scientific Advisory Board and providing independent biostatistical support, the registry team developed an infrastructure that enhanced the credibility of the research uses of this observational database.

Key Point

Registries can be developed to fulfill more than one purpose, but this added complexity requires careful

planning to ensure that the final registry data collection burden and procedures are feasible. Making sure that the advisory board includes representatives with clinical and operational perspectives can help the board to maintain its focus on feasibility. As a registry database gains large amounts of data, the registry team will likely receive research proposals from groups interested in using the data. The registry team may want to set up a publication process during the registry design phase.

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Case Example 3: Using a registry to track emerging infectious diseases

Description:	The Avian/Pandemic Flu Registry is a multi-country observational study of the diagnosis, treatment, and outcomes of human cases of highly pathogenic avian influenza (HPAI) H5N1 virus. The registry gathers data through collaborations with national governments and health care professionals in affected countries; it also includes information abstracted from detailed, published case studies.
Sponsor:	Hoffman-La Roche
Year Started:	2007
Year Ended:	Ongoing
No. of Sites	Data are collected from 12 countries.
No. of Patients:	541 cases of lab-confirmed, likely and possible HPAI

Challenge

H5N1 is a major concern for global public health. Among World Health Organization-confirmed cases worldwide, the virus has exhibited a mortality rate of almost 60 percent but limited capacity for person-to-person transmission. Should it change to allow more transmission between humans, the virus may have the potential to spark a global flu outbreak, resulting in high mortality rates similar to those seen in historical influenza pandemics. To establish a first-line scientific and medical response to this threat, health care professionals and governments need accurate and current information about the epidemiology and health consequences of the spread of the disease and the effectiveness of interventions. Additionally,

analysis of human cases of H5N1 has thus far primarily been country-specific. Since cases are still relatively rare, there is a need for a pooled analysis of structured data from many countries, which presents logistical, administrative, and political challenges to data collection and dissemination of information. There are also practical challenges to collaborating with governmental agencies in multiple countries.

Proposed Solution

A global registry was developed to provide up-to-date epidemiologic information rapidly to scientific and medical communities interested in recognizing and understanding the real-world clinical course of avian influenza and the effectiveness of current treatments. Cases are identified from publications in medical literature, through collaboration with national and local government agencies, and from varied information available on the internet. Once cases have been identified, efforts are made to seek the source data about each patient. Public health and infectious disease professionals work within their countries to locate and include diagnostic, clinical, treatment, and outcomes patient data that may be available from existing records and/or from medical personnel who may have treated cases of avian influenza. All patients believed to have avian influenza are eligible for inclusion in the registry, and cases in the registry are classified as likely, probable, or lab-supported cases. Data are collected and analyzed in an observational framework.

Case reporters may enter the data directly through the web-based electronic data capture tool or through an off-line data capture tool that uploads case report forms to the registry when an Internet connection is established. Data are collected and stored in the English language, but user interfaces in other languages have been developed to facilitate international data collection. Case-report forms are also filled out from reviewing literature and other public data sources.

Collaborators in each country have access to their own data as well as to aggregate data reports from all countries combined. Because the registry is web-based, participants have immediate access to current information on treatment practices, including timing of treatment initiation, dosing, duration of use, and survival. Collaborators are also able to request specific information from the registry to support national and regional health needs.

Results

The registry has assembled data from 12 countries. To date, fairly complete data has been assembled on more than 350 cases through on-site abstraction of medical and governmental records. In addition, nearly 200 more cases have partial information abstracted from on-line publications and detailed case studies published in the peer-reviewed literature are under investigation. Registry findings have been presented at international scientific conferences, and manuscripts are in progress.

Key Point

A patient registry can be an effective tool for quickly collecting and disseminating information on a global scale regarding the clinical course, outcomes and treatment effectiveness of emerging infectious diseases, especially when a web-based, multilingual interface is used.

For More Information

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Case Example 4: Using a collaborative approach to plan and implement a registry

Description:	The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is a national registry of patients receiving FDA-approved mechanical circulatory support device (MCSD) therapy to treat advanced heart failure. The registry is a joint effort of the National Heart, Lung and Blood Institute (NHLBI), the Centers for Medicare and Medicaid Services (CMS), the Food and Drug Administration (FDA), clinicians, scientists, and industry representatives, in conjunction with the University of Alabama at Birmingham (UAB) and United Network for Organ Sharing (UNOS).
Sponsor:	Primary funding is provided by the National Heart, Lung and Blood Institute.
Year Started:	2005
Year Ended:	Ongoing
No. of Sites	98
No. of Patients:	2,078

Challenge

In 2003, an NHLBI working group was convened to prioritize recommendations for optimizing outcomes in patients receiving left-ventricular assist device (LVAD) therapy, a specific type of MCSD therapy.

One of the recommendations of this working group was to establish a database to organize data on patient experiences with circulatory support. The working group suggested that cardiac transplant centers be enlisted to provide baseline and followup data for the registry. In addition, the working group expressed concerns about public access to data in privately-sponsored registries and recommended that the registry data be stored in a central, federally-funded and -managed database.

Proposed Solution

Based on the working group recommendations, the NHLBI decided to provide financial support for a national registry and issued a call for proposals. The winning proposal came from the University of Alabama at Birmingham (UAB). UAB proposed a multi-stakeholder registry, using feasibility data collected by the United Network for Organ Sharing (UNOS). The proposal included the collaboration of federal partners (NHLBI, FDA, and CMS), device companies, and academic and clinical stakeholders from the Cleveland Clinic, the University of Pittsburgh, and Brigham and Women's Hospital.

Results

The NHLBI awarded the contract to UAB in 2005, and INTERMACS was established. The goals of the registry are "(1) to facilitate the refinement of patient selection to maximize outcomes with current and new device options, (2) to identify predictors of good outcomes and risk factors for adverse events after device implantation, (3) to develop "best practice" guidelines to improve clinical management by reducing short- and long-term complications of MCSD therapy, (4) to utilize Registry information to guide improvements in technology, particularly as next generation devices evolve, and (5) to guide clinical testing and approval of new devices" (Kirklin 2008).

Currently, 98 sites participate in the registry, with another 35 sites in the process of activation. Data for 2,078 patients have been entered into the database. Participation is open to any medical center in the U.S. that has an active ventricular device therapy program. Participation is not mandatory, but it is currently the only registry that meets CMS and Joint Commission data reporting requirements that call for "submission to a national audited registry of health data on all VAD destination therapy patients from the date of implantation throughout the remainder of their lives."

Primary funding and scientific oversight for the registry is provided by the NHLBI. The regulatory partnership between the registry and the FDA facilitates automatic reporting of serious adverse device events to the FDA through the registry. The registry also aims to improve and expedite new device clinical trials by providing historical control data from the registry that can act as Objective Performance Criteria standards for the FDA. CMS requires participation in the registry for Medicare reimbursement of MCSD systems in specific circumstances. The registry has eight sub-committees that are made up of scientific and clinical experts, and, depending on the committee, industry representatives. Device companies and participating medical centers also receive customized reports based on the registry data.

Key Point

A collaboration between government, industry, and academia can be an effective approach to registry development, particularly in cases where there is a clear need for a registry, but no single, capable stakeholder exists, or where previous efforts by single stakeholders have not been successful.

For More Information

www.intermacs.org

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Case Example 5: Using a scientific advisory board to support investigator research projects

Description:	The National LymphoCare Study (NLCS) is a large, prospective, disease-based registry in the area of follicular lymphoma in the U.S. There are a number of open clinical questions related to follicular lymphoma treatment, including whether anthracyclines should be used early in the course of disease and whether there is a group of patients for whom observation (as opposed to active treatment) is the best choice given the indolent nature of the disease. The registry follows patients for up to 10 years, and specific outcomes of interest include overall response rate, progression-free survival, time to subsequent therapy, and overall survival for common front-line and subsequent therapeutic strategies.
Sponsor:	Genentech, Inc. and Biogen Idec, Inc.
Year Started:	2004
Year Ended:	Ongoing
No. of Sites	250 community and academic sites
No. of Patients:	Over 2,700 patients

Challenge

The National LymphoCare Study (NLCS) includes a large number of community-based sites in addition to many academic sites. Many of the principal investigators at the community-based sites are interested in using the registry data to answer clinical questions, but they do not have sufficient research experience to design a research question, conduct data analysis, and share the results with the scientific community. One aim of the registry sponsors and Scientific Advisory Board (SAB) is to facilitate research among the community investigators, both to increase interest in the registry and to increase the scope of research questions that are addressed using registry data.

Proposed Solution

The registry sponsors and the SAB developed a plan to allow investigators at enrolling sites to propose questions of interest, work with a SAB member, clinical scientists, epidemiologists, and biostatisticians to develop an analysis plan to answer the question, and present findings at scientific meetings. The plan was implemented in 2007, when the registry issued a call for research proposals to all participating investigators. The proposal outlined the types of data that were available at that point (e.g., descriptive data on demographics, initial treatments, etc.). Several community-based investigators sent in proposals, which were then reviewed by the SAB. The SAB selected the proposals that it felt were most appropriate for the available data and that answered the most valuable questions from a clinical standpoint.

The community investigator for each selected proposal was then paired up with a member of the SAB to further develop the research question. This process included conference calls and emails to refine the question and the high-level analytic plan. Once the high-level analytic plan was ready, the investigator

and the SAB member submitted the proposal and analytic plan to the registry sponsor. The sponsor provided support for analytic design and biostatistics. The investigator, in consultation with the SAB member, developed an abstract based on the results. Abstracts were reviewed by the full SAB before being submitted for presentation.

Results

In 2007, a community-based investigator project developed through this process was accepted for abstract presentation at the annual American Society of Hematology (ASH) meeting. In 2009, a community-based investigator and a fellow at an academic institution developed abstracts that have been submitted for presentation at the annual ASH meeting.

With outcomes data now available in the registry, registry sponsors plan to issue calls for proposals twice per year, with the goal of generating abstracts for the annual ASH meeting and the annual American Society of Clinical Oncology (ASCO) meeting. To date, the research program has been well-received by community-based investigators, who have the opportunity to author their own research projects with mentoring from an experienced advisor. The SAB has also been enthusiastic about working with community-based physicians on research methodology and adding to the scientific knowledge about this disease.

Key Point

Community-based investigators who participate in a registry may be interested in pursuing research opportunities, but may not have all of the necessary resources or expertise. By utilizing an engaged advisory board, it is possible to provide investigators with research opportunities, resulting in more publications and presentations based on registry data, and potentially more engaged investigators.

For More Information

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Case Example 6: Determining when to stop an open-ended registry

Description:	The Bupropion Pregnancy Registry was an observational, exposure-registration and followup study to monitor prenatal exposure to bupropion and detect any major

	teratogenic effect.
Sponsor:	GlaxoSmithKline
Year Started:	1997
Year Ended:	The registry closed to new enrollments on November 1, 2007 and continued to follow existing cases through March 31, 2008.
No. of Sites	N/A
No. of Patients:	1,597

Challenge

Bupropion, an antidepressant with the potential for prenatal exposure, was labeled with a pregnancy category C by the U.S. Food and Drug Administration (FDA) due to prior animal data. The manufacturer established a prospective pregnancy registry to monitor pregnancy exposures to bupropion for any potential, increased risk of congenital anomalies. Because the purpose of the registry was post-marketing safety surveillance, the duration of the registry was open-ended. The registry had collected data on over 1,500 exposed pregnant women over 10 years when a potential signal suggestive of a bupropion-related increase in cardiovascular birth defects emerged.

Proposed Solution

The Advisory Committee reviewed the registry data to assess the potential signal. However, due to the potential bias from the large percentage of cases lost to followup (35.8 percent) and retrospective reports, and the incomplete descriptions of the reported cardiovascular defects, it was not possible to determine the credibility of the potential signal using registry data alone. Further, the sample size was not adequate to reach definitive conclusions regarding absolute or relative risk of any specific birth defects in women using bupropion during pregnancy (as the registry was powered to examine the rate of birth defects overall) and was unlikely to achieve its goal as structured.

The Advisory Committee recommended a study to expedite the accumulation of pregnancy outcome data among women exposed to bupropion during pregnancy. In response, a large, claims-based, retrospective cohort study was conducted. This study enrolled 1,213 first trimester exposed women and did not confirm a consistent pattern of defects (Cole *et al*, 2007). The prevalence of cardiovascular defects associated with first trimester exposure to bupropion was 10.7 per 1,000 infants.

Results

The Advisory Committee reviewed the evidence and concluded that the signal did not represent an increased risk. The Committee recommended discontinuation of the registry based on findings from the retrospective cohort, ten years of surveillance through the registry, and the position that sufficient information had accumulated to meet the scientific objective of the registry. The high lost to followup rate was also taken into consideration. The registry closed to new enrollments on November 1, 2007 and continued to follow existing cases through March 31, 2008.

Key Point

In a registry without a specified end date or target size, it is important to periodically review the registry data to determine if the registry has met its scientific objectives and to ensure that the registry purpose is still relevant.

For More Information

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Chapter 3: Registry Design

This chapter is intended as a high-level practical guide to the application of epidemiologic methods that are particularly useful in the design of registries that evaluate patient outcomes; it is not intended to replace a basic textbook on epidemiologic design. Table 1 below summarizes the key considerations for study design that are discussed in this chapter. Throughout the design process, registry planners may want to discuss options and decisions with the registry stakeholders and relevant experts to ensure that sound decisions are made. The choice of groups to be consulted during the design phase generally depends on the nature of the registry, the registry funding source and funding mechanism, and the intended audience for registry reporting. Note, a more detailed discussion of registry design, specific to product safety, is provided in Chapter 4.

Table 1: Considerations for Study Design

Construct	Relevant questions
Research question	What are the clinical and/or public health questions of interest?
Resources	What resources, in terms of funding, sites, physicians, and patients, are available for the study?
Exposures and outcomes	How do the clinical questions of interest translate into measurable exposures and outcomes?
Data sources	Where can the necessary data be found?
Study design	What types of design can be used to answer the questions or fulfill the purpose?
Study population	What types of patients are needed for study? Is a comparison group needed? How should patients be selected for study?
Sampling	How should the study population be sampled, taking into account the target populations and study design?
Study size and duration	For how long should data be collected, and for how many patients?
Internal and external validity	What are the potential biases? What are the concerns about generalizability of the results (external validity)?

Research Questions That Are Appropriate for Registries

The questions typically addressed in registries range from purely descriptive questions aimed at understanding the characteristics of people who develop a disease and how the disease generally progresses, to highly focused questions that are intended to support decisionmaking. Registries focused on determining clinical or cost effectiveness or assessing safety or harm are generally hypothesis driven and concentrate on evaluating the effects of specific treatments on patient outcomes. Research questions should address the registry purpose, as broadly described in Table 2 below:

Table 2. Overview of Registry Purposes

• Assessing natural history, including estimating the magnitude of a problem; determining the underlying incidence or prevalence rate; examining trends of disease over time; conducting surveillance; assessing service delivery and identifying groups at high risk; documenting the types of patients served by a health provider; and describing and estimating survival.
• Determining clinical effectiveness, cost effectiveness, or comparative effectiveness of a test or

treatment, including evaluating the acceptability of drugs, devices, or procedures for reimbursement.

- Measuring or monitoring safety and harm of specific products and treatments, including comparative evaluation of safety and effectiveness.
- Measuring or improving quality of care, including conducting programs to measure and/or improve the practice of medicine and/or public health.

Observational studies derived from registries are often considered as alternatives to conducting randomized controlled trials (RCTs). While these can be complementary research methodologies, some research questions are better answered by one method than the other. RCTs are considered by many to provide the highest grade evidence for evaluating whether a drug has the ability to bring about an intended effect in optimal or "ideal world" situations, a concept also known as "efficacy."[95] In some situations, registries may be preferable designs for studies of effectiveness—that is, whether a drug, device, procedure, or program in fact achieves its desired effect in the real world. (See Case Example 7.) This is particularly true when the factors surrounding the decision to treat are an important aspect of understanding treatment effectiveness.

In many situations, nonrandomized comparisons either are sufficient to address the research question or, in some cases, may be necessary because of the following issues with randomized treatment:

- *Equipoise:* Can providers ethically introduce randomization between treatments when the treatments are not clinically equivalent?
- *Ethics:* If reasonable suspicion about the safety of a product has become known, would it be ethical to conduct a trial that deliberately exposes patients to potential harm? For example, can pregnant women be ethically exposed to drugs that may be teratogenic? (See Case Example 8.)
- *Practicality:* Will patients enroll in a study where they might not receive the treatment, or might not receive what is likely to be the best treatment? How can compliance and adherence to a treatment be studied, if not by observing what people do in real-world situations?

Registries are particularly suitable for situations where experimental research is not feasible or practical, such as:

- Natural history studies where the goal is to observe clinical practice and patient experience but not to introduce any intervention.
- Measures of clinical effectiveness, especially as related to compliance, where the purpose is to learn about what patients and practitioners actually do and how that affects outcomes, if at all, rather than to observe the effects of products used according to a study protocol. This is especially important for treatments that have poor compliance.
- Studies of effectiveness and safety for which physician training and technique (e.g., a procedure such as placement of carotid stent) is part of the treatment under study
- Studies of heterogeneous patient populations, since unlike randomized trials, registries generally have much broader inclusion criteria and fewer exclusion criteria. These characteristics lead to studies with greater generalizability (external validity).
- Followup for delayed or long-term benefits or harm, since registries can extend over much longer periods than most clinical trials (because of their generally lower costs to run and lesser burden on participants).
- Surveillance for rare events or of rare diseases.

- Studies for treatments in which randomization is unethical, such as intentional exposure to potential harm (as in safety studies of marketed products that are suspected of being harmful).
- Studies for treatments in which randomization is not necessary, such as when certain therapies are only available in certain places owing to high cost or other restrictions (e.g., proton beam therapy).
- Studies for which blinding is challenging or unethical (e.g., studies of surgical interventions, acupuncture).
- Studies of rapidly changing technology.
- Studies of conditions with complex treatment patterns and treatment combinations.
- Studies of health care access and barriers to care.
- Evaluation of actual standard medical practice. (See Case Example 9.)

Registry studies may also include embedded substudies as part of their overall design. These substudies can themselves have various designs (e.g., highly detailed prospective data collection on a subset of registry participants, case-control study focused on either incident or prevalent cases identified within the registry). (See Case Example 10.) The registry can also be used as a sampling frame for randomized controlled trials.

Translating Clinical Questions into Measurable Exposures and Outcomes

The specific clinical questions of interest in a registry will guide the definitions of study subjects, exposure, and outcome measures, as well as the study design, data collection, and analysis. In the context of registries, the term "exposure" is used broadly to include treatments and procedures, health care services, diseases, and conditions.

The clinical questions of interest can be defined by reviewing published clinical information, soliciting experts' opinions, and evaluating the expressed needs of the patients, health care providers, and payers. Examples of research questions, key outcome and exposure variables, and sources of data are shown in Table 3. As these examples show, the outcomes (generally beneficial or deleterious outcomes) are the main endpoints of interest posed in the research question. These typically represent measures of health or onset of illness or adverse events, but also commonly include quality of life measures, and measures of health care utilization and costs.

Table 3: Examples of Research Questions and Key Exposures and Outcomes

Research question	Key Exposure (source of data)	Key Outcome (source of data)
What is the expected time to rejection for first kidney transplants among adults, and how does that differ according to immunosuppressive regimen?	All immunosuppressants, including dosage and duration (clinician)	Organ rejection (clinician)
Are patients using a particular treatment better able to perform activities of daily living than others?	Treatments for the disease of interest (clinician)	Ability to independently perform key activities related to daily living (patient)
Do patients undergoing gastric bypass surgery for weight loss utilize fewer health care resources in the year following surgery?	Surgery (clinician)	Number of inpatient and outpatient visits, medications dispensed, associated costs (administrative databases,

		clinician)
Are patients using a particular drug more likely to have serious adverse pregnancy outcomes?	Drug use by mother during pregnancy (clinician or patient)	Pregnancy outcome (clinician or patient)

Relevant exposures also derive from the main research question and relate to why a patient might experience benefit or harm. Evaluation of an exposure often includes the exposure of interest as well as information that affects or augments the main exposure, such as dose, duration of exposure, route of exposure, or adherence. Other exposures of interest include independent risk factors for the outcomes of interest (e.g., comorbidities, age), as well as variables, known as potential confounding variables, that are related to both the exposure and the outcome and are necessary for clarifying analyses. Confounding can result in the statistical detection of a significant association between the study variables, where no real association between them exists. For example, in a study of asthma medications, prior history of treatment resistance should be collected or else results may be biased. The bias could occur because treatment resistance may relate both to the likelihood of receiving the new drug (meaning that doctors will be more likely to try a new drug in patients who have failed other therapies), and the likelihood of having a poorer outcome (e.g., hospitalization). Refer to Chapter 5 for a discussion of selecting data elements.

Finding the Necessary Data

The identification of key outcome and exposure variables and patients will drive the strategy for data collection, including the choice of data sources. A key challenge to registries is that it is generally not possible to collect all desired data. As discussed in Chapter 5, data collection should be both parsimonious and broadly applicable. For example, while experimental imaging studies may provide interesting data, if the imaging technology is not widely available, the data will not be available for enough patients in order to be useful for analysis. Moreover, the registry findings will not be generalizable if only sophisticated centers that have such technology participate. Instead, registries focus on collecting relevant data with relatively modest burden on patients and physicians. Registry data can be obtained from patients, clinicians, medical records, and linkage with other sources (in particular, extant databases) can occur, depending on the available budget. (See Chapter 10.)

Examples of patient data include quality of life; utilities (i.e., patient preferences); use of over-the-counter (OTC), complementary, and alternative medication; behavioral data (e.g., smoking and alcohol use); family history; and biological specimens. These data have the characteristics of relying on the subjective interpretation and reporting of the patient (e.g., quality of life, utilities); being difficult to otherwise track (e.g., use of complementary and alternative medication, smoking and alcohol use); or being unique to the patient (e.g., biological specimens). Resource utilization is another important construct that reflects both on cost of care (burden of illness) and also on quality of life. The primary advantage of this form of data collection is that it provides direct information from the entity that is ultimately of the most interest– the patient. The primary disadvantages are that the patient is not necessarily a trained observer and that various forms of bias, such as recall bias, may influence subjective information. For example, people may selectively recall certain exposures because they believe they have a disease that was caused by that exposure, or their recall may be influenced by recent news stories claiming cause-and-effect relations.

Examples of clinician data include clinical impressions, clinical diagnoses, clinical signs, differential diagnoses, laboratory results, and staging. The primary advantage of clinician data is that clinicians are trained observers. Even so, the primary disadvantages are that clinicians are not necessarily accurate reporters of patient perceptions, and their responses may also be subject to recall bias. Moreover, the time that busy clinicians can devote to registry data collection is often limited.

Medical records also are a repository of clinician-derived data. Certain data, such as data on OTC medications, smoking and alcohol use, complementary and alternative medicines, and counseling activities by the clinician on lifestyle modifications, are often not consistently captured in medical records of any type. Medical records are often relied upon as a source of detailed clinical information that may be required to adjudicate medical diagnoses corresponding to study endpoints in a standard manner across a study, especially when external reviewers are involved.

Electronic medical records, increasingly available, improve access to the data within medical records. The advent and growth of electronic health records has facilitated the development of a number of registries within large health plans. Kaiser Permanente has created several registries of patients receiving total joint replacement, bariatric surgery, and non-surgical conditions (e.g., diabetes), all of which rely heavily on existing electronic health record data. As discussed further in Chapter 10, the availability of medical records data in electronic format does not, by itself, guarantee consistency of terminology and coding. Examples of other data sources include health insurance claims, pharmacy data, laboratory data, other registries, and national data sets, such as Medicare claims data and the National Death Index. These sources can be used to supplement registries with data that may otherwise be difficult to obtain, subject to recall bias, not collected because of loss to followup, or likely inaccurate by self-report (e.g., in those patients with diseases affecting recall, cognition, or mental status). See Table 8 in Chapter 6 for more information on data sources.

Resources and Efficiency

Though ideally a proposed study is designed to optimally answer a research question of interest, and based on the requirements of the design, sufficient funding is obtained, frequently finite resources are available at the outset of a project that dictate the approaches that may be pursued. Often, through efficiencies in the selection of a study design and patient population (observational vs. RCT, case-control vs. prospective cohort), through data sources employed to collect required information (medical records based studies vs. information collected directly from physicians or patients), restriction of the number of study sites, or other approaches, studies may be planned that provide adequate evidence for addressing a research question with limited resources.

The section below on Study Designs for Registries discusses how certain designs may be more efficient for addressing some research questions.

Study Designs for Registries

Although studies derived from registries are, by definition, observational studies, the framework for how the data will be analyzed drives the data collection and choices of patients for inclusion in the study.

The conventional study models of cohort, case-control, and case-cohort are commonly applied to registry data and are described briefly here. Other models that are also useful in some situations, but are not covered here, include: case-crossover studies which are efficient designs for studying the effects of

intermittent exposures (e.g., use of erectile dysfunction drugs) on conditions with sudden onset; and quasi-experimental studies in which providers are randomized as to which intervention or quality improvement tools they use, but patients are observed without further intervention. Also, there has been recent interest in applying the concept of adaptive clinical trial design to registries. An adaptive design has been defined as a design that allows adaptations or modifications to some aspects of a clinical trial after its initiation without undermining the validity and integrity of the trial.[96] While many long-term registries are modified after initiation, the more formal aspects of adaptive trial design have yet to be applied to registries and observational studies.

Determining what framework will be used to analyze the data is important in designing the registry and the registry data collection procedures. Readers are encouraged to consult textbooks of epidemiology and pharmacoepidemiology for more information. (Many of the references in Chapter 13 relate to study design and analysis.)

Cohort

Cohort studies follow, over time, a group of people who possess a characteristic to see if they develop a particular endpoint or outcome. Cohort studies are used for descriptive studies as well as for studies seeking to evaluate comparative effectiveness and/or safety or quality of care. Cohort studies may include only people with exposures (such as to a particular drug or class of drugs) or disease of interest. Cohort studies may also include one or more comparison groups, in which data are collected using the same methods during the same period. A single cohort study may, in fact, include multiple cohorts, each defined by a common disease or exposure. Cohorts may be small, such as those focused on rare diseases, but often they target large groups of people (e.g., safety studies), such as all users of a particular drug or device. Some limitations of registry-based cohort studies may include limited availability of treatment data and underreporting of outcomes if a patient leaves the registry or is not adequately followed up.[97] These pitfalls should be considered and addressed when planning a study.

Case-Control

In a case-control design, one gathers "cases" of patients who have a particular outcome or who have suffered an adverse event and "controls" that have not, but are representative of the source population from which the cases arise.[98] If properly designed and conducted, it should usually yield results similar to those expected from a cohort study of the population from which the cases were derived. This design is often employed for understanding the etiology of rare diseases[99] because of its efficiency. As information is collected only from cases and a sample of non-cases, it is more efficient and cost-effective than a cohort study that would collect equivalent information on the entire underlying population of exposed and unexposed patients, whether or not they experienced the outcome of interest.

Depending on the outcome or event of interest, cases and controls may be identifiable within a single registry. For example, in the evaluation of re-stenosis after coronary angioplasty in patients with end-stage renal disease, investigators identified both cases and controls from an institutional percutaneous transluminal coronary angioplasty registry; in this example, controls were randomly selected from the registry and were matched by age and gender.[100] Alternatively, cases can be identified in the registry, and controls from outside the registry. Care must be taken, however, that the controls chosen from outside the registry meet the same requirement of arising from the same source population as the cases to which they will be compared. Matching in case-control designs, for example, ensuring that patient characteristics

such as age and gender are similar in the cases and their controls, may yield additional efficiency, in that a smaller number of subjects may be required to answer the study question with a given power. Matching variables must then be accounted for in the analysis, as a form of selection bias similar to confounding will have been introduced.

Properly executed, a case-control study can add efficiency to a registry if more extensive data are collected by the registry *only* for the smaller number of subjects selected for the case-control study. This design is sometimes referred to as a "nested" case-control study, since subjects are taken from a larger cohort. Nested case-control studies have been conducted in a wide range of patient registries, from studying the association between oral contraceptives and various types of cancer using the Surveillance Epidemiology and End Results (SEER) program[101,102,103] to evaluating the possible association of depression with Alzheimer's disease. As an example, in the latter case-control study design, probable cases were enrolled from an Alzheimer's disease registry and compared to randomly selected nondemented controls from the same base population.[104]

Case-Cohort

Case-cohort design is a variant of a case-control study. In traditional case-control studies, each person in the source population has a probability of being selected as a control that is, ideally, in proportion to his or her person-time contribution to the cohort; in a case-cohort study, however, each control has an equal probability of being sampled from the source population.[105] This allows for collection of pertinent exposure data for the subcohort and the cases only, instead of the whole cohort. For example, in a case-cohort study of histopathologic and microbiological indicators of chorioamnionitis, including the identification of specific microorganisms in the placenta, cases consisted of extreme preterm infants with cerebral palsy. Controls, which can be thought of as a randomly selected subcohort of subjects at risk of the event of interest, were selected from all infants enrolled in a long-term study of preterm infants.[106]

Choosing Patients for Study

The purpose of a registry is to provide descriptive information or to be used to generate hypotheses about a specific patient population to whom all study results are meant to apply. Studies can be conducted of people who share common characteristics, with or without including comparison groups. For example, studies can be conducted of:

- Those with a particular disease/outcome or condition. (These are person focused.)
    - Examples include studies of the occurrence of cancer or rare diseases, pregnancy outcomes, and recruitment pools for clinical trials.
- Those with a particular exposure. (These exposures may be to a product, procedure, or other health service.)
    - Examples include general surveillance, pregnancy registries for particular drug exposures, and studies of exposure to medications and devices, such as stents.[107] They also include studies of people who were treated under a quality improvement program, as well as studies of a particular exposure that requires controlled distribution, such as drugs with serious safety concerns (e.g., isotretinoin, clozapine, natalizumab [Tysabri®]), where the participants in the registry are identified because of their participation in a controlled distribution/risk management program.
- Those who were part of a program evaluation, disease management effort, or quality improvement project.

- An example is the evaluation of the effectiveness of evidence-based program guidelines on improving treatment.

Target Population

Selecting patients for registries can be thought of as a multistage process that begins with understanding the target population (the population to which the findings are meant to apply, such as all patients with a disease or a common exposure) and then selecting a sample of this population(s) for study. The accessible population is that portion of the target population to which the participating sites have access. The actual population is the subset of those who can actually be identified, invited, and agree to participate.[108] While it is desirable for the patients who participate in the study to be representative of the target population, it is rarely possible to study groups that are fully representative from a statistical sampling perspective, either for budgetary reasons or for reasons of practicality. An exception is registries composed of all users of a product (as in post-marketing surveillance studies or registry participation as a condition of receiving an intervention), an approach which is becoming more common either to manage expensive interventions and/or to track potential safety issues.

There are certain populations that pose greater difficulties in assembling an actual population that is truly representative of the target population. Children and other vulnerable populations present special challenges in recruitment, as they typically will have more restrictions imposed by IRBs and other oversight groups.

As with any research study, very clear definitions of the inclusion and exclusion criteria are necessary and should be clearly documented, including the rationale for these criteria. A common feature of registries is that they typically have few inclusion and exclusion criteria, thus enhancing their applicability to broader populations. Restriction, or limiting eligibility for entry, to individuals within a certain range of values for a confounding factor, such as age, may be considered to reduce the effect of a confounding factor when it cannot otherwise be controlled, but may, however, reduce the generalizability of results beyond those with similar covariate values to patients included in the study.

These criteria will largely be driven by the study objectives and any sampling strategy. For a more detailed description of target populations and their subpopulations, and how these choices affect generalizability and interpretation, see Chapter 13.

Once the patient population has been identified, attention shifts to selecting the groups from which patients will be selected (e.g., choosing the institutions and providers). For more information on recruiting patients and providers, see Chapter 9.

Comparison Groups

Once the target population has been selected and the mechanism for their identification (e.g., providers) is decided, the next decision involves determining whether to collect data on comparators (sometimes called parallel cohorts). Depending on the purpose of the registry, internal, external, or historical groups can be used to strengthen the understanding of whether the observed effects are real, and, in fact, different from what would have occurred under other circumstances. Comparison groups are most useful in registries where it is important to distinguish between alternative decisions or to assess differences, the magnitude of differences, or the strength of associations between groups. Registries without comparison groups can be used for descriptive purposes, such as characterizing the natural history of a disease or condition, or for

hypothesis generation. The addition of a control group may add significant complexity, time, and cost to a registry.

Although it may be appealing to use more than one comparison group in an effort to overcome the limitations that may result from using a single group, multiple comparison groups pose their own challenges to the interpretation of registry results. For example, the results of comparative safety and effectiveness evaluations may differ depending on the comparison group used. Generally, it is preferable to make judgments about the "best" comparison group for study during the design phase and then concentrate resources on these selected subjects. Alternatively, sensitivity analyses can be used to test inferences against alternative reference groups to determine the robustness of the findings. (See Chapter 13.)

The choice of comparison groups is more complex in registries than in clinical trials. Whereas clinical trials use randomization to try to achieve an equal (or nearly equal) distribution of known and unknown risk factors that can confound the drug-outcome association, registry studies need to use various design and analytic strategies to control for the confounders that they have measured. The concern for observational studies is that people who receive a new drug or device have different risk factors for adverse events than those who choose other treatments or receive no treatment at all. In other words, the treatment choices are often related to demographic and lifestyle characteristics and the presence of coexisting conditions that affect physician decisionmaking about whom to treat.[109]

Design strategies that are used frequently to assure comparability of groups relate to individual matching of exposed patients and comparators with regard to key demographic factors, such as age and gender. Matching is also achieved by inclusion criteria that could, for example, restrict the registry focus to patients who have had the disease for a similar duration or are receiving their first drug treatment for a new condition. These inclusion criteria make the patient groups more similar but add constraints to the external validity by defining the target population more narrowly. Other design techniques include matching study subjects on the basis of a large number of risk factors, such as by using statistical techniques (e.g., propensity scoring) to create strata of patients with similar risks. As an example, consider a recent study of a rare side effect in coronary artery surgery for patients with acute coronary syndrome. In this instance, the main exposure of interest was the use of antifibrinolytic agents during revascularization surgery, a practice that had become standard for such surgeries. This practice complicated the planned design because only the sickest patients, who were most likely to have adverse events, received alternative treatments. To address this, the investigators measured more than 200 covariates (by drug and by outcome) per patient and used this information in a propensity analysis. The results of this large-scale, observational study revealed that the traditionally accepted practice (aprotinin) was associated with serious end-organ damage and that the less expensive generic medications were safe alternatives.[110] Incorporation of propensity-scores in analysis is discussed further in Chapter 13.

Case-control studies present special challenges with regard to control selection. More information on considerations and strategies can be found in a set of papers by Wacholder.[111,112,113]

An internal comparison group refers to simultaneous data collection for patients who are similar to the focus of interest (i.e., those with a particular disease or exposure in common), but who do not have the condition or exposure of interest. For example, a registry might collect information on patients with arthritis who are using acetaminophen for pain control. An internal comparison group could be arthritis

patients who are using other medications for pain control. Data regarding similar patients, collected during the same calendar period and using the same data collection methods, are useful for subgroup comparisons, such as for studying the effects in certain age categories or among people with similar comorbidities. However, the information value and utility of these comparisons depend largely on having adequate sample sizes within subgroups, and such analyses may need to be specified a priori to ensure that recruitment supports them. Internal comparisons are particularly useful because data are collected during the same observation period as for all study subjects, which will account for time-related influences that may be external to the study. For example, if an important scientific article is published that affects general clinical practice, and the publication occurs during the period in which the study is being conducted, clinical practice may change. The effects may be comparable for groups observed during the same period through the same system, whereas information from historical controls, for example, would be expected to reflect different practices.

An external comparison group refers to patients who are similar to the focus of interest but who do not have the condition or exposure of interest and for whom relevant data that have been collected outside of the registry are available. For example, the SEER program maintains national data about cancer and has provided useful comparison information for many registries where cancer is an outcome of interest.[114] External comparison groups can provide informative benchmarks for understanding effects observed, as well as for assessing generalizability. Additionally, large clinical and administrative claims databases can contribute useful information on comparable subjects for a relatively low cost. A drawback of external comparison groups is that the data are generally not collected the same way and the same information may not be available. The underlying populations may be different. In addition, plans to merge data from other databases require the proper privacy safeguards to comply with legal requirements for patient data; Chapter 8 covers patient privacy rules in detail.

A historical comparison group refers to patients who are similar to the focus of interest, but who do not have the condition or exposure of interest, and for whom information was collected in the past (such as before the introduction of an exposure or treatment or development of a condition). Historical controls may actually be the same patients who later become exposed, or they may consist of a completely different group of patients. This design provides weak evidence because symmetry is not assured (i.e., the patients in different time periods may not be as similar as desired). Historical controls are susceptible to bias by changes over time in uncontrollable, confounding risk factors, such as differences in climate, management practices, and nutrition. Bias stemming from differences in measuring procedures over time may also account for observed differences.

A related concept to the use of historical controls is the use of Objective Performance Criteria (OPC) as a comparator, which has been described as an alternative to randomized trials particularly for the study of devices.[115] OPC are "performance criteria based on broad sets of data from historical databases (e.g., literature or registries) that are generally recognized as acceptable values. These criteria may be used for surrogate or clinical endpoints in demonstrating the safety or effectiveness of a device."[116] The FDA Medical Devices Guidance document, "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry," includes this description of study designs that should be considered as an alternative to randomized clinical trials, which may contribute to meeting the statutory criteria for pre-approval as well as post-approval evidence,: "Study designs employing non-concurrent controls, such as historical controls (e.g., literature, patient records),

objective performance criteria (OPC), and patients as their own control."[117] Registries serve as a source of reliable historical data in this context. New registries with safety or effectiveness endpoints may also be planned that will incorporate previously existing OPC as comparator (e.g. for a safety endpoint for a new cardiac device, using prior clinical study data to set the "complication-free rate" as comparator).

There are several situations in which conventional prospective design is impossible and historical controls may be considered:

- When one cannot ethically continue the use of older treatments or practices, or when physicians and/or patients refuse to continue their use, thus preventing the researcher from identifying relevant sites using the older treatments.
- When uptake of a new medical practice has been rapid, concurrent controls may differ so markedly in regard to factors related to outcomes of interest, that their selection is not feasible or valid.
- When conventional treatment has been consistently unsuccessful and the effect of new intervention is obvious and dramatic (e.g., first use of a new product for a previously untreatable condition).
- When collecting the control data is too expensive.
- When the Hawthorne effect (a phenomenon that refers to changes in the behavior of subjects because they know they are being studied or observed) makes it impossible to replicate actual practice in a comparison group during the same period.
- When the desired comparison is to usual care or "expected" outcomes at a population level, and data collection is too expensive due to the distribution or size of that population.

Sampling

Various sampling strategies for patients and sites can be considered. Each of these has tradeoffs in terms of validity and information yield. The representativeness of the sample, with regard to the range of characteristics that are reflective of the broader target population, is often a consideration, but mainly affects generalizability rather than the internal validity of the results. Representativeness in terms of patients (e.g., men and women, children, the elderly, different racial or ethnic groups) and sites (academic medical centers, community practices) should be considered. For sites (health care providers, hospitals, etc.), representativeness is often considered in terms of geography, practice size, and academic or private practice type. Reviewing and refining the research question can help to define an appropriate target population and a realistic strategy for subject selection.

Registry studies often restrict eligibility for entry to individuals within a certain range of characteristics to assure that enough meaningful information will be available for analysis. Alternatively, they may use some form of sampling: random selection, systematic sampling, or a nonrandom approach. Often-used sampling strategies include the following:

- *Probability sampling:* Some form of random selection is used, and each person in the population must have a known (often equal) probability of being selected. Despite their best intentions, humans cannot choose a sample in a random fashion without a formal randomizing mechanism. Examples are:
    - *Census:* A census sample includes every individual in a population or group (e.g., all known cases). A census is not feasible when the group is large, relative to the costs of obtaining information from individuals.

    - *Simple random sampling:* The sample is selected in such a way that each person has the same probability of being sampled.
    - *Stratified sampling:* The group from which the sample is to be taken is first stratified into subgroups on the basis of an important, related characteristic (e.g., age, parity, weight) such that each individual in a subgroup has the same probability of being included in the sample, but the probabilities for different subgroups or strata are different. Stratified random sampling assures that the different categories of the characteristic that is the basis of the strata are sufficiently represented in the sample, but the resulting data must be analyzed using more complicated statistical procedures (such as Mantel-Haenszel) in which the stratification is taken into account.
    - *Systematic sampling:* Every nth person in a population is sampled.
    - *Cluster (area) sampling:* The population is divided into clusters, these clusters are randomly sampled, and then some or all patients within selected clusters are sampled. This technique is particularly useful in large geographic areas or when cluster-level interventions are being studied.
    - *Multistage sampling:* Multistage sampling can include any combination of the sampling techniques described above.
- *Nonprobability sampling:* Selection is systematic or haphazard but not random. The following sampling strategies affect the type of inferences that can be drawn (e.g., it would be preferable to have a random sample if the goal were to estimate the prevalence of a condition in a population). However, systematic sampling of "typical" patients can generate useful data for many purposes, and is often used in situations where probability sampling is not feasible.[118]
    - *Case series or consecutive (quota) sampling:* All consecutive eligible patients treated at a given practice or by a given physician are enrolled, until the enrollment target is reached. This approach is intended to reduce conscious or unconscious selection bias on the part of physicians as to whom to enroll in the study, especially with regard to factors that may be related to prognosis.
    - *Haphazard, convenience, volunteer, or judgmental sampling:* This includes any sampling not involving a truly random mechanism. A hallmark of this form of sampling is that the probability that a given individual will be in the sample is unknown before sampling. The theoretical basis for statistical inference is lost, and the result is inevitably biased in unknown ways.
    - *Modal instance:* The most typical subject is sampled.
    - *Purposive:* Several predefined groups are deliberately sampled.
    - *Expert:* A panel of experts judges the representativeness of the sample or is the source that contributes subjects to a registry.

Individual matching of cases and controls is sometimes used as a sampling strategy for controls. Cases are matched with individual controls who have similar confounding factors, such as age, to reduce the effect of the confounding factors on the association being investigated in analytic studies.

Patients are recruited in a fashion that accomplishes individual matching. For example, if a 69-year-old "case" participates in the registry, a comparator near in age will be sought. Individual matching for prospective recruitment is challenging and not customarily used. More often, matching is used to create subgroups for supplemental data collection for case-control studies and cohort studies when subjects are limited and/or stratification is unlikely to provide enough subjects in each stratum for meaningful evaluation.

There are a number of other sampling strategies that have arisen from survey research (e.g., snowball, heterogeneity), but they are of less relevance to registries.

Registry Size and Duration

Precision in measurement and estimation corresponds to the reduction of random error; it can be improved by increasing the size of the study and by modifying the design of the study to increase the efficiency with which information is obtained from a given number of subjects.[119]

During the registry design stage, it is critical to explicitly state how large the registry will be, how long patients should be followed, and the justifications for these decisions. These decisions are based on the overall purpose of the registry. For example, in addressing specific questions of product safety or effectiveness, the desired level of precision to confirm or rule out the existence of an important effect should be specified, and is linked to policy or practice decisions that will be made based on the evidence. For registries with aims that are descriptive or hypothesis-generating, study size may be arrived at through other considerations.

The duration of registry enrollment and followup is determined both by required sample size (number of patients or person-years to achieve the desired power), as well as time-related considerations. The induction period for some outcomes of interest must be considered, and sufficient followup time allowed for the exposure under study to have induced or promoted the outcome. Biological models of disease etiology and causation usually indicate the required time period of observation for an effect to become apparent. Calendar time may be a consideration in studies of changes in clinical practice or interventions that have a clear beginning and end. The need for evidence to inform policy may also determine a timeframe within which the evidence must be made available to decision-makers.

A detailed discussion of the topic of sample size calculations for registries is provided in Appendix A. For the present purposes, it is sufficient to briefly describe some of the critical inputs to these calculations that must be provided by the registry developers:

- The expected timeframe of the registry and the time intervals at which analyses of registry data will be performed.
- Either the size of clinically important effects (e.g., minimum clinically important differences) or the desired precision associated with registry-based estimates.
- Whether or not the registry is intended to support regulatory decisionmaking. If the results from the registry will affect regulatory action—for example, the likelihood that a product may be pulled from the market—then the precision of the overall risk estimate is important , as is the necessity to predict and account for attrition.

In a classical calculation of sample size, the crucial inputs that must be provided by the investigators include either the size of clinically important effects or their required precision. For example, suppose that the primary goal of the registry is to compare surgical complication rates in general practice with those in randomized trials. The inputs to the power calculations would include the complication rates from the randomized trials (e.g., 4 percent) and the complication rate in general practice, which would reflect a meaningful departure from this rate (e.g., 6 percent). If, on the other hand, the goal of the registry is simply to track complication rates (and not to compare the registry with an external standard), then the investigators should specify the required width of the confidence interval associated with those

rates. For example, in a large registry, the 95-percent confidence interval for a 5-percent complication rate might extend from 4.5 percent to 5.5 percent. If all of the points in this confidence interval lead to the same decision, then an interval of ±0.5 percent is considered sufficiently precise, and this is the input required for the estimation of sample size.

Specifying the above inputs to sample size calculations is a substantial matter and usually involves a combination of quantitative and qualitative reasoning. The issues involved in making this specification are essentially similar for registries and other study designs, though for registries designed to address multiple questions of interest, one or more primary objectives or endpoints must be selected that will drive the selection of a minimum sample size to meet those objectives..

Other considerations which should sometimes be taken into account when estimating sample sizes include: whether levels of expected attrition or lack of adherence to therapy may require a larger number of patients to achieve the desired number of person-years of followup or exposure; whether individual patients can be considered "independent;" and whether multiple comparisons are being made and subjected to statistical testing. In some cases, patients under study who share some group characteristics, such as patients treated by the same physician or practice, or at the same institution, may not be entirely independent from one another with regard to some outcomes of interest or when studying a practice-level intervention. To the extent they are not independent, a measure of interdependence, the intraclass correlation (ICC), and so-called "design effect" must be considered in generating the overall sample size calculation. A reference addressing sample size considerations for a study incorporating a cluster-randomized intervention is provided.[120] A hierarchical or multilevel analysis may be required to account for one or more levels of "grouping" of individual patients, discussed further in Chapter 13. One approach to addressing multiple comparisons in the surgical complication rate example above is to use control chart methodology, a statistical approach used in process measurement to examine the observed variability and determine whether out-of-control conditions are occurring. Control chart methodology is used in sample size estimation, largely for studies with repeated measurements, so as to adjust the sample size as needed and therefore maintain reasonably precise estimates of confidence limits around the point estimate. Accordingly, for registries that involve ongoing evaluation, sample size per time interval could be determined by the precision associated with the related confidence interval, and decision rules for identifying problems could then be based on control chart methodology.

Although most of the emphasis in estimating study size requirements is focused on patients, it is equally important to consider the number of sites needed to recruit and retain enough patients to achieve a reasonably informative amount of person-years for analysis. The science of estimating the number of sites needed for study is less well developed than the calculations used to estimate study size in terms of patients and person-years.

In summary, the aims of a registry, the desired precision of information sought, and hypotheses to be tested, if any, determine the process and inputs for arriving at a target sample size and specifying the duration of followup. Registries with mainly descriptive aims, or those that provide quality metrics for physicians or medical centers, may not require the choice of a target sample size to be arrived at through power calculations. In either case, the costs of obtaining study data, in monetary terms, as well as researcher, physician, and patient time and effort, may set upper as well as lower limits on study size. Limits to study budgets and the number of sites and patients that could be recruited may be apparent at

the outset of the study. However, an underpowered study involving substantial data collection, that is ultimately unable to satisfactorily answer the research question(s), may prove to be a waste of finite monetary as well as human resources that could better be applied elsewhere.

Internal and External Validity

The potential for bias refers to opportunities for systematic errors to influence the results. Internal validity is the extent to which study results are free from bias, and the reported association between exposure and outcome is not due to unmeasured or uncontrolled for variables. Generalizability, also known as external validity, is a concept that refers to the utility of the inferences for the broader population that the study subjects are intended to represent. In considering potential biases and generalizability, we discuss the differences between RCTs and registries, since these are the two principal approaches to conducting clinically relevant prospective research.

The strong internal validity that earns RCTs high grades for evidence comes largely from the randomization of exposures that helps ensure that the groups receiving the different treatments are similar in all measured or unmeasured characteristics. Thus, any differences in outcome (beyond those attributable to chance) can be reasonably attributed to differences in the efficacy or safety of the treatments. However, it is worth noting that RCTs are not without their own biases, as illustrated by the "intent-to-treat" analytic approach, in which people are considered to have used the assigned treatment, regardless of actual compliance. The intent-to-treat analyses can minimize a real difference, known as bias toward the null, by including the experience of people who adhered to the recommended study product along with those who did not.

Another principal difference between registries and RCTs is that RCTs are often focused on a relatively homogeneous pool of patients from which significant numbers of patients are purposefully excluded at the cost of external validity—that is, generalizability to the target population of disease sufferers. Registries, in contrast, usually focus on generalizability so that their population will be representative and relevant to decision makers.

Generalizability

The strong external validity of registries is achieved by studying typical patients, which often include more heterogeneous populations than RCT (e.g., wide variety of age, ethnicity, co-morbidities, etc.). Registries are often evaluated in terms of the extent to which study subjects are representative of the target population. Therefore, registry data represent the course of disease and impact of interventions in actual practice and, for some purposes, may be more relevant than the data derived from the artificial constructs of the clinical trial for decisionmaking. In fact, even though registries have more opportunities to introduce bias (systematic error) because of their non-experimental methodology, well-designed observational studies can approximate the effects of interventions as well as RCTs on the same topic[121,122] and, in particular, in the evaluation of health care effectiveness.[123]

The choice of groups from which patients will be selected directly affects generalizability. No particular method will assure that an approach to patient recruitment is adequate, but it is worthwhile to note that the way in which patients are recruited, classified, and followed can either enhance or diminish the external validity of a registry. Some examples of how these methods of patient recruitment and followup can lead to systematic error follow.

Information bias

If the registry's principal goal is the estimation of risk, it is possible that adverse events or the number of patients experiencing them will be underreported if the reporter will be viewed negatively for reporting them. It is also possible for those collecting data to introduce bias by misreporting the outcome of an intervention if they have a vested interest in doing so. This type of bias is referred to as information bias (also called detection, observer, ascertainment, or assessment bias), and it addresses the extent to which the data that are collected are valid (represent what they are intended to represent), and accurate. This bias arises if the outcome assessment can be interfered with, intentionally or unintentionally. On the other hand, if the outcome is objective, such as whether or not a patient died or the results of a lab test, then the data are unlikely to be biased.

Selection bias

A registry may create the incentive to enroll only patients who either are at low risk of complications, or who are known not to have suffered such complications, biasing the results of the registry toward lower event rates. Those registries for which participants derive some sort of benefit from reporting low complication rates, such as surgical registries, are at particularly high risk for this type of bias. Another example of how patient selection methods can lead to bias is the use of volunteers, which may lead to selective participation from subjects most likely to perceive a benefit, distorting results for studies of patient-reported outcomes. Enrolling patients who share a common exposure history, such as having used a drug that has been publicly linked to a serious adverse effect, could distort effect estimates for cohort and case-control analyses. Registries also have the potential to selectively enroll people who are at higher risk of developing serious side effects, since having a high risk profile can motivate a patient to participate in a registry.

The term “selection bias” refers to situations where the procedures used to select study subjects lead to an effect estimate among those participating in the study that is different from the estimate that is obtainable from the target population.[124] Selection bias may be introduced if certain subgroups of patients are routinely included or excluded from the registry.

Channeling bias (confounding by indication)

Channeling bias, also called confounding by indication, is a form of selection bias, where drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences.[125] For example, physicians may prescribe new treatments more often to those patients who have failed on traditional, first-line treatments.

One approach to designing studies to address channeling bias is to conduct a prospective review of cases in which external reviewers are blinded as to the treatments that were employed and are asked to determine whether a particular type of therapy is indicated and to rate the overall prognosis for the patient.[126] This method of blinded prospective review was developed to support research on ruptured cerebral aneurysms, a rare and serious situation. The results of the blinded review were used to create risk strata for analysis so that comparisons could be conducted only for candidates for whom both therapies under study were indicated, a procedure much like applying additional inclusion and exclusion criteria in a clinical trial.

A computed “propensity score” (i.e., the predicted probability of use of one therapy over another based on medical history, health care utilization, and other characteristics measured prior to the initiation of

therapy) is increasingly incorporated in study designs to address this type of confounding.[127,128] Propensity scores may be used to create cohorts of initiators of two different treatments matched with respect to probability of use of one of the two therapies, for stratification, or for inclusion as a covariate in a multivariate analysis. Studies incorporating propensity scores as part of their design may be planned prior to and implemented shortly following the time of launch of a new drug as part of a risk management program, with matched comparators being selected over time, so that differences in prescribing patterns following drug launch may be taken into account.[129]

Instrumental variables, or factors that are strongly associated with treatment, while related to outcome only through their association with treatment, may provide additional means of adjustment for confounding by indication.[130] Types of instrumental variables include providers' preferences for one therapy over another, which exploit variation in practice as a type of natural experiment, as well as variation or changes in insurance coverage or economic factors (e.g. cigarette taxes) that are associated with an exposure.[131,132] Variables that serve as effective instruments of this nature are not always available. While use of physician or study site may, in some specific cases, offer potential as an instrumental variable for analysis, the requirement that use of one therapy over another be very strongly associated with the instrument is often difficult to meet in real world settings. In most cases, instrumental variable analysis provides an alternative for secondary analysis of study data that will either support the conclusions drawn or raise additional questions regarding the impact of confounding by indication on the results.[133]

In some cases, differences in disease severity or prognosis between patients receiving one therapy rather than another may be so extreme and/or unmeasurable that confounding by indication is not remediable in an observational design.[134] This represents special challenges for observational studies of comparative effectiveness, as the severity of underlying illness may be a strong determinant of both choice of treatment and treatment outcome.

Bias from study of existing rather than new product users

If there is any potential for tolerance to affect the use of a product, such that only those who perceive benefit or are free from harm continue, the recruitment of existing users rather than new users may lead to the inclusion of only those who have tolerated or benefited from the intervention, and would not necessarily capture the full spectrum of experience and outcomes. Selecting only existing users may introduce any number of biases, including incidence/prevalence bias, survivorship bias, and followup bias. By enrolling new users (an inception or incidence cohort), the study is ensuring that the population will reflect all users of the product, that the longitudinal experience of all users will be captured, and that the ascertainment of their experience will be comparable.[135]

Loss to followup

Loss to followup or attrition of patients and sites threatens generalizability as well as internal validity if there is differential loss – for people with a particular exposure or disease, or with different outcomes, which could substantially affect the conclusions and interpretation of results. As with loss to followup, attrition is generally a serious concern only when it is nonrandom (that is, when there are systematic differences between those who leave or are lost and those who remain). The magnitude of loss to followup or attrition determines the potential impact of any bias. Given that the differences between patients who remain enrolled and those who are lost to followup is often unknown (unmeasurable),

preventing loss to followup in long term studies to the full extent possible will increase the credibility, as well as the validity, of the results.[136] Attrition should be considered with regard to both patients and study sites, as results may be biased or less generalizable if only some sites (e.g., teaching hospitals) remain in the study while others discontinue participation.

Assessing the magnitude of bias

Remaining alert for any source of bias is important, and the value of a registry is enhanced by its ability to provide a formal assessment of the likely magnitude of all potential sources of bias. Any information that can be generated regarding non-respondents, missing respondents, and the like, even if it is just an estimation of their raw numbers, is helpful. As with many types of survey research, an assessment of response rate and differential patient selection can sometimes be undertaken when key data elements are available for both registry enrollees and nonparticipants. Such analyses can easily be undertaken when the initial data source or population pool is that of a health care organization, employer, or practice that would have access to data other than key selection criteria (e.g., demographics, comorbidities). Another tool is the use of sequential screening logs, in which all subjects fitting the inclusion criteria are enumerated and a few key data elements are recorded for all those who are screened. This technique allows quantitative analysis of nonparticipants and assessments of the effects, if any, on representativeness. Whenever possible, quantitative assessment of the likely impact of bias is desirable to determine their robustness to varying assumptions. A recent text on quantitative analysis of bias through validation studies, and probabilistic approaches provides a guide for planning and implementing these methods.[137]

Qualitative assessments, although not as rigorous as quantitative approaches, may provide users with a framework for drawing their own conclusions regarding the effects of bias on study results if the basis for the assessment is made explicitly in reporting.

Accordingly, two items that can be reported to help the user assess generalizability are a description of the criteria used to select registry sites, and the characteristics of these sites, particularly those characteristics that might have an impact on the purpose of the registry. For example, if a registry designed for the purpose of assessing adherence to lipid screening guidelines requires that its sites have a sophisticated electronic medical record in order to collect data, it will probably report better adherence than usual practice because this same electronic medical record facilitates the generation of real-time reminders to engage in screening. In this case, a report of rates of adherence to other screening guidelines (for which there were no reminders), even if these are outside the direct scope of inquiry, would provide some insight as to the degree of overestimation.

Finally, and most importantly, whether or not study subjects need to be evaluated on their representativeness depends on the purpose and kind of inference needed. For example, for understanding biological effects, it is not necessary to sample in proportion to the underlying distribution in the population. It is more important to demonstrate to the stakeholders the degree to which patients who are included in a registry are representative of the population from which they were derived.

Summary

In summary, the key points to consider in designing a registry include study design, data sources, patient selection, comparison groups, sampling strategies, considerations of possible sources of bias, and ways to address them to the extent that is practical and achievable.

Case Example 7: Designing a registry for a health technology assessment

Description:	The Nuss procedure registry was a short-term registry designed specifically for the health technology assessment of the Nuss procedure, a novel, minimally invasive procedure for the repair of pectus excavatum. The registry collected procedure outcomes, patient reported outcomes, and safety outcomes.
Sponsor:	National Institute for Health and Clinical Excellence (NICE), United Kingdom
Year Started:	2004
Year Ended:	2007
No. of Sites	13 hospitals
No. of Patients:	260 patients

Challenge

The Nuss procedure is a minimally invasive intervention for the repair of pectus excavatum. During a review of the evidence supporting this procedure in 2003, the National Institute for Health and Clinical Excellent (NICE) determined that the existing data included relatively few patients, few quality of life outcomes, and did not sufficiently address safety concerns. NICE concluded in the 2003 review that the evidence was not adequate for routine use and that more evidence was needed to make a complete assessment of the procedure.

Proposed Solution

Gathering additional evidence through a randomized controlled trial was not feasible for several reasons. First, a blinded trial would be difficult because the other procedures for the repair of pectus excavatum produce much larger scars than the Nuss procedure. It may also be considered unethical to randomize patients to procedures that do not produce satisfactory cosmetic results. Surgeons also tend to either perform only the Nuss procedure or only another procedure, which would complicate randomization efforts. In addition, only a small number of procedures are done in the United Kingdom. The sample for a randomized trial would likely be very small, making it difficult to detect rare adverse events.

Due to these limitations, NICE decided to develop a short-term registry to gather evidence on the Nuss procedure. The advantages of a registry were its ability to gather data on all patients undergoing the procedure in the UK to provide a more complete safety assessment and its ability to collect patient-reported outcomes.

The registry was developed by an academic partner, with input from clinicians. Hospitals performing the procedure were identified and asked to enter data into the registry on all patients undergoing the intervention. Once the registry was underway, the cases in the registry were compared against cases included in the Hospital Episodes Statistics (HES) database (a nationwide source of routine data on hospital activity), and non-participating hospitals were identified and prompted to enter their data.

Results

NICE conducted a re-assessment of the Nuss procedure in 2009, comparing data from the registry to other published evidence on safety and efficacy. The quantity of published literature had increased substantially between 2003 and 2009. The new publications primarily focused on technical and safety outcomes, while the registry included patient reported outcomes. The literature and the registry reported similar rates of major adverse events such as bar displacement (2-10%). Based on the registry data and the new literature, the review committee found that the evidence was now sufficient to support routine use

of the Nuss procedure, and no further review of the guidance is planned. Committee members considered that the registry made a useful contribution to guidance development.

Key Point

The Nuss registry demonstrated that a small, short-term, focused registry with recommended (but not automatic or mandatory) submission can produce useful data – both about safety and about patient-reported outcomes.

Case Example 8: Assessing the safety of products used during pregnancy

Description:	The Antiretroviral Pregnancy Registry is the oldest ongoing pregnancy exposure registry. This multisponsor, international collaborative registry monitors prenatal exposures to all marketed antiretroviral drugs, which include several drug classes and multiple drugs in each class.
Sponsor:	Abbott Laboratories, Aurobindo Pharma Ltd, Barr Laboratories Inc, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Cipla Ltd, Gilead Sciences Inc, GlaxoSmithKline, Hetero USA, Merck & Co. Inc, Mylan Laboratories, Novartis Pharmaceuticals, Pfizer Inc, Ranbaxy Inc, Roche, and Tibotec BVBA
Year Started:	1998
Year Ended:	Ongoing
No. of Sites	Not site based; open to all health care providers. Over 1,200 health care providers have enrolled patients.
No. of Patients:	12,500

Challenge

Data on the teratogenic effects of pharmaceutical products is often difficult to obtain. Most clinical trials exclude pregnant women because of the ethical concerns of potentially exposing the fetus to harm. While data on the teratogenic risk is available from preclinical animal testing, this information is not always predictive of the effects of a drug taken during human pregnancy. As a result, data to help patients and physicians understand the potential risk and benefits of continuing a treatment during pregnancy are often lacking.

There is a great need for this information, as pregnant women may receive drugs for various reasons. For example, a pregnant woman may need drugs to treat an illness that arises during pregnancy or to treat a chronic mental or physical illness. Women may also become pregnant while taking a drug, resulting in an unintended exposure. This last scenario is particularly likely, given that 50 to 60 percent of all pregnancies in the United States are unintended, and most are not recognized until late in the first trimester.

Antiretroviral treatments represent an area of particular concern, as women may need to take the drugs during pregnancy to manage their HIV infection. In addition, these drugs can reduce the risk of transmitting HIV to the infant, but that benefit must be weighed against the possible risk of teratogenic effects. Because of these factors, it is extremely important for clinicians and patients to understand the potential risks of using antiretroviral drugs during pregnancy in order to make an informed decision. However, ethical and practical concerns make a randomized trial to gather these data difficult, if not

impossible.

Proposed Solution

In 1989, the first manufacturer of an antiretroviral drug voluntarily initiated a pregnancy exposure registry to track outcomes of women who had used its product during pregnancy. The purpose of the registry is to collect information on any teratogenic effects of the product by prospectively enrolling women during the course of their pregnancy and following up with them to determine the outcome of the pregnancy. Physicians enroll a patient by providing information on the pregnancy dates, characteristics of the HIV infection, drug dosage, length of therapy, and trimester of exposure to the antiretroviral drug. Information on the pregnancy outcome is gathered through a followup form sent to the physician after the expected delivery date.

In 1993, the registry expanded to include all antiretroviral drugs, as other manufacturers voluntarily joined the registry once their drugs were on the market. The registry is international in scope and allows any health care provider to enroll a patient who has intentional or unintentional use of an antiretroviral drug during pregnancy. The U.S. Food and Drug Administration (FDA), which has used this registry as a model for new pregnancy registries, now requires participation in the registry for all new and generic antiretroviral drugs.

Results

Since its inception 20 years ago, the registry has provided many lessons in how to monitor the safety of these drugs during pregnancy. The registry has developed processes to monitor and assess the safety of these drugs in pregnancy. To ensure both rigor and consistency, it has predefined analytic methods and criteria for recognizing a potential teratogenic signal.

The monitoring system developed by the registry includes several groups, which provide different levels of monitoring. The groups include:

- Steering Committee (comprised of all groups below).
- Scientific Advisory Committee (comprised of experts from FDA, Centers for Disease Control and Prevention, National Institutes of Health, and academia).
- Birth Defect Review Committee (comprised of representatives from the other groups).
- Sponsor Committee (comprised of epidemiologists and safety experts).
- Consultants (geneticist and pharmacoepidemiologist).
- Coordinating Center staff (epidemiologist, project manager, and clinical research associates).

Tools for coding and classifying birth defects have been developed specifically for the registry to maximize identification of a teratogenic signal. This unique system groups birth defects by etiology or embryology rather than by general location or category, as in the Medical Dictionary for Regulatory Activities (MedDRA). Grouping like defects together increases the likelihood of detecting a potential signal. Another unique aspect of this registry that aids in signal detection is coding the temporal association between timing of exposure and formation of the birth defect.

Specific monitoring criteria have been developed for evaluating signals at various levels, including:

- Individual and composite data.
- Rule of Three (3 exposure-specific cases with the same birth defect requires immediate evaluation) based on the statistical principle that the likelihood of finding at least 3 of any specific defect in a cohort of 600 or fewer by chance alone is less than 5%.
- Primary analysis (statistical considerations, including power/relative risk calculation and statistical probabilities associated with detecting various birth defects using internal and external comparators).

- Complementary data, including clinical studies in pregnancy, retrospectively reported data, other registries or epidemiological studies, published studies, and case studies.

These efforts to monitor and study the teratogenic effects of antiretroviral use during pregnancy have produced many publications. Registry data have been used in nine publications, seven abstracts, and 22 presentations, and the registry design and operation have been the subject of many publications and presentations. The registry data and publications can help to provide clinicians and patients with information to make informed decisions regarding use of antiretroviral drugs during pregnancy.

Key Point

An observational registry can collect data to answer research questions in cases where a randomized trial is not feasible for ethical or practical reasons. For pregnancy exposure registries, the observational model allows the researchers to gather data on women and infants exposed to products during pregnancy without deliberately introducing the exposure.

For More Information

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Case Example 9: Designing a registry to study outcomes

Description:	The Carotid Artery Stenting with Emboli Protection Surveillance Post-Marketing Study (CASESPMS) was designed to assess the outcomes of carotid artery stent procedures for the treatment of obstructive artery disease during real-world use. The primary purpose of the registry was to evaluate outcomes in the periapproval setting, including the use of a detailed training program for physicians not experienced in carotid artery stenting.
Sponsor:	Cordis Corporation
Year Started:	2004
Year Ended:	2006
No. of Sites	74
No. of Patients:	1,493

Challenge

In 2004, the sponsor received approval for a carotid stent procedure from the U.S. Food and Drug Administration (FDA), largely because of the results of the Stenting and Angioplasty With Protection in Patients at HIgh Risk for Endarterectomy (SAPPHIRE) clinical trial. The SAPPHIRE trial studied the

results of stent procedures performed by experts in the field. While the trial provided strong data to support the approval of the carotid stent, FDA and the Centers for Medicare & Medicaid Services (CMS) both questioned whether the outcomes of the trial were generalizable to procedures performed by physicians without prior experience in carotid artery stenting.

To respond to FDA and CMS requests, the sponsor needed to design a study to confirm the safety and effectiveness of carotid artery stenting in a variety of settings. The study needed to gather data from academic and nonacademic settings, from physicians with various levels of carotid stenting experience, from settings with varying levels of carotid stenting volume, and from a geographically diverse mix of sites. The study would also need to examine the effectiveness of a training program that the sponsor had designed to teach physicians about the stenting procedure.

Proposed Solution

The sponsor designed a comprehensive training program for physicians and other health care professionals. The training program, which began in 2004, included didactic review, case observations and simulation training, and hands-on experience. To study the effectiveness of the training program and to provide data on the clinical safety and effectiveness of carotid stenting in a variety of settings, the sponsor designed and launched the registry in 2004.

The registry was a multicenter, prospective, observational study designed to assess stenting outcomes in relation to the outcomes of the SAPPHIRE trial (historic comparison group). The study enrolled 1,493 patients from 74 sites, using inclusion and exclusion criteria that matched those of the SAPPHIRE trial. The patients in the study were high-surgical-risk patients with de novo atherosclerotic or postendarterectomy restenotic obstructive lesions in native carotid arteries. Study participants completed clinical followups at 30 days and again at 1 year after the procedure. The 30-day assessments included a neurological examination by an independent neurologist and an evaluation of adverse events. The study defined the 30-day major adverse event rate as the 30-day composite of all deaths, myocardial infarctions, and strokes.

Results

The 30-day major adverse event rate of 5.0 percent met the criteria for noninferiority to the outcomes of stented patients from the pivotal SAPPHIRE trial. Outcomes were similar across levels of physician experience, carotid stent volume, geographic location, and presence/absence of the training program. The initial findings show that a comprehensive, formal training program in carotid stenting enables physicians from multiple specialties with varying levels of experience in carotid stenting to achieve outcomes similar to those achieved by the experts in the clinical trial.

Key Point

An observational registry can provide the necessary data for a postmarket evaluation of devices that are dependent on newly acquired skills. The registry can provide data to assess both the clinical safety of the device and the effectiveness and success of a training program.

For More Information

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Case Example 10: Analyzing clinical effectiveness and comparative effectiveness in an observational study

Description:	The National Cooperative Growth Study (NCGS) collects data on children with growth disorders who are treated with a specific growth hormone (GH). The purpose of the multicenter, observational, postmarketing surveillance registry is to collect long-term safety and efficacy information on the GH preparations, with the goal of better understanding the growth response to GH therapy.
Sponsor:	Genentech, Inc.
Year Started:	1985
Year Ended:	Ongoing
No. of Sites	More than 500 centers have participated over the life of the registry.
No. of Patients:	47,226 at time of analysis

Challenge

Clinical trials of GH therapy for short children without GH deficiency and without known etiology for their growth failure (idiopathic short stature, or ISS) have generally only included a small number of patients. The registration trial for the sponsor's GH therapy for the ISS condition was comprised of 118 children at baseline. While the trial demonstrated the efficacy of the treatment and an indication was obtained, physicians and families had lingering concerns about the applicability (safety and effectiveness) of the results to clinical practice.

Proposed Solution

To provide further safety and effectiveness data, the sponsor compared the data in the registration trial with data in the existing NCGS registry. In the 18-year period used in the analysis, the registry contained 8,018 children without GH deficiency and with no identified etiology for their growth failure. The analysis team extracted the data from these 8,018 children as a comparator to the 118 children in the sponsor's clinical registration trial.

For the purposes of the safety analysis, the analysis team summarized all reportable adverse events, serious adverse events, and certain targeted adverse events specified by the protocol for the registry cohort and compared these data with data from the clinical trial cohort. For the purposes of effectiveness, the analysis team selected children from the registry who matched the clinical characteristics of the trial cohort (age 5 years or older, prepubertal, maximum stimulated GH 10 ng/ml or more, no text report of contraindicating diagnosis, naive to previous therapy, and receiving a dose of GH similar to that in the clinical trial). The team found 1,721 patients who had at least 1 year of treatment data reported. The team compared these data with the growth rates of the children in the registration trial by year of treatment.

In addition, the team performed an analysis to look at children in the registry younger than those in the registration trial to provide clinical data that would be useful to clinicians but could not be obtained easily

in a clinical trial. Lastly, the team completed an analysis on children in puberty, another group that could not be studied in the registration trial because of the confounding variable of the puberty group and insufficient numbers in the trial to account for this variable vs. the effect of GH alone.

Results

The results of these analyses using the registry data and the sponsor's registration trial data demonstrated that ISS patients in a clinical setting had a significant increase in height similar to that of patients in the registration trial, with no new safety signals. Children in groups not studied in the registration trial had characteristic growth patterns that could be used by clinicians as comparators not available from the registration trial. Finally, the lack of new safety signals from any of the groups in the registry provided data in numbers and in years of exposure to GH that could never be obtained from a small registration trial.

Key Point

A large registry can provide a resource of study subjects for focused investigations. Inclusion and exclusion criteria can be designed to match those of a registration trial to provide more robust data on outcomes and safety.

For More Information

Kemp SF, Kuntze J, Attie KM et al. Efficacy and safety results of long-term growth hormone treatment of idiopathic short stature. J Clin Endocrinol Metab 2005;90:5247-53.

Chapter 4: Use of Registries in Product Safety Assessment

Once a drug or device is approved for use by a regulatory authority, the product is generally used by larger and more diverse populations than are typically studied in the clinical trials leading up to approval. As a result, the period after approval is an important phase for identifying and understanding product safety concerns associated with both acute and chronic use. The need for post-approval (also called post-marketing) safety assessment as it exists today was, for the most part, born out of well-publicized product safety issues which were initially detected by clinicians recognizing a pattern of rare serious events, such as phocomelia caused by prenatal exposure to thalidomide[138] and rare vaginal cancers that occurred in young women who had *in utero* exposure to diethylstilbestrol.[139] The detection of serious adverse drug reactions post-authorization has led to much debate about the adequacy of both industry and regulatory approaches to pre-authorization assessment and testing. However, the decision to authorize a medicine is a balance between wanting to know as much as possible about the safety of a product and the need to make new drugs available for patients.[140] The implications of this are that authorization cannot mean that a medicine is completely safe; rather, it is an assessment that at the time of authorization, the known benefits for the average patient in the approved indication outweigh the known risks. But, the degree to which the known risks represents the actual safety profile of a product will depend upon the size, duration, representativeness, and thoroughness of the clinical trial program, which, in turn, is related to the complexity of the patients and the state of knowledge of the disease being targeted. Trials conducted as part of clinical development are, by necessity, of limited duration and size and generally focus on a narrowly defined population that represents only a small segment of the population of people with the disease or product use of interest. Clinical trial populations tend to be restricted to those who have limited concurrent disease and who are on few, if any, concomitant medications. Typically, trial protocols include lengthy lists of inclusion and exclusion criteria that further restrict the trial population. Unless intended for a very narrow indication or a very rare disease, requiring clinical trials to be inclusive of all types of patients likely to ever be exposed to the product is not feasible. Even in the case of a narrow indication, the potential long-term and delayed effects of a product are unlikely to be established during most clinical trial development programs.

To address the acknowledged limitations of what is known about the safety profile of a product at the time of authorization, post-marketing pharmaco- and medical device vigilance is traditionally, and by regulation, performed through spontaneous adverse event reporting. The exact requirements for spontaneous reporting to the regulatory authorities vary internationally and are dependent upon the country/region, approval type, and product type. It is widely acknowledged, however, that spontaneous reporting captures an extremely small percentage of the actual events occurring, and, while it is useful for identifying rare and potentially significant events,[141,142] it has limited use in the detection of other equally important types of events, including increases in events with a high background rate. This form of post-marketing surveillance is reactive in that one waits for adverse events/reactions to be spontaneously reported, assesses them for causality, and estimates the importance of the information.

As well as collecting only an indeterminate fraction of adverse reactions, this method of surveillance depends upon someone reporting the events of interest. There is some evidence that physicians who report adverse events are not typical of physicians in general, and other reporters such as patients, lawyers, and consumer groups may have unclear motivations for reporting, which introduces further bias into the equation.[143,144,145] The current methods available for adverse event reporting are seen by many as burdensome and not amenable to incorporation into a physician's normal workflow. Waiting for reports to arrive and accumulate may also delay the detection of adverse reactions. On the other hand, a massive uptake of a new drug or device, such as seen with Viagra® (sildenafil citrate) or coronary artery stents, may lead to a sudden flood of reports of non-serious as well as serious adverse events that could potentially overwhelm established systems. To overcome some of the difficulties associated with managing large databases of spontaneous adverse events, many employ statistical methods to identify signals of disproportionate reporting (SDR). These methods identify adverse events that are reported more frequently with a drug or device than would be expected compared with other event/product pairs in the database and do not imply any kind of causal relationship.[146] It is important to be precise as to what is meant when using the term "signal" or "signal detection" since the terms are ambiguous; in the context of automated methods of detecting statistical anomalies, the term "SDR" should be used.[147] However, these statistical methods may not be reliable in certain situations, such as when there is major confounding or when the increased risk is small compared with the background incidence of the event.[148] All these above-mentioned limitations mean that there are situations when spontaneous reporting may not be adequate as the sole method of post-marketing surveillance. To address problems with traditional pharmaco- or medical device vigilance when there are particular known limitations of knowledge of the safety profile of a product and/or to further address unresolved safety concerns, some products are approved subject to post-marketing commitments, which may be requested for safety purposes as well as to address other outstanding questions. In Europe, in response to concerns over pharmacovigilance, marketing authorization applicants are required to submit a European Union-risk management plan (EU-RMP) when seeking a marketing authorization for the majority of new chemical entities and biologics. This EU-RMP states what is known and not known about the safety profile of a medicinal product, how its safety profile will be monitored, investigated, and characterized, and what risk minimization activities will be undertaken. While many products will require only routine pharmacovigilance, for others more pro-active methods of pharmacovigilance will be necessary to supplement the use of spontaneous adverse reaction reporting and periodic safety update reports. Although additional clinical trials may be occasionally mandated, it is more common for observational pharmacoepidemiologic studies to be conducted to ascertain the safety profile of a product under real world use.

Other observational methods of tracking and evaluating safety data have historically included active surveillance systems, such as prescription event monitoring (PEM) systems used in the United Kingdom (Drug Safety Research Unit)[149], New Zealand (NZ Intensive Monitoring Programme), Japan (J-PEM) and elsewhere targeting new products, and the retrospective use of administrative claims data. In the UK, the requirement that access to most secondary care is through a general practitioner has led to the use of their electronic health care systems for pharmacovigilance purposes; however, this type of integrated approach is not yet widely accessible elsewhere. In May 2008, the U.S. Food and Drug Administration (FDA) launched the Sentinel Initiative, an effort to create an integrated, electronic system in the U.S. for adverse event monitoring incorporating multiple existing data sources including claims data and electronic medical record systems.[150]

Medical devices in the U.S. have different surveillance programs than drugs. The Safe Medical Devices Act of 1990 requires that high-risk medical devices be tracked after marketing and that product corrections and removals be reported to the FDA if the actions were taken to reduce health risks. Most medical device safety tracking is accomplished through reports submitted to the FDA from medical facilities when devices are implanted or explanted. In addition, hospitals, nursing homes, ambulatory surgery centers, and outpatient treatment facilities are required to report to the FDA whenever they believe that a device caused or contributed to the death of a patient, though this reporting is a voluntary requirement and not enforceable or audited.[151]

Whether as part of a post-marketing requirement or as a desire to supplement spontaneous reporting, prospective product and disease registries are also increasingly being considered as a resource for examining unresolved safety issues and/or as a tool for proactive risk assessment in the post-approval setting. The advantage of registries is that their observational and inclusive design may allow for surveillance of a diverse patient population that can include sensitive subgroups and other groups not typically included in initial clinical trials such as pregnant women, minorities, older patients, children, or patients with multiple co-morbidities and those taking concomitant medications. In contrast to clinical trials, in which the inclusion criteria are generally tightly focused and restrictive by design, registry populations are generally more representative of the population actually using the product or undergoing a procedure, since the inclusion criteria are usually broad and may potentially include all patients exposed regardless of age, co-morbidities, and concurrent treatments. Data collection may lead to insights in provider prescribing practices or off-label use and information regarding the potential for studying new indications within the expanded patient population. Followup duration can be long to encompass delayed risks, consequences of long-term use, and/or effects of various combinations and sequencing of treatments. Such information can be used as a source of publications, to assist the medical community with developing recommendations for monitoring patient safety and product usage, and/or to contribute to the understanding of the natural history of the disease.

There are also many challenges to the utility of using registry data for providing more clarity about safety concerns and for prospective risk surveillance. These challenges relate largely to how products are used and the legal, regulatory, and ethical responsibilities of registry sponsors. Most registries that follow specific products do so through cooperation from physicians who prescribe (or implant) those medical products. Depending on the set-up and legal constraints of the registry, sometimes only a subsection of prescribing physicians may be involved in entering patients, raising questions about the representativeness of the physicians and their patients. However, the registry approach has the potential to be very useful for studying products that are used according to their labeled indications; it also allows for effective surveillance of products that are used off-label but still by the same practitioners who would use it for the labeled indication. For example, a product might be approved for moderate-to-severe asthmatics and used off-label in patients with mild asthma, yet the same medical providers would already be included in the registry and could easily provide information about all their product use. Off-label use is much more difficult to study when medical product is used by a wide variety of medical care providers, such as drugs that promote wakefulness or are thought to increase a patient's ability to concentrate, or immunomodulators. The legal, regulatory, and ethical aspects of registry sponsors also affect whether they are required to report any adverse events that may be observed, since only those legal entities that market (or distribute) a medical product are required to report adverse events. For all other parties, such reporting is ethical and desirable, but not enforceable or required.

The purpose of this chapter is to examine the role of registries as one of the available tools for enhanced understanding of product safety through adverse event detection and evaluation. Both the role of registries created specifically for the purposes of safety assessment and those in which the collection of safety data is ancillary to the registry's primary objectives will be examined. The legal obligations of regulated industries are discussed in other references and only mentioned briefly here. Similarly, issues to consider in the design and analysis of registries are covered in Chapter 3 and Chapter 13, respectively. Chapter 12 discusses practical and operational issues with reporting adverse event data from registries. The potential ethical obligations, technical limitations, and resource constraints that face registries with multiple different purposes in considering their role in adverse event detection and reporting are also discussed. Case Examples 11, 12, and 13 provide examples of how some registries have provided data for product safety assessments.

Registries Specifically Designed for Safety Assessment

Disease and product registries that systematically collect data on all eligible patients are a tremendous resource for capturing important information on safety. Registries commonly enroll patients that are not just different from, but are particularly more complicated than those included in clinical trials, in terms of the complexity of their underlying disease, their co-morbidities, and their concomitant medications.

Design considerations: Disease registry versus product registry

Product registries, by definition, focus on patients treated with a particular medical product. To be particularly useful, it is important to record specific information about the products of interest, including route of administration, dose, duration of use, start and stop date, and, ideally, information about whether a generic or branded product was used (and which), and/or specific information about the product. Biologic medicines and devices have their own challenges, ideally requiring information about device identifiers, production lots and batches, for example. Disease registries include information not only on products or procedures of interest, but also on similar patients who receive other treatments, other procedures, or no treatment for the same clinical indications. By characterizing events in the broad population of people with conditions of interest, disease registries can make a meaningful contribution to understanding adverse event rates by providing large, systematic data collection for target populations of interest. Their generally broad enrollment criteria allow systematic capture on a diverse group of patients, and, provided that they collect information about the potential events of interest, the registry can be used to provide a background rate of the occurrence of these events in the affected population in the absence of a particular treatment, or in association with relevant treatment modalities for comparison. The utility of this information, of course, depends on these registries capturing relatively specific and clear information about the events of interest among "typical" patients, and the ability of readers and reviewers to gauge how well the registries cover information about the target population of interest. Generating these type of real world data as part of disease registries can be informative when either designing subsequent product registries (e.g., to establish appropriate study size estimations) or incorporating new treatments into the data collection as they become available, since they can provide useful benchmarks against which to assess the importance of any signals. Some would argue that disease registries, rather than specific product registries, are more likely to be successful in systematically collecting interpretable long-term safety data, thereby allowing legitimate comparisons, to the extent possible, across types and generations of drugs, devices or other interventions.[152]

Consideration should be given during registry design to inclusion/exclusion criteria, appropriate comparator groups, defining the exposure and relevant risk window(s), and analysis planning (see Chapter 3). Registries involving products new to the market must be cognizant of selection bias and channeling bias whereby patients prescribed the new product are not comparable to the general disease population. For example, channeling bias occurs when sicker patients receive new treatments because they are non-responsive to existing treatments; conversely, patients who are doing well on existing treatments are unlikely to be switched to new treatments. For example, consider oncology products where new products are frequently used initially, only as second or third line therapy for patients for whom other treatments have failed. In some countries, cost considerations imposed by reimbursement status (whether dictated by government agencies or private insurance) mean that new therapies are restricted to narrower populations than indicated by the approved indication. For new devices or procedures, provider learning curves and experience are additional factors that must be considered in analysis planning. Since bias is inherent in observational research, the key is to recognize it and control it to the extent possible. In some cases, the potential for bias may be reduced through inclusion/exclusion criteria or other design considerations (i.e., enrollment logs) (see Chapter 3.) In other cases, additional data may be collected and analytic techniques used to help assess bias (See Chapter 13). Any recognized potential for bias should be discussed in any publications resulting from the registry.

In some settings, registries are used to collect specific adverse events or events of interest. Once the types of adverse events and/or other special events of interest have been identified, the registry must be designed to collect the data efficiently. Without adequate training of clinical site staff to recognize and report events of interest, the registry will be reduced to haphazard and inconsistent reporting of adverse events. Upon registry inception, clinicians or other healthcare professionals who may encounter patients participating in the registry should be educated about what adverse events or other special events of interest should be noted, and how and within what parameters (e.g., time) they should report untoward events that may occur while they are participating in the registry. They also should be reminded about the need to followup on events that may not obviously be of immediate interest. For example, if a physician asked a patient how he was feeling and the patient replied that he just returned from the hospital, it would be incumbent on the physician to obtain additional information to determine whether this might be a reportable event, regardless of whether the patient may have recognized it as such. This is particularly important in registries designed to capture all suspected adverse reactions as opposed to specific adverse events. Such an active role by participants as well as their treating clinicians can contribute to a robust safety database. In addition to identifying events known to be of interest, the systematic collection of followup data can also capture information regarding risks not previously identified, risks associated with particular subgroups (e.g., pediatric or geriatric patients, patients with liver impairment, fast or slow metabolizers), or differences in event severity or frequency not appreciated during clinical development. Consideration should also be given to implementation of routine followup of all registry patients for key adverse events, as well as vital status and patient contact and enrollment information at pre-specified visits or intervals, to ensure that analyses of the occurrence of adverse events among the registry population are not hampered by extensive missing data. Otherwise, the possibility that patients "lost to followup" may differ from those with repeat visits, with regard to risk of adverse events, cannot be excluded.

Healthcare provider and patient reported outcomes

Registries and other prospective data collection approaches have the advantage of incorporating both healthcare provider and patient reported data. Although patients and their advocates may spontaneously report post-marketing adverse events to manufacturers (e.g., via inquiries directed to medical information departments) and directly to regulatory bodies, this is relatively uncommon. Furthermore, spontaneous reports received directly from patients that lack healthcare provider confirmation may fall outside of standard aggregating processes by regulatory bodies. In Europe, there are schemes in some countries to encourage patient reporting directly to regulatory authorities; throughout Europe, manufacturers have an obligation to followup patient reports with their healthcare provider. However, significant events that are not clinically recognized may be substantially under-reported.

In addition, registries may collect healthcare provider level data, such as training level, number of patients seen annually, and practice type and locations, that may contribute to understanding differences in event rates and reporting. This, along with the patient data not routinely or consistently captured in the medical record (such as concomitant environmental and lifestyle exposures and adherence to prescribed regimes), differentiates registries from other electronic data sources, and in many cases, allows for improved assessment of confounding and ability to assess the potential of a signal internally, prior to further signal evaluation or action.

Effects observed in larger population over time

Registries, including those used to follow former clinical trial participants, are well suited to identify effects that can only be observed in a large and diverse population over an extended period of time. The ability to follow patients longitudinally may identify long-term device failures or consequences, such as in the case of orthopedic implants increasingly being placed in more active, younger patients. Similarly, such followup facilitates evaluation of drug-drug interactions (including with new drugs as they come to market and are utilized) and genetic and other patient characteristic-related differences in drug metabolism. One of the most consistent risk factors for adverse events is the total number of medications taken by a patient.[153] Polypharmacy is commonplace, especially in the elderly, and healthcare providers are often unaware of over-the-counter, herbal, and other complementary medications taken by the patient. Registries that collect data directly from patients can seek information about use of over-the-counter, herbal, and other complementary (alternative) products, or, if the registry is used solely by healthcare practitioners, data collection forms can be designed specifically to request that patients are asked about such use.

When designing a registry for the purposes of safety, the size of the registry, the enrolled population, and the duration of followup are all critical to ensure applicability of the inferences made, based on the data collected. If the background rate of the adverse event in the population of interest is not established and the time period for induction is not well understood, it is extremely difficult to determine an exact meaningful target size or observation period for the registry, and the registry may be too small and have too brief an observation period to detect any, or enough, events of interest to provide a meaningful estimate of the true adverse event rate. In addition, the broad inclusion criteria typical of registries make it likely that sub-groups of exposed patients may be identified and analyzed separately. Such stratified analyses may require a larger sample size to achieve rate estimations with confidence intervals narrow enough to allow meaningful interpretation within strata.

As is also true for clinical trials, which are often not powered for safety, but rather, for efficacy endpoints, describing safety outcomes from observational studies in statistical terms is not always straightforward. Post-marketing data may or may not confirm event rate estimates seen in clinical trials and may also identify events not previously observed. During clinical development, risk of events not yet seen but possibly associated with a product class or the product's mechanism of action are often identified as part of ongoing risk assessment, and these events usually continue to be events of interest post-approval. An inferential challenge arises when such an event is never observed. The "rule of three" is often cited as a means of interpreting the significance of a specific event *not* being observed (therefore a numerator of zero) in a finite population. Using asymptotic risk estimation, the rule posits that in a large enough study (i.e., > 30 patients) if no event occurs, and if the study were repeated over and over again, there can be 95% confidence that the event (or events) would not actually occur more often than one in n/3 people, where n is the number of people studied.[154] The rule, originally described by Hanley and Lippman-Hand in 1983, is probably summarized best as a means for "estimating the worse case that is compatible with the observed data."[155] For the purposes of registries, this rule must be carefully applied since it assumes complete reporting of all events that occur in the study population and that the study population is an accurate representation of the intended population. Nonetheless, this rule of thumb provides some guidance regarding registry size and interpretation of results.

Challenges

In planning a registry for safety, it is essential to consider how patients will be identified and recruited from the perspective of understanding which types of patients are included, and equally, if not more importantly, what types of patients are likely *not* to be included in the registry. For example, safety registries often seek information about all treated patients, regardless of whether the product is prescribed for an approved indication. While it is conceptually straightforward to design a registry that would include information on all product users, the practical difficulties include raising awareness about the existence of the registry, the desirability and importance of collecting information on all treated patients, and the challenge of specifying the adverse events and other events of interest without causing undue concern about product safety. Drawing attention to the registry among healthcare providers who use the treatments off-label is especially challenging, due to competing concerns of being inclusive enough to capture all use – on-label or not – and, if the sponsor of the registry is also a manufacturer, avoiding the appearance of promoting off-label use when contacting physician specialties who are known to use the product off-label. In addition, diseases targeted for off-label use may be markedly different from indicated uses and pose different safety issues. In Europe, when there is limited knowledge about the safety of the product pre-authorization and a registry is part of a risk management plan, manufacturers may be required, prior to launch of the product, to notify all physicians who may possibly prescribe the product about the existence of a registry (sometimes also called in this context a post-authorization safety study or PASS), including details of how to register patients.

It is more challenging to be able to evaluate the utility of a registry when the entire population-at-risk has not been included; however, this situation is far more common than registries capturing every single treated patient, and therefore merits careful consideration. Registries organized for research purposes are typically voluntary by design, thereby undermining most efforts for inclusiveness. Two key questions concern the target population, in terms of representativeness and the potential to generalize the results, and the size of the registry. When considering the target population, it is important to assess (1) whether the patients in the registry are representative of typical patients and (2) what types of patients may be

systematically excluded or not enrolled in the registry. For example, do patients come from a diverse array of health care settings or are they only recruited from tertiary referral hospitals, in which case the patients can be expected to be more complicated or have more advanced disease than other patients with a similar diagnosis? Are there competing activities in the target population, such as large registration trials or other observational studies, that may skew participation of sites or patients? (See Chapters 3 and 13 for more information on representativeness). The ability to use registries for quantification of risk is highly dependent on understanding the relationship between the enrolled population and the target population. While it is intellectually appealing to dismiss the value of any registry that does not have complete enrollment of all treated patients or a documented approach to sampling the entire population, registries that systematically enroll typical patients can be tremendously informative and may be the only way that data can be collected because of legal constraints on the use of registries.

Consider, for example, the National Registry for Myocardial Infarction (NRMI), one of the first cardiac care registries.[156] NRMI was originally intended to obtain information about time to treatment for patients presenting with myocardial infarction to acute care hospitals. The program ultimately resulted in 70 publications (out of more than 500) that provided detailed information on both specific adverse events for specific products and comparative information on safety events. Although this registry was quite large in terms of hospitals and patients, it included neither all MI patients nor all patients on the product for which it described safety information, but was considered to be broadly representative of typical MI patients who presented for medical care.

Defining exposure and risk windows. Many patients will enter a registry at various stages in their disease course or medical management of their disease. Therefore, it is essential to collect information on the timing of events in relation to the initial diagnosis and in relation to the timing of treatments. It is simplest to collect pre-specified clinical data recorded on standardized forms at scheduled assessments, which leads to uniformity within the analysis. However, many registry patients present themselves for data collection on a more naturalistic schedule (i.e., data are collected whenever the patient returns for followup care, whether or not the visit corresponds to a pre-specified data collection schedule). The more haphazard schedule is more reflective of 'real-world' settings, yet results in non-uniform data collection for all subjects. Rather than discard this non-uniform data, it can be analyzed both by categorizing patient visits in terms of time windows of treatment duration (e.g., consider data from all visits occurring within thirty days of first treatment, then within 90 days, 180 days, etc.), and also by using time in terms of patient days/years of treatment. This type of analysis facilitates characterization of the type and rate of occurrence for various adverse events in terms of their induction period and patient time at risk. When the collection of adverse event data is completed through an ongoing active process and is expected to be long term, periodic analysis and reporting should be structured around specified time points (e.g., annually, semi-annually or quarterly) and may align with the periodic safety update reports. The rigor of pre-specified reporting schedules requires periodic assessment of safety and can support systematic identification of delayed effects.

In addition to variability in the timing of followup, consideration must be given to other recognized aspects of product use in the real world, namely switching therapies during followup, use of multiple products in combination or in sequence, dose effects, delayed effects, and patient compliance. The current real world practices for the treatment of many conditions, such as chronic pain and many autoimmune diseases, include either agent rotation schemes or frequent switching until a balance between

effectiveness and tolerability is reached, which creates significant difficulties in determining exposure-outcome relationships. Switching between biologics may lead to problems with immunogenicity because even products that are clinically the same, as in the case of the erythropoietins, will have different immunogenic potential due to differences in manufacturing processes and starting cell lines. In addition, as with many clinical studies, patient adherence during registry followup is an important confounder to consider. Over time, patients may take drug holidays and self-adjust dosages, and these actions should be, but are not always, captured via the data collected in the registry, especially if the interval between followup time points is long or the action is not known by the treating physician. Assessing the temporality of unanticipated events may then be hampered by the inability to fully characterize exposure.

Delayed effects may include late onset immunogenicity, the development of subclinical effects associated with chronic use that are not appreciated until years later, and effects that develop after stopping treatment as a result of products with a long half-life or extended retention in the body. An example of this can be seen in the case of bisphosphonates used for bone resorption inhibition in the treatment of osteoporosis where the product is retained in the bone for at least 10 years after stopping therapy, and there is some evidence that long-term bone turnover suppression puts patients at increased risk of osteonecrosis and nonspinal fractures.[157] In addition, many biologics aimed at immunomodulation carry an increased risk of future malignancy that is not fully appreciated, as do novel therapies directed at angiogenesis. Although registries are well suited to long term followup, consideration must be made for how long is long enough to appreciate these effects.

Non-compliance can have a substantial effect on the ability to assess adverse events, in particular if dose or cumulative dose effects are suspected. Patient compliance may be affected by expense, complexity of dosing schedule, convenience/mode of administration, and misunderstanding of appropriate administration, and is not fully ascertained by data sources that capture prescriptions rather than actual product use. With products used to treat chronic diseases it is possible to estimate compliance in electronic health records by first estimating when repeat prescriptions should be issued, and then measuring the observed versus expected frequency. Although registries may be directly designed to track compliance through patient diaries and other methods of direct reporting, challenges remain in accurately capturing compliance and minimizing recall bias.

Special Conditions: Pregnancy Registries

The use of specially-designed registries for specific safety monitoring has a long history. For example, pregnancy registries are commonly used to monitor the outcomes of pregnancies during which the mother or father was exposed to certain medical products. The Antiretroviral Pregnancy Registry is an example of a registry that collected information on a broad class of products to determine the risk of teratogenesis.[158] Pregnancy registries provide in-depth information about the safety of one or more products and are particularly useful since, unless the product is used for life-threatening diseases or to treat a pregnancy related illness, pregnant women are generally excluded from clinical investigations used for product approval. Registries and other observational studies, by virtue of being sustainable over longer periods of time and more amenable to small site-to-patient ratios than registration trials, can facilitate the active surveillance of safety in these populations. In addition, using computerized claims or billing data for pregnancy safety monitoring is hampered by patients often not presenting early in pregnancy, lack of relevant data on other exposures (since these are often unrelated to reimbursement), and difficulty linking maternal and infant records. Therefore, direct, prospective data collection currently

remains the best source of meaningful safety data related to pregnancy. A challenge for pregnancy registries is to identify and recruit women early enough in pregnancy to obtain reliable information on treatments used during the first trimester, which is a critical time for organogenesis, and to obtain information about early pregnancy loss, since this information is not always volunteered by women. It is also important to obtain information on treatments and other putative exposures before the outcome of the pregnancy is known, so as to avoid selective recall of exposures by women experiencing bad pregnancy outcomes.

Special Conditions: Orphan Drugs

A product may be designated an orphan drug (or biologic, or medicine in the EU) if it fulfils certain conditions which include being used for the diagnosis, prevention, or treatment of life-threatening or chronically debilitating conditions affecting a small number of patients. Often these diseases are extremely rare, and dossiers submitted for authorization purposes may have only tens of patients included in clinical trials. Obviously, the safety profile of such products is extremely limited, and follow up of patients treated with the product post-authorization is likely to be a requirement.

With some orphan drugs, the disease may have been usually fatal before therapy was available. These products pose special problems in trying to determine the safety profile of the product, in that the natural history of the disease when treated is not known, and trying to disentangle the effects of the product from those of the ongoing disease may be particularly problematic. In many of these diseases, the problem may be due to faulty enzymes in metabolic pathways leading to accumulation of toxic substrates that cause the known manifestations of the disease. Treatment may involve blocking another enzyme or pathway leading to the accumulation of different substances for which the effects may also not be known but are less immediately toxic. In this situation, with a fatal disease and a first product with proven efficacy, it would not be ethical to randomize patients in a trial versus placebo for an extended period of time, and so a registry may be the only effective means of obtaining long-term safety data. Registries in these situations may make meaningful contributions to understanding the natural history of the disease and the long-term effects of treatment, sometimes largely by virtue of the fact that most patients can be included and long-term followup obtained for orphan products.

Special Conditions: Controlled Distribution/PLAS

Registries may also be part of risk evaluation and mitigation strategies (REMS) in the U.S., such as restricted distribution systems, referred to as performance-linked access systems (PLAS), which may be used to monitor the safety of marketed products. One of the earliest PLAS was a blood-monitoring program for clozapine ("no blood, no drug") implemented in 1990 to prevent agranulocytosis. Other examples include the STEPS program for thalidomide (System for Thalidomide Education and Prescribing Safety), implemented in 1998 to prevent fetal exposure; the TOUCH controlled distribution for nataluzimab (Tysabri) for patients with multiple sclerosis to detect the occurrence of progressive multifocal leukoencephalopathy (PML); and the iPLEDGE system implemented for isotretinoin in 2006, which tightly links the dispensing of isotretinoin for female patients of child-bearing potential to documentation of a negative pregnancy test, to prescriber confirmation that contraceptive counseling has occurred, and to prescriber and patient identification of contraceptive methods chosen. In many of these programs, access to the product is linked directly to participation in a registry. Therefore, all patients treated with this product should be in the registry because they cannot otherwise obtain access to this treatment. The registry is looking for a known adverse event (such as PML) and collects data specifically

related to that adverse event. The registry also collects information on other factors that may raise a patient's individual risk for developing this adverse event, which helps provide important clinical context that would not otherwise be available in a systematic fashion on a large population of treated patients.[159] While PLAS registries are driven by safety concerns, they are primarily focused on prescribing or dispensing controls rather than signal detection. As a result, they utilize very limited data collection forms to minimize burden, and this can limit their utility for certain types of analyses.

In Europe, use of registries for risk minimization activities can be more problematic due to differences in national legislation and enactment of the data protection directive. In some countries, it is possible to mandate registration of patients in relation to particular products (e.g., clozapine in the UK and Ireland), but, in others, other methods must be found. For these reasons, registries are more frequently used on a voluntary basis to monitor safety and capture adverse events, while controlled distribution with compulsory distribution of educational material, prescribing algorithms, and treatment initiation forms to anyone likely to prescribe the product, forms the risk minimization component. Despite the fact that patient registration is voluntary, high enrollment rates can be achieved particularly when physicians recognize that information on the safety profile of the product is limited.[160] Obviously, if a product has a high potential for off-label use, patients enrolled in a registry may not be generalizable to all those treated with the product, but this can be factored into data analysis and interpretation. A voluntary registry coupled with controlled distribution may, in fact, be reasonably representative, since off-label use may be severely limited by difficulties in obtaining the product.

Special Conditions: Medical Devices

Medical devices pose different analytic and data challenges from drugs. On the one hand, it is much more straightforward to identify when a device is implanted and explanted if those records can be obtained; however, since not all medical devices are covered by medical insurance, it can be more difficult to identify all the appropriate practitioners and to locate all the records. Medical devices that can be attached and detached by the consumer, such as hearing aids, are very difficult to study, in that, much like products used on an as-needed basis, special procedures are required to document their use; these procedures are costly and intrusive, and are rarely used.

Nonetheless, despite the challenges, the safety of medical devices is very important due to their widespread use; in particular, long-term in-dwelling devices, for which recall in the event of a malfunctioning product, is inherently complicated. For example, in the late-1970s/early-1980s when a particular type of Bjork-Shiley prosthetic heart valve was found to be defective and prone to fracture, leading to sudden cardiac death in the majority of cases, detailed studies of explanted devices, patient factors, and manufacturing procedures led to important information that was used to guide decision-making about which devices should be explanted.[161,162] Identification of the characteristics of valves at high risk of failure was very important due to the peri-operative mortality risk from explanting a heart valve, regardless of its potential to fail. This same logic applies to many other medical devices that are implanted and intended for long-term use. Some of the challenges relating to studying medical devices have to do with being able to characterize and evaluate the skill of the "operator," or the medical professional who inserts or implants the device. These operator characteristics may be as, or more, important in terms of understanding risk than the characteristics of the medical devices, themselves.[163]

Registries Designed for Purposes Other Than Safety

The role of registries not specifically designed for safety to detect adverse events is not clearly defined. These registries may be designed to fulfill any number of other purposes, including examining comparative effectiveness, studying the natural history of a disease, providing evidence in support of national coverage decisions, or documenting quality improvement efforts. These registries may gather data on adverse events and report those data (to regulatory authorities, manufacturers or others), but the registry may not be able to reliably detect all events, which would result in an underestimation of the true risk in the exposed population(s). A strength of comparative effectiveness registries, however, lies in the systematic collection of data for both the product of interest and concomitant, internal controls.

As an example of the limitations of assessing safety events in registries not designed for safety, a registry may be sponsored by a payer to collect data on every person receiving a certain medication. The purpose of the registry may be to assess prescribing practices and determine which patients are most likely to receive this product. The registry may also contain useful data on events experienced by patients exposed to the product, but may not be considered a comprehensive collection of safety data, or may provide information regarding a known risk or outcome rather than generating data that could identify a previously unappreciated event. Alternatively, a registry may be designed to study the effectiveness of a new product among a population subset, such as the elderly. The registry may be powered to analyze certain outcomes, such as re-hospitalizations for a condition or quality of life, but may not be specifically powered to assess overall safety in this population.

It is more challenging to accurately and precisely detect adverse events of interest when a registry has not been designed for a specific safety purpose. In this situation, the registry must collect a wide range of data from patients to try to catch any possible events, or be adapted later should safety become a primary objective. Some events may be missed because the registry did not anticipate them and did not solicit data to identify those events. Also, much the same as for registries designed specifically to detect adverse events, some events may be so rare that they do not occur in the population enrolled in the registry or do not occur during the registry followup period. In these circumstances, registries can be designed to provide useful data on some of the events that may occur in the exposed population. Such data should not be considered complete or reliable for determining event rates however, but, when combined with other sources of safety data, trends, or signals, may become more apparent within the dataset.

Ad Hoc Data Pooling

One way to capitalize on data collected for another purpose, which may be insufficient for meaningful stand-alone analysis and interpretation due to study size or lack of comparators, is to pool with other, similar data. As with any pooling of disparate data, the use of appropriate statistical techniques and the creation of a core dataset for analysis is critical and is highly dependent on the consistency in treatment and event coding and case identification. Adverse event data coded using the same coding dictionary (i.e., MedDRA) may still be plagued by an inconsistency in the application of coding guidelines and standards. Re-coding of verbatim event reports may be required, if feasible, prior to analysis. Depending upon the purpose for which the data were collected, data on the treatments of interest are not always recorded, or are recorded with the specificity needed to understand risk (e.g., branded versus generic; dosage; route of administration, batch). Another consideration is differential followup, including the duration and vigor of followup in the registries to be pooled. Particular care is needed when combining datasets from different European countries since differences in medical practice and reimbursement may

mean that superficially similar data may actually represent different subgroups of an overall disease. Similar caution is also advisable when combining information from disparate health systems within a single country, as some treatments of interest may be non-covered benefits and consequently not recorded in health system records. An alternative to pooling data is to conduct meta-analyses of various studies using appropriate statistical and epidemiologic methods.

While the types of registries described above may not be individually powered to detect safety issues, combining data from registries for other purposes could significantly enhance the ability to identify and analyze safety signals across broader populations. Core datasets for adverse events have been suggested for electronic health records systems and as part of national surveillance mechanisms (e.g., through distributed research networks). In such a network, each participating registry or data source collects a standardized core data set, from which results can be aggregated, to address specific surveillance questions. For example, there is significant national interest in understanding the long-term outcomes of orthopedic joint implants. Currently, there are several prominent registries in the U.S. with varying numbers of types of patients and types of implants. Many of these registries collect data for quality improvement purposes, but have sufficient data elements to potentially report on adverse events. However, only by aggregating common datasets across many of these registries can a representative population be evaluated and enough data accrued to understand the safety profile of specific types of devices in particular populations.[A]

As described above, while not every registry is designed to evaluate safety, even registries designed for other purposes might contribute to aggregate information about potential harm from healthcare products or services. Yet, many registries, especially disease registries, are conducted by non-regulated entities, such as provider associations, academic institutions, and non-profit research groups, whose role in adverse event reporting is unclear. Furthermore, sample sizes needed to understand safety signals are generally much larger than those needed to achieve useful information on quality of care or the natural history of certain diseases, and the analyses can require a high degree of statistical sophistication. Enrolling additional patients or committing additional resources for specialized analyses in order to achieve a general societal benefit through safety reporting is not feasible for most registries whose primary purpose is not safety. However, encouraging registries to participate in aggregation of data when such participation is at minimal cost and enhances the common good may be both reasonable and appropriate. Many efforts are underway to improve the feasibility of broader safety reporting from both registries and electronic health records that serve other purposes. These efforts include recommending standardized core data sets for safety to enhance the aggregation of information in distributed networks and making registries interoperable with facilitated safety reporting mechanisms or other registries designed for safety.[164] As facilitated reporting methodologies become more common and easy for registries to implement, there will be fewer reasons for non-participation. In addition, linkage of population-based registries, such as the Surveillance, Epidemiology and End Results cancer registry

[A] It is essential to have an understanding of how every data set that will be used was created. For example, what is recorded in administrative health insurance claims depends largely on what benefits were covered and how medications are dispensed. Non-covered items generally are not recorded. For example, mental health services are often contracted for under separate coverage (so-called 'carve-outs'), and not covered under traditional health insurance coverage; thus the mental health consultations are not likely to be included in administrative databases derived from billing claims data. Also, some injectable medications (e.g., certain antibiotics) may be administered in the physician's office and thus would not be recorded through commonly used pharmacy reporting systems that are based on filling and refilling prescriptions. The absence of information may lead to false conclusions about safety issues.

program(SEER), with other data sources, such as Medicare, have proven invaluable for evaluating safety and other outcomes.

Signal Detection in Registries and Observational Studies

Although subject to debate, according to the World Health Organization (WHO) definition, a safety signal is defined as, "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously." Hauben and Aronson (2009) define a signal as, "information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verificatory and, when necessary, remedial actions."[165] The authors further posit that signals, following assessment, could subsequently be categorized as indeterminate, verified, and refuted.

Additional attempts at defining or describing a safety signal for purposes of guiding product sponsors, regulators, and other researchers have come from various sources, including CIOMS, the FDA, and the MHRA. Nelson and colleagues recently provided the FDA with a comprehensive evaluation of signal detection methods for use in post-market surveillance, and included a discussion of "conventional Phase IV observational safety studies," which would encompass registries, as part of a multi-pronged approach to surveillance.[166] They note that despite a focus on automated health care data sources, such as large health care claims databases for primary surveillance and as the basis for the Sentinel Network, the need for more detailed data regarding exposure and outcome measurement, as well as collection of relevant confounder data, will require that prospective observation studies be conducted to address pre-specified safety-related hypotheses.

Establishing a threshold of effect size and robustness of data that would justify action, such as initiation of additional studies, FDA action, or changes in payer coverage, remains an important question and is unlikely to be uniformly applicable to all products and situations. A draft guidance report is expected from the CIOMS Working Group VIII, whose main goal is to harmonize the development, application, and interpretation of signal detection methods for use with drugs, vaccines, and biologics.

Once a signal that warrants further evaluation is identified, it is typically assessed based on the strength of the association between exposure and the event; biological plausibility; any evidence provided by dechallenge and rechallenge; the existence of experimental or animal models; and the nature, consistency, and quality of the data source.[167] Signals may present themselves as idiosyncratic events affecting a subset of the exposed population who are somehow susceptible, events related to the pharmacological action of the drug, or increased frequency of events normally occurring in the population (such as in the example of cardiovascular events and rofecoxib). Signals may involve the identification of novel risks, or new (or more refined) information regarding previously identified risks. If an event does appear to be product-related, further inquiry is required to examine whether the occurrence appears to be related to a specific treatment, a combination or sequence of treatments, or a particular dosage and/or duration of use. Events with long induction periods are particularly challenging for ascribing a causal relationship, since there are likely to be many intervening factors, or confounders, that could account for the apparent signal.

The constant challenge is to separate a potential safety signal from the "noise," or, in other words, to detect meaningful trends and to have a basis for evaluating whether the signal is something common to

people who have the underlying condition for which treatment is being administered, or whether it appears to be causally related to use of a particular product. All methods currently used for signal detection have their limitations. Attempts to use quantitative, and in some cases, automated signal detection methods as part of pharmacovigilance, including data mining using Bayesian algorithms or other disproportionality analyses, are hampered by confounders and other biases inherent to spontaneously reported data.[168,169] Other methodologies also attempt to identify trends over time and include potential patterns associated with other patient characteristics, such as concomitant drug exposures.

These methods of automated signal detection lack clinical context and only draw attention to deviations from independence between product exposure and events. No conclusions regarding causality can be drawn without a further qualitative assessment of extrinsic factors (e.g., an artificial spike in reporting due to media attention) and potential confounders. Depending on the original data source, the ability to address these issues within the database, itself, may be impossible and either abstracted medical record data or prospective data collection is required to gather reliable data. The long-term followup and longitudinal data generated by many registries merits particular methodological considerations, including how often to perform testing, what threshold is meaningful for a given event, and does that threshold change over time.

While some registries can serve as a source of initial safety signaling or hypothesis generation, they also may be utilized for further investigation of a signal generated from surveillance and quantitative analysis. As an example, existing data from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), sponsored by the Swedish Health Authorities, was used to look at long term outcomes related to bare-metal and drug-eluting stents once it became clear through FDA-designed and other registries in the post-market setting that off-label use was very common and the risk of restenosis and other long-term outcomes in the real world patient population were not fully understood. Due to the existence of comprehensive national population registries in Sweden, researchers were able to reliably combine SCAAR data, which captured unselected ,consecutive angiography and percutaneous coronary intervention procedure data with vital status and hospitalization data, to examine fatality rates and cardiac events on a population level.[170] This use of procedure and national registries provides an example of a registry including a well-defined population allowing for safety assessments coincident with comparative effectiveness.

Potential Obligations for Registry Developers in Reporting Safety Issues

In considering what actual and potential obligations there are, or may be, for registries in product safety assessment, it is useful to separate the issues into several parts. First, there are two key questions that can be asked for each registry: (1) What is the role of registries not designed for safety purposes to look for adverse events? and (2) what are the obligations, especially for those registries not sponsored by regulated manufacturers, to further investigate and report these findings? As discussed above, registries can be classified by whether or not they were designed for a safety purpose, and also by whether or not they have specified regulatory obligations for reporting. Beyond these distinctions, several factors need to be considered, including the ethical obligations of the registry developer, the technical limitations of the signal detection, and resource constraints.

Registries designed for safety assessment purposes should have a clear and deliberate plan in place for not only detecting the signal of interest, but for how they intend to handle unanticipated events and what, and how, any such events will be reported to appropriate authorities. Only in the case of registries supported by the regulated industries are rules for reporting drug or device adverse events explicit. Therefore, it would be helpful if other registries would also formulate plans that ensure appropriate information will reach the right stakeholders (either through reporting to the manufacturer or directly to the regulator) in a timely manner similar to those required by the regulated industries, as there should not be two different standards for reporting information intended to safeguard the health and well-being of all.

Registries that are not designed specifically for safety assessment purposes, particularly those that are not sponsored by a manufacturer, raise issues that are more complex. While researchers have an obligation to the patients enrolled in any research activity to alert them should information regarding potential safety issues become known, it is less clear how far this obligation extends. In the UK, the General Medical Council includes in its advice on "Good Medical Practice" the requirement to "report suspected adverse drug reactions in accordance with the relevant reporting scheme." [171] It is therefore clear that contributing to the safety profile of a medicine is regarded there as part of the duties of a medical practitioner. During its review of research registries, an institutional review board (IRB) or ethics committee (EC) may specify the creation of an explicit incidental findings plan prior to approval. Such a plan is often a part of studies producing or compiling non-clinical imaging and genetic data. In addition, some investigators will have an obligation to report to an IRB or EC any unanticipated problems involving risks to subjects or others under the federal regulations on human research protections. In turn, IRBs and ECs have an obligation to report such incidents to relevant federal authorities.

At a minimum, all registries should ensure that standard reporting mechanisms for adverse event information are described in the registry's procedural documents. These mechanisms should also be made clear to investigators and, where feasible, those efforts can be facilitated. For example, all registries in the U.S. can make available to registry participants access to the MedWatch forms [172] and train those investigators on appropriate use of those forms for reporting spontaneous events. As described earlier, in the near future it should be possible for registries that collect data electronically to actually facilitate the reporting of adverse events by using open standards. This is attractive because it both reduces the work of the investigator in generating the report, and ensures that it will go to a surveillance program that is prepared to investigate and manage both events and potential safety signals.

Obligations beyond facilitation are less clear. Furthermore, there are both technical and resource obstacles to thoroughly investigating potential signals and risks of generating inaccurate and potentially injurious information (e.g., publicized product safety issues can result in discontinuation of use of potentially life-saving products by some patients, regardless of the strength of the scientific evidence). As described earlier, registries designed for safety assessment should ideally have both adequate sample size and signal evaluation expertise in order to assess safety issues. Registries not designed for safety purposes may not have enough patients or statistical signal detection expertise to investigate potential signals, or it may not have the economic resources to devote to unplanned analyses and investigations. It would seem that, as a minimum, registries not designed for safety purposes should use facilitated reporting (via training, providing forms, etc.) of individual events through standard channels to meet their ethical obligations, and that they should check with any institutions with which they are affiliated to

determine whether they are subject to additional reporting requirements. However, should a registry identify potential signals through its own analyses, there are obligations that arise.

While registries that are approved under IRBs report safety issues to those IRBs, what may need more definition is how incidental analytic findings, which may represent true or false signals, should best be further investigated and reported for the public good. One approach would be to report summary information to the relevant regulatory authority for further evaluation. For avoidance of doubt, registry developers should consider these issues carefully during the planning phase of a registry, and should explicitly define the practices and procedures for adverse event detection and reporting, the planned analyses of adverse events, and how incidental analytic findings will be managed. Such a plan should lay out the extent to which registry owners will analyze their data for adverse events, the timing of such analyses, what types of unanticipated issues will be investigated internally, what thresholds would merit action, and when information will be provided to regulators or other defined government entities, depending on the nature of the safety issue.

Conclusion

The ongoing challenge in the use of both existing data and prospective data collection efforts, such as registries, is casting a wide enough net to capture not only rare events, but moreover, more common events and events that are not anticipated (i.e., not part of a pre-approval or post-approval potential risk assessment). In some cases, existing registries may add additional data collection to address questions regarding possible adverse events that arise after registry initiation. In addition, it must be considered that all observational data sources are only as strong as their ability to measure and control for potential biases, including confounding and misclassification. Large registries, linkage and distributed network schemes, and sentinel surveillance are all tools being actively developed to create an integrated approach to medical product safety and, specifically, to signal detection and verification. In contributing to the evidence hierarchy surrounding the generation of signals for detection and confirmation of potential adverse events, registries are likely to make their strongest contributions through: detection of novel adverse events associated with product use as reported by treating physicians, which, in turn, constitutes a signal necessitating further study; through the establishment of registries of pregnant women and other hard to study subpopulations of product users; through the linkage of registries with additional data sources such as the Medicare-SEER data linkage, thereby broadening the range of questions that can be addressed beyond the constraints of data collected for a registry; and through the use of registries to confirm or validate signals generated in other data, such as from automated signal generation in large claims databases. Ideally, a clear and prospective understanding among stakeholders is needed regarding if, and under what, circumstances signal monitoring within registries is appropriate, the timing or periodicity of any such analyses, what should be done with the information once it is identified, and what, if any, are the ethical obligations for collecting, analyzing, and reporting safety information, if not a planned objective of the registry, and the registry sponsor is not directly required to conduct such reporting by regulation.

Thoughtfully designed registries can play an important role in these newly emerging strategies that seek to utilize multiple available data sources to generate and strengthen hypotheses in product safety. However, as with all data sources, it is important to assess the effects of registry design, the type of data, reason for the data collection, how the data were collected, and the generalizability to the target

population to assess the strengths, weaknesses, and validity of the results provided and their contribution to the knowledge of the safety profile of the medicine or device under study.

Case Example 12: Using a registry to assess long-term product safety

Description:	The British Society for Rheumatology Biologics Register (BSRBR) is a prospective observational study conducted to monitor the routine clinical use and long-term safety of biologics in patients with severe rheumatoid arthritis and other rheumatic conditions. The United Kingdom-wide national project was launched after the introduction of the first tumor necrosis factors (TNF) alpha inhibitors.
Sponsor:	The British Society for Rheumatology (BSR) commissioned registry, which receives restricted funding from Abbott Laboratories, Biovitrum, Schering Plough, Roche, and Wyeth Pharmaceuticals. The registry is managed by the BSR and the University of Manchester.
Year Started:	2001
Year Ended:	Ongoing
No. of Sites	All consultant rheumatologists in the United Kingdom who have prescribed anti-TNF therapy participate.
No. of Patients:	Over 17,000

Challenge

Rheumatoid arthritis (RA) is a progressive inflammatory disease characterized by joint damage, pain, and disability. Among the pharmacologic treatments, non-biologic disease-modifying anti-rheumatic drugs (DMARDs) are considered the first-line treatment. Novel biologic therapies represent a new class of agents that prevent inflammation and have demonstrated efficacy in RA patients. The most commonly used biologics are tumor necrosis factors (TNF) α inhibitors (i.e., etanercept, infliximab, and adalimumab). However, results from clinical trials and pharmacovigilance studies have raised potential safety concerns, and limited long-term data on these therapies are available. Of particular concern has been an increase of tuberculosis observed in patients treated with anti-TNF therapy.

Proposed Solution

A prospective observational registry was launched in 2001 to monitor the safety of new biologic treatments. The registry collects data on response to treatment and potential adverse events every six months, and patients are followed for the life of the registry. Over 4,000 patients are enrolled for each of the anti-TNF agents (i.e. etanercept, infliximab, and adalimumab), and the registry represents approximately 80 percent of RA patients treated with these biologics in the United Kingdom. In addition to patients receiving anti-TNFα therapy, the registry has enrolled a control cohort of patients receiving non-biologic DMARDs.

Results

Data from the registry was analyzed to determine whether an increased risk of tuberculosis existed in RA patients treated with anti-TNF therapy (Dixon et al, 2009). In over 13,000 RA patients included up to April 2008, 40 cases of TB were observed in the anti-TNF cohort and no cases in the DMARD group. A differential risk was reported among the three anti-TNF agents, with the lowest risk observed in the etanercept group. The incidence rates were 144, 136, and 39 cases per 100,000 person years for adalimumab, infliximab, and etanercept, respectively. In addition, the incidence rate ratio, median time to events, and influence of ethnicity were evaluated.

Key Point

As novel drugs and treatments are developed and licensed, registries may be useful tools for collecting long-term data to assess known and emerging safety concerns.

For More Information

Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A, Symmons DPM. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: Results from the British Society for Rheumatology Biologics Register (BSRBR). Annals of the Rheumatic Diseases. Published online 22 Oct 2009; doi: 10.1136/ard.2009.118935.

Zink A, Askling J, Dixon WG, Klareskog L, Silman AJ, and Symmons DPM. European biological registers: methodology, selected results and perspectives. Annals of the Rheumatic Diseases. 2009; 68: 1240-1246.

Case Example 12: Using a registry to monitor long-term product safety

Description:	SINCERE™ (Safety in Idiopathic arthritis: NSAIDs and Celebrex Evaluation REgistry) is a multi-center registry designed to monitor the long-term safety of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with juvenile idiopathic arthritis (JIA). The registry includes patients ages 2 to 17 and collects demographic, developmental, clinical, and safety data. The followup period is at least 2 years, and may be as long as 4 years for some patients.
Sponsor:	Pfizer, Inc.
Year Started:	2009
Year Ended:	Ongoing
No. of Sites	16 sites in the U.S.
No. of Patients:	Planned enrollment of 200 patients on celecoxib and 200 patients on other NSAIDs

Challenge

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used for more than 30 years to relieve pain and inflammation in juvenile idiopathic arthritis (JIA), and it is estimated that 80 to 90 percent of JIA patients will use a NSAID at some point. However, little is known about the long-term safety of chronic use of NSAIDs in children with JIA. This question is particularly important as many children with JIA will continue to use NSAIDs well into adulthood. Due to the rarity of JIA and the special ethical issues surrounding children's participation in experimental studies, randomized controlled trials of NSAIDs in JIA are considerably smaller and of shorter duration than adult arthritis trials; the pivotal trial for celecoxib in JIA, one of the largest NSAID JIA studies, had 100 patient-years of exposure. In addition, randomized trials may not be generalizable to typical JIA populations. Lastly, it is unclear if the emerging safety concerns in adult NSAID and celecoxib users translate to children who are much less likely to develop serious thromboembolic cardiovascular or gastrointestinal bleeding events.

The development of a long-term, observational study was necessary to address these knowledge gaps, fulfill a post-marketing safety commitment, and respond to concerns of regulators, patients, and physicians.

Proposed Solution

This multicenter registry was designed to gather long-term safety data on NSAIDs use in children with JIA and is currently enrolling a quasi-inception cohort of patients aged 2-17 years and >10 kg prescribed (not more than 6 months prior) either celecoxib (n = 200) or other NSAIDs (n = 200). Pediatric rheumatologists from 16 sites in the U.S. enter data quarterly for the first 12 months and twice annually thereafter. The registry intends to follow all patients for at least 2 years but may be as long as 4 years, as all patients are encouraged to remain in the registry until the last patient completes the minimum follow up. Concomitant medications and treatment switches are permitted, and patients will be followed for residual effects even if NSAID treatment is discontinued.

Targeted events of interest (i.e., cardiovascular, gastrointestinal, and hypertension) and general safety (serious and non-serious adverse events (AE)) are collected in a systematic manner. The Common Terminology Criteria for Adverse Events (CTCAE ver 3.0) criteria are used to both code and grade all AEs to minimize variability across physicians. In designing the registry, particular attention was paid to collect potential covariates relevant to confounding by indication, given the expected differential prescribing between celecoxib and other NSAIDs. The analyses will summarize the incidence of the targeted events and AEs in general, and exploratory analyses may further characterize AE rates by JIA subtype, dose/duration of NSAID therapy, or other clinical and demographic factors.

Results

When complete, the registry should provide substantial (800 patient-years, at minimum), additional safety data on NSAIDs and celecoxib used for JIA in routine clinical practice. This information may facilitate appropriate therapeutic decision-making for doctors and patients.

Key Point

Registries may be a useful tool for examining long-term product safety, particularly in populations such as children, that are difficult to study in a randomized controlled trial.

Case Example 13: Identifying and responding to adverse events found in a registry database

Description:	The Kaiser Permanente National Total Joint Replacement Registry (TJRR) was developed by orthopedic surgeons to improve patient safety and quality and to support research activities. The TJRR tracks all Kaiser Foundation Health Plan members undergoing elective primary and revision total knee and hip replacement. The purposes of the registry are to 1) monitor revision, failure, and rates of key complications; 2) identify patients at risk for complications and failures; 3) identify the most effective techniques and implant devices; 4) track implant usage; and 5) monitor and support implant recalls and advisories in cooperation with the U.S. Food and Drug Administration. The TJRR uses an electronic medical record (EMR) system to collect uniform data at the point of care. Data are abstracted from the EMR to the registry and followup data is collected through several methods.
Sponsor:	Funded by the Kaiser Foundation Health Plan
Year Started:	2001
Year Ended:	Ongoing
No. of Sites	350 surgeons at 50 medical centers
No. of Patients:	85,000 total joint replacements

Challenge

The registry collects standardized total joint pre-operative, operative, and post-operative data to supplement administrative data collected through the electronic medical record system. The registry database includes information on patient demographics, implant characteristics, surgical techniques, and outcomes. As a result, the registry provides opportunities for total joint replacement surveillance and monitoring, butthe depth and breadth of the data make manual data reviews for adverse events too resource-intensive and time-consuming.

Proposed Solution

Electronic screening algorithms were developed to detect adverse events (AEs) in the registry database in a timely, efficient manner. The algorithms use ICD-9 codes and CPT codes to identify complications of joint replacement surgery, such as revisions, re-operations, infection, and pulmonary embolism. All complications that are picked up by the screening algorithms are validated with a chart review. The screening algorithms are run and the results monitored on a regular basis to identify any trends.

The registry can also run specific queries to respond to physician concerns. For example, if physicians at participating medical centers notice a problem with an implant or hear about a problem from colleagues, they can request an ad-hoc query of the registry database. The query can identify all patients receiving a particular implant and assess outcomes. In cases where the outcome of interest is not part of the registry database, the registry staff may perform additional followup through chart review. The staff may also check the Food and Drug Administration's Medical Product Surveillance Network (MedSun) to validate their findings against other data sources.

Once an implant has been recalled or when there is an advisory or concern, the registry can immediately generate a list of all patients who received that implant and notify their physicians. The registry can also identify complications and assess revision rates among its patients who received that implant. In addition, the registry staff monitors the outcomes of patients who received the implant through the revision surgery,

death, or loss to followup.

Results

Since its launch in 2001, the registry has assisted participating physicians with their response to several implant recalls and advisories. Data from the registry were used to identify surgical techniques that resulted in higher revision rates. The registry staff shared this information with physicians, resulting in reduced use of these techniques.

Key Point

Electronic screening algorithms offer an efficient method of identifying potential AEs in large data sets in a timely manner. For such algorithms to be effective, the registry database must collect detailed information on the implants' lots and catalog numbers and must be updated frequently, as new and modified products become available. In addition, when using medical codes, it is important to validate the results of the screening algorithm to ensure that coding errors have not affected the findings.

Chapter 5: Data Elements

Selection of data elements for a registry requires a balancing of potentially competing considerations. These considerations include the importance of the data elements to the integrity of the registry, their reliability, their necessity for the analysis of the primary outcomes, their contribution to the overall response burden, and the incremental costs associated with their collection. Registries are generally designed for a specific purpose, and data elements that are not critical to the successful execution of the registry or to the core planned analyses should not be collected unless there are explicit plans for their analysis.

The selection of data elements for a registry begins with the identification of the domains that must be quantified to accomplish the registry purpose. The specific data elements can then be selected, with consideration given to clinical data standards, common data definitions, and the use of patient identifiers. Next, the data element list can be refined to include only those elements that are necessary for the registry purpose. Once the selected elements have been incorporated into a data collection tool, the tool can be pilot tested to identify potential issues, such as the time required to complete the form, data that may be more difficult to access than realized during the design phase, and practical issues in data quality (such as appropriate range checks). This information can then be used to modify the data elements and reach a final set of elements.

Identifying Domains

Registry design requires an explicit articulation of the goals of the registry and a close collaboration among disciplines, such as epidemiology, statistics, and clinical specialties. Once the goals of the study are determined, the domains most likely to influence the desired outcomes must be defined. Registries generally include personal, exposure, and outcomes information. The personal domain consists of data that describe the patient, such as information on patient demographics, medical history, health status, and any necessary patient identifiers. The exposure domain describes the patient's experience with the product, disease, device, procedure, or service of interest to the registry. Exposure can also include other treatments that are known to influence outcome but are not necessarily the focus of the study, so that their confounding influence can be adjusted for in the planned analyses. The outcomes domain collects information on the patient outcomes that are of interest to the registry; this domain should include both the primary endpoints and any secondary endpoints that are part of the overall registry goals.

In addition to the goals and desired outcomes, it is necessary to consider the need to create important subsets when defining the domains. Measuring potential confounding factors (variables that are linked with both the exposure and outcome) should be taken into account in this stage of registry development. Collecting data on potential confounders will allow for analytic or design control. (See Chapters 3 and 13.)

Understanding the time reference for all variables that can change over time is critical in order to distinguish cause-and-effect relationships. For example, a drug taken after an outcome is observed cannot possibly have contributed to the development of that outcome. Time reference periods can be addressed by including start and stop dates for variables that can change; they can also be addressed categorically, as

is done in some quality improvement registries. For example, the Paul Coverdell National Acute Stroke Registry organized its patient-level information into categories to reflect the timeframe of the stroke event from onset through treatment to followup. In this case, the domains were categorized as prehospital, emergency evaluation and treatment, in-hospital evaluation and treatment, discharge information, and postdischarge followup.[173]

Selecting Data Elements

Once the domains have been identified, the process of selecting data elements begins with the identification of the data elements that best quantify that domain and the source(s) from which those data elements can be collected. When selecting data elements, gaining consensus among the registry stakeholders is important, but this must be achieved without undermining the purpose of the registry by including elements solely to please a stakeholder. Each data element should support the purpose of the registry and answer an explicit scientific question or address a specific issue or need. The most effective way to select data elements is to start with the study purpose and objective and then decide what types of groupings, measurements or calculations will be needed to analyze that objective. Once the plan of analysis is clear, it is possible to work backwards to define the data elements necessary to implement that analysis plan. This process keeps the group focused on the registry purpose and limits the number of extraneous ("nice to know") data elements that may be included.[174] (See Case Example 14.)

The data element selection process can be simplified if clinical data standards for a disease area exist. While there is a great need for common core data sets by condition, currently there are few consensus or broadly accepted sets of standard data elements and data definitions for most disease areas. Thus, different studies of the same disease state may use different definitions for fundamental concepts, such as the diagnosis of myocardial infarction or the definition of worsening renal function.

To address this problem and to support more consistent data elements so that comparisons across studies can be more easily accomplished, some specialty societies and organizations are beginning to compile clinical data standards. For example, the American College of Cardiology has created clinical data standards for acute coronary syndromes, heart failure, and atrial fibrillation.[175,176,177] In cancer, the National Cancer Institute(NCI) provides the Cancer Data Standards Registry and Repository (caDSR) to find the common cancer data elements developed by the NCI along with its caBIG partners.[178] The North American Association of Central Cancer Registries (NAACCR) has developed a set of standard data elements and a data dictionary and promotes and certifies the use of these standards.[179] The American College of Surgeons National Cancer Database (NCDB) considers its data elements to be nationally standardized and open source.[180] To a lesser extent, other disease areas also have begun to catalogue data element lists and definitions. In trauma, the International Spinal Cord Society has developed an International Spinal Cord Injury Core Data Set to facilitate comparison of studies from different countries[181] and the National Center for Injury Prevention and Control has developed Data Elements for Emergency Department Systems (DEEDS), which are uniform specifications for data entered into emergency department patient records.[182] In neurological disorders, the National Institute of Neurological Disorders and Stroke (NINDS) maintains a list of several hundred data elements and definitions (Common Data Elements),[183] and, in infection control, in 2007 the National Vaccine Advisory Committee (NVAC) approved a new set of core data elements for immunization information systems.[184] Currently, there are more than one set of lists in some conditions (e.g., cancer) and no central method to search broadly across disease areas.

Some standards organizations are also working on core data sets. The Clinical Data Standards Consortium (CDISC) Clinical Data Acquisition Standards Harmonization (CDASH) is a global, consensus-based effort to recommend minimal data sets in 16 domains. While developed primarily for clinical trials, these domains have significant utility for patient registries. They currently include: demographic, adverse events, comments, prior and concomitant medications, demographics, disposition, drug accountability, ECG test results, exposure, inclusion and exclusion criteria, laboratory test results, medical history, physical examination, protocol deviations, subject characteristics, substance abuse, and vital signs. The document also includes a table on best practices for developing case report forms.[185]

The use of established data standards, when available, is essential so that registries can maximally contribute to evolving medical knowledge. Standard terminologies, and to a greater degree, higher level groupings into core data sets for specific conditions, improve not only efficiency in establishing registries, but promote more effective sharing, combining or linking of data sets from different sources. Furthermore, the use of well-defined standards for data elements and standards for data structure ensure that the meaning of information captured in different systems is the same. This is critical for 'semantic' interoperability between information systems, which will be increasingly important as health information system use grows. This is discussed more in Chapter 11.

Although clinical data standards are important to allow comparisons between studies, conversely overlapping different sets of standards (i.e., not harmonized) may cause confusion during analyses. To consolidate and align standards that have been developed for clinical research, the Clinical Data Interchange Standards Consortium (CDISC), the HL7 Regulated Clinical Research Information Management Technical Committee (RCRIM TC), the National Cancer Institute (NCI), and the US Food and Drug Administration (FDA) have collaborated to create the Biomedical Research Integrated Domain Group (BRIDG) model. The purpose of this project is to provide an overarching model that can be used to harmonize standards between the clinical research domain and the health care domain. BRIDG is a Domain Analysis Model (DAM), meaning that it provides a common representation of the semantics of protocol-driven clinical and preclinical research, along with the associated data, resources, rules, and processes used to formally assess a drug, treatment, or procedure.[186] The BRIDG model is freely available to the public as part of an open-source project at www.bridgmodel.org. It is hoped that the BRIDG model, when completed, will guide clinical researchers in selecting approaches that will enable their data to be compared with other clinical data, regardless of the study phase or data collection method.[187,188]

In cases where clinical data standards for the disease area do not exist, established data sets may be widely used in the field. For example, United Network of Organ Sharing (UNOS) collects a large amount of data on organ transplant patients. Creators of a registry in the transplant field should consider aligning their data definitions and data element formats with those of UNOS to simplify the training and data abstraction process for sites. Other examples of widely used data sets are the Joint Commission and the Centers for Medicare & Medicaid Services (CMS) data elements for hospital data submission programs. These data sets cover a range of procedures and diseases, from heart failure and acute myocardial infarction to pregnancy and surgical infection prevention. Hospital-based registries that collect data on these conditions may want to align their data sets with the Joint Commission and CMS. However, one limitation of tying elements and definitions to another data collection program rather than a fixed standard

is that these programs may change their elements or definitions. With Joint Commission core measure elements, for example, this has occurred with some frequency.

If clinical data standards for the disease area and established data sets do not exist, it is still possible to incorporate standard terminology into a registry. This will make it easier to compare the data with the data of other registries and reduce the training needs and data abstraction burden on sites. Examples of several standard terminologies used to classify important data elements are listed in Table 4.[189] In addition to these standard terminologies, there are numerous useful commercial code listings that target specific needs such as proficiency in checking for drug interactions or compatibility with widely-used EMR systems. Mappings between many of these element lists are also increasingly available. For example, SNOMED CT can currently be mapped to ICD-9-CM, and mapping between other standards are planned or underway.[190]

Table 4: Standard Terminologies

Standard	Acronym	Description and Website	Developer
Billing-related			
Current Procedural Terminology	CPT®	Medical service and procedure codes commonly used in public and private health insurance plans and claims processing. Website: http://www.ama-assn.org/ama/pub/category/3113.html	American Medical Association
International Classification of Diseases	ICD, ICECI, ICPC	International standard for classifying diseases and other health problems recorded on health and vital records. ICD-9-CM, a modified version of the ICD-9 standard, is used for billing and claims data in the U.S. The U.S. will transition to ICD-10-CM in 2013. The ICD is also used to code and classify mortality data from death certificates in the U.S. ICD adaptations include ICD-O (oncology), ICECI (External Causes of Injury), ICF (Functioning, Disability, & Health), and ICPC-2 (Primary Care, second edition). Website: http://www.who.int/classifications/icd/en	World Health Organization
Clinical			
Systemized Nomenclature of Medicine	SNOMED CT	Clinical healthcare terminology that maps clinical concepts with standard descriptive terms. Formerly SNOMED RT and SNOP. Website: http://www.ihtsdo.org/snomed-ct	International Health Terminology Standards Development Organization
Unified Medical Language System	UMLS	Database of 100 medical terminologies with concept mapping tools. Website: http://www.nlm.nih.gov/research/umls/	National Library of Medicine
Classification of Interventions	OPCS-4	Code for operations, surgical procedures, and interventions. Mandatory for use in National Health Service (England). Website:	Office of Population Censuses and

and Procedures		http://www.datadictionary.nhs.uk/web_site_content/supporting_information/clinical_coding/opcs_classification_of_interventions_and_procedures.asp	Surveys
Diagnostic and Statistical Manual	DSM	The standard classification of mental disorders used in the United States by a wide range of health and mental health professionals. The current version in use is the DSM-IV. Website: http://www.psych.org/MainMenu/Research/DSMIV.aspx	American Psychiatric Association
Drugs			
Medical Dictionary for Regulatory Activities	MedDRA	Terminology covering all phases of drug development, excluding animal toxicology. Also covers health effects and malfunctions of devices. Replaced COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms). Website: http://www.meddramsso.com	International Conference on Harmonisation (ICH)
VA National Drug File Reference Terminology	NDF-RT	Extension of the VA National Drug File; used for modeling drug characteristics including ingredients, chemical structure, dose form, physiologic effect, mechanism of action, pharmacokinetics, and related diseases. Website not available.	U.S. Department of Veterans Affairs
National Drug Code	NDC	Unique 3-segment number used as the universal identifier for human drugs. Website: http://www.fda.gov/cder/ndc/	U.S. Food and Drug Administration
RxNorm	RxNorm	Standardized nomenclature for clinical drugs. The name of a drug combines its ingredients, strengths, and/or form. Links to many of the drug vocabularies commonly used in pharmacy management and drug interaction software. http://www.nlm.nih.gov/research/umls/rxnorm/	National Library of Medicine
World Health Organization Drug Dictionary	WHODRUG	International drug dictionary. Website: http://www.who.int/druginformation/index.shtml	World Health Organization
Lab-specific			
Logical Observation Identifiers Names and Codes	LOINC®	Concept-based terminology for lab orders and results. Website: http://www.regenstrief.org/loinc/	Regenstrief Institute for Health Care
Other			
HUGO Gene Nomenclature Committee	HGNC	Recognized standard for human gene nomenclature. Website: http://www.genenames.org/aboutHGNC.html	Human Genome Organization
Dietary Reference Intakes	DRIs	Nutrient reference values developed by the institute of medicine to provide the scientific basis for the development of food guidelines in Canada and the United States. Website:	Institute of Medicine Food and Nutrition Board

		http://www.iom.edu/CMS/54133.aspx	
Substance Registry Services	SRS	The Environmental Protection Agency's (EPA) central system for standards identification of, and information about, all substances tracked or regulated by the EPA. Website: http://iaspub.epa.gov/sor_internet/registry/substreg/home/overview/home.do	Environmental Protection Agency

After investigating clinical data standards, registry planners may find that there are no useful standards or established data sets for the registry, or that these standards comprise only a small portion of the data set. In these cases, the registry will need to define and select data elements with the guidance of its project team, which may include an advisory board. When selecting data elements, it is often helpful to gather input from statisticians, epidemiologists, psychometricians, and experts in health outcomes assessment who will be analyzing the data, as they may notice potential analysis issues that need to be considered at the time of data element selection. Data elements may also be selected based on performance or quality measures in a clinical area. (See Case Example 15.)

When beginning the process of defining and selecting data elements, it can be useful to start by considering the registry design. Since many registries are longitudinal, sites often collect data at multiple visits. In these cases, it is necessary to determine which data elements can be collected once and which data elements should be collected at every visit. Data elements that can be collected once are often collected at the baseline visit. In other cases, the registry may be collecting data at an event level, so all of the data elements will be collected during the course of the event rather than in separate visits. In considering when to collect a data element, it is also important to determine the most appropriate order of data collection. Data elements that are related to each other in time (e.g., dietary information and a fasting blood sample for glucose or lipids) should be collected in the same visit rather than in different visit case report forms.

International physician and patient participation may be required to meet certain registry data objectives. In such situations, it is desirable to consider the international participation in the context of data element selection, especially if it will be necessary to collect and compare data from individual countries. Examination and laboratory test results or units may differ among countries, and standardization of data elements may become necessary at the data-entry level. Data elements relating to cost-effectiveness studies may be particularly challenging, since there is substantial variation among countries in practice and the costs of medical "inputs," relating largely to differences in national or regional coverage practices and national health policies. Alternatively, if capture of internationally standardized data elements is not desirable or cannot be achieved, registry stakeholders should consider provisions to capture data elements according to local standards. Later, separate data conversions and merging outside the database for uniform reporting or comparison of data elements captured in multiple countries can be evaluated and performed as needed if the study design ensures that all data necessary for such conversions have been collected.

Table 5 provides a listing of sample baseline data elements. These elements will vary depending on the design, nature, and goals of the registry. Examples listed include patient identifiers (e.g., for linkage to other databases), contact information (e.g., for followup), and residence location of enrollee (e.g., for

geographic comparisons). Other administrative data elements that may be collected include the source of enrollment, enrollee sociodemographic characteristics, and information on provider locations.

Table 5: Sample Baseline Data Elements

Enrollee contact information	• Enrollee contact information for registries with direct-to-enrollee contact • Another individual who can be reached for followup (address, telephone, e-mail)
Enrollment data elements	• Patient identifiers (e.g., name [last, first, middle initial], date of birth, place of birth, Social Security Number) • Permission/consent • Source of enrollment (e.g., provider, institution, phone number, address, contact information) • Enrollment criteria • Sociodemographic characteristics, including race, gender, age or date of birth • Education and/or economic status, insurance, etc. • Preferred language • Place of birth • Location of residence at enrollment • Source of information • Country, State, city, county, ZIP Code of residence

Depending on the purpose of a registry, other sets of data elements may be required (Table 6). In addition, data elements needed for specific types of registries are outlined below.

- For registries examining questions of safety for drugs, vaccines, procedures, or devices, key information includes history of the exposure and data elements that will permit analysis of potential confounding factors which may affect observed outcomes, such as enrollee characteristics (e.g., comorbidities, concomitant therapies, socioeconomic status, ethnicity, environmental and social factors) and provider characteristics. For drug exposures, data on use (start and stop dates), as well as providing continuing evidence that the drug was actually used (data on medication persistence and/or adherence), may be important. In some instances, it is also useful to record reasons for discontinuation and whether pills were split or shared with others.
- For registries examining questions of effectiveness and cost effectiveness, key information includes the history of exposure and data elements that will permit analysis of potential confounding factors which may affect observed outcomes. In addition to those mentioned above for safety, these may include individual behaviors and provider and/or system characteristics. For assessment of cost effectiveness, information may be recorded on the financial and economic burden of illness, such as office visits, visits to urgent care or the emergency room, and hospitalizations, including length of stay. For some studies, a quality-of-life instrument that can

be analyzed to provide quality-adjusted life years (QALYs) or similar comparative data across conditions may be useful.

- For registries assessing quality of care and quality improvement, data that categorize and possibly differentiate among the services provided (e.g., equipment, training or experience level of providers, type of health care system) may be sought, as well as information that identifies individual patients as potential candidates for the treatment. In addition, self-reported data are valuable to assess the patients' perception of quality of care
- For registries examining the natural history of a condition, the selection of data elements would be similar to those of effectiveness registries.

If one goal of a registry is to identify patient subsets that are at higher risk for particular outcomes, more detailed information on patient and provider characteristics should be collected (and a higher sample size may be required). This information may be important in registries that look at the usage of a procedure or treatment. Quality improvement registries also use this information to understand how improvement differs across many types of institutions.

When selecting patient identifiers, there are a variety of options to use, including the patient's name, date of birth, Social Security Number (or some combination thereof), that are subject to legal and security considerations. When the planned analyses require linkage to other data (such as medical records), more specific patient information may be needed depending on the planned method of linkage (e.g. probabilistic or deterministic). For more information on linkage considerations, see Chapter 7. In selecting patient identifiers, some thought should be given to the possibility that patient identifiers may change during the course of the registry. For example, patients may change their name during the course of the registry following marriage/divorce, or patients may move or change their telephone number. Patient identifiers can also be inaccurate because of intentional falsification by the patient (e.g., for privacy reasons in a sexually transmitted disease registry), unintentional misreporting by the patient or a parent (e.g., wrong date of birth), or typographical errors by clerical staff. In these cases, having more than one patient identifier for linking patient records can be invaluable. In addition, identifier needs will differ based on the registry goals. For example, a registry that tracks children will need identifiers related to the parents, and registries that are likely to include twins (e.g., immunization registries) should plan for the duplication of birth dates and other identifiers. In selecting patient identifiers for use in a registry, registry planners will need to determine what data are necessary for their purpose and plan for potential inaccurate and changing data.

Generally, patient identifiers can simplify the process of identifying patients and tracking patients for followup. Patient identifiers also allow for the possibility of identifying patients who are lost to followup due to death (i.e., through the National Death Index) and linking to birth certificates for studies in children. In addition, unique patient identifiers allow for analysis to remove duplicate patients.

When considering the advantages of patient identifiers, it is important to take into account the potential challenges that collecting patient identifiers can present. Obtaining consent for the use of patient-identifiable information can be an obstacle to enrollment, as it can lead to the refusal of patients to participate. Chapter 8 contains more information on the ethical and legal considerations of using patient identifiers. In addition to the data points related to primary and secondary outcomes, it is important to plan for patients who will leave the registry. While the intention of a registry is generally for all patients

to remain in the study until planned followup is completed, planning for patients to leave the study before completion of full followup may reduce analysis problems. By designing a final study visit form, registry planners can more clearly document when losses to followup occurred and possibly collect important information about why patients left the study. Not all registries will need a study discontinuation form, as some studies collect data on the patient only once and do not include followup information (e.g., in-hospital procedure registries).

Table 6: Sample Additional Enrollee, Provider, and Environmental Data Elements

**Note: HEDIS = Health plan Employer Data and Information Set*

Pre-enrollment history	
Medical history	• Morbidities/conditions • Onset/duration • Severity • Treatment history • Medications • Adherence • Health care resource utilization • Diagnostic tests and results • Procedures and outcomes • Emergency room visits, hospitalizations (including length of stay), long-term care, or stays in skilled nursing facilities • Genetic information • Comorbidities • Development (pediatric/adolescent)
Environmental exposures	• Places of residence
Patient characteristics	• Functional status (including ability to perform tasks related to daily living), quality of life, symptoms • Health behaviors (alcohol, tobacco use, physical activity, diet) • Social history • Marital status • Family history • Work history • Employment, industry, job category • Social support networks • Economic status, income, living situation • Sexual history • Foreign travel, citizenship • Legal (e.g., incarceration, legal status) • Reproductive history • Health literacy • Individual understanding of medical conditions and the risks and benefits of interventions • Social environment (e.g., community services) • Enrollment in clinical trials (if patients enrolled in clinical trials are

	eligible for the registry)
Provider/system characteristics	• Geographical coverage • Access barriers • Quality improvement programs • Disease management, case management • Compliance programs • Information technology use (e.g., computerized physician order entry, e-prescribing, electronic medical records) • Quality improvement metrics (e.g., health plan level [HEDIS], hospital level [Joint Commission], group level [pay for performance], or individual practitioner [Bridges to Excellence])
Financial/economic information	• Disability, work attendance (days lost from work), or absenteeism/ presenteeism • Out-of-pocket costs • Health care utilization behavior, including outpatient visits, hospitalizations (and length of stay), and visits to the emergency room or urgent care • Patient assessments of the degree to which they avoid health care because of its cost • Patients' reports of insurance coverage to assist/cover the costs of outpatient medications • Destination when discharged from a hospitalization (home, skilled nursing facility, long-term care, etc.) • Medical costs, often derived from data on physician office visits, hospitalizations (especially length of stay), and/or procedures
Followup	
Key primary outcomes	• Safety: adverse events (see Chapter 12) • Effectiveness and value: intermediate and endpoint outcomes; health care resource use and hospitalizations; diagnostic tests and results. Particularly important are outcomes meaningful to patients, including survival, symptoms, function, and quality of life • Quality measurement/improvement: key selected measures at appropriate intervals • Natural history: progression of disease severity; use of health care services; diagnostic tests, procedures, and results; quality of life; mortality; cause/date of death
Key secondary outcomes	• Economic status • Social functioning
Other potentially important information	• Changes in medical status • Changes in patient characteristics • Changes in provider characteristics • Changes in financial status

- Residence
- Changes, additions, or discontinuation of exposures (medications, environment, behaviors, procedures)
- Changes in health insurance coverage
- Sources of care (e.g., where hospitalized)
- Changes in individual attitudes, behaviors

Creating explicit data definitions for each variable to be collected is essential to the process of selecting data elements. This is important to ensure internal validity of the proposed study so that all participants in data collection are acquiring the requisite information in the same reproducible way (See Chapter 10.) The data definitions should also include the ranges and acceptable values for each individual data element, as well as the potential interplay of different data elements. For example, logic checks for the validity of data capture may be created for data elements that should be mutually exclusive.

When deciding on data definitions, it is important to determine which data elements are required and which elements may be optional. This is particularly true in cases where the registry may collect a few additional "nice to know" data elements. It will differ depending on whether the registry is using existing medical record documentation to obtain a particular data element or if the clinician is being asked directly. For example, New York Heart Association Functional Class for heart failure is an important staging element but is often not documented.[191] However, if clinicians are asked to provide the data point prospectively, they can readily do so. Consideration should also be given to how to account for missing or unknown data. In some cases, a data element may be unknown or not documented for a particular patient, and followup with the patient to answer the question may not be possible. Including an option on the form for "not documented" or "unknown" will allow the person completing the case report form to provide a response to each question rather than leaving it blank. Depending on the analysis plans for the registry, the distinction between undocumented data and missing data may be important.

When collecting data for patient outcomes analysis, it is important to use patient-centered outcomes that are valid, reliable, responsive, interpretable, and translatable. Patient-centered outcomes reflect the patients' perceptions of their status and their perspective on health and disease. Patient-centered outcomes have become an increasingly important avenue of investigation, particularly in light of the 2001 Institute of Medicine report calling for a more patient-centered health care system.[192] The U.S. FDA also noted the importance of PRO data in understanding certain treatment effects in its 2006 draft guidance.[193]

Among the most important patient-centered outcomes to quantify is health status. Health status includes the manifestations of a disease—its symptoms; the degree to which a disease limits patients physically, emotionally, and socially; and the impact on patients' quality of life—as seen by the patient. There are several methods for quantifying patients' health status, including the use of generic, disease-specific, and utility measures. Generic health status and utility measures seek to quantify the overall status of a patient's health. Whereas generic health status measures often have several domains,[194] utility measures distill patients' health to a single value between 0 (indicating death) and 1.0 (indicating perfect health) that can be used in economic analyses.[195,196,197,198] In contrast to these approaches that seek to quantify the overall effects of patients' health on their health status, disease-specific measures focus on the specific

symptoms, limitations, and quality-of-life (QOL) impairment associated with a particular disease.[199] Because of the more narrow focus of disease-specific instruments, they are often more sensitive to clinical change[200,201,202] and "actionable" by physicians who are familiar with the clinically oriented domains assessed by these instruments.[203]

Prior to their use, however, patient-centered health status measures need to have appropriate psychometric characteristics. There are at least five key attributes that a health status measure should demonstrate prior to its incorporation into a clinical study or registry. Relevant attributes of a potential instrument (Table 7) include its validity, reliability, responsiveness to change, interpretability, and the availability of translations in other languages.[204] Often, explicit demonstration of these properties prior to the initial use of the instrument is needed to be sure that the results are meaningful.

Table 7: Key Attributes of a Health Status Instrument

Measurement Property	Description
Validity	The measure quantifies what it is intended to
Reliability	Reproducible results are obtained when repeatedly given to stable patients
Responsiveness	The measure is sensitive to clinical change
Interpretability	A clinical framework is available to interpret cross-sectional data and changes in scores
Translations exist	Linguistically and culturally appropriate translations are available

When no instrument exists and a new one needs to be developed, a series of methodological studies should be performed to test or, ideally, validate the instrument, thereby ensuring that the instrument meets these requisite qualities prior to investing in it for a larger study. While several resources exist for creating new measures, clearinghouses for previously created measures and the literature should be carefully searched before embarking on the lengthy and challenging process of new measure creation. (See Case Examples 16, 17, and 18.)

When using an instrument to gather data on patient-centered health status, it is important to collect both the individual question responses as well as to calculate the summary or composite score. The summary score, which may be for the entire instrument or for individual domains, is ultimately used to report results. However, if the registry only collects the summary score, it will not be possible to examine how the patients scored on different components of the instrument during the registry analysis phase.

Registry Data Map

Once data elements have been selected, a data map should be created. The data map identifies all sources of data (Chapter 6) and explains how the sources of data will be integrated. Data maps are useful to defend the validity and/or reliability of the data, and they are typically an integral part of the data management plan (Chapter 10).

Pilot Testing

After the data elements have been selected and the data map created, it is important to pilot test the data collection tools to determine the time needed to complete the form and the resulting subject/abstractor burden. For example, through pilot testing, registry planners might determine that it is wise to collect certain highly burdensome (or "nice to know") data elements in only a subset of participating sites (nested

registry) that agree to the more intensive data collection, so as not to endanger participation in the registry as a whole. Pilot testing should also help to identify the missing data rate and any validity issues with the data collection system.

The burden of form collection is a major factor determining a registry's success or failure, with major implications for the cost of participation and for the overall acceptance of the registry by hospitals and health care personnel. Moreover, knowing the anticipated time needed for patient recruitment/enrollment will allow better communication to potential sites regarding the scope and magnitude of commitment required to participate in the study. Registries that obtain information directly from patients include the additional issue of participant burden, with the potential for participant fatigue, leading to failure to answer all items in the registry. Highly burdensome questions can be collected in a pre-specified subset of subjects. The purpose of these added questions should be carefully considered when determining the subset so that useful and accurate conclusions can be achieved.

Pilot testing the registry also allows the opportunity to identify issues and make refinements in the registry data collection tool, including alterations in the format or order of data elements and clarification of item definitions. Piloting may also uncover problems in registry logistics, such as the ability to accurately or comprehensively identify subjects for inclusion.

A fundamental aspect of pilot testing is evaluation of the accuracy and completeness of registry questions and the comprehensiveness of both instructional materials and training in addressing these potential issues. Gaps in clarity concerning questions can result in missing or misclassified data, which, in turn, may cause bias and result in inaccurate or misleading conclusions. For example, time points, such as time to radiologic interpretation of imaging test, may be difficult to obtain retrospectively, and, if they do exist in the chart, may not be consistently documented. For example, for the time to radiologic interpretation, without additional instruction, some hospitals may indicate the time the image was read by the radiologist and others may use the time when the interpretation was recorded into the chart. The two time points can have significant variation depending on the documentation practices of the institution.

Pilot testing ranges in practice from ad hoc assessments of the face validity of instruments and materials in clinical sites, to trial runs of the registry in small numbers of sites, to highly structured evaluations of inter-rater agreement. The level of pilot testing is determined by multiple factors. Accuracy of data entry is a key criterion to evaluate during the pilot phase of the registry. When a "gold standard" exists, the level of agreement with a reference standard (construct validity) may be measured.[205] Data collected by seasoned abstractors or auditors following strict operational criteria can serve as the gold standard on which to judge accuracy of abstraction for chart-based registries.[206] In instances where no reference standard is available, reproducibility of responses to registry elements by abstractors (inter-rater reliability) or test-retest agreement of subject responses may be assessed.[207] Reliability and/or validity of data elements should be tested in the pilot phase whenever the element is collected in new populations or for new applications. Similar mechanisms to those used during the pilot phase can be used during data quality assurance (Chapter 10). A Kappa statistic measure of how much the level of agreement between two or more observers exceeds the amount of agreement expected by chance alone is the most common method for measuring reliability of categorical and ordinal data. Intraclass correlation coefficient, or inter-rater reliability coefficient, provides information on the degree of agreement for continuous data. It is a proportion that ranges from zero to one. Item-specific agreement represents the highest standard for

registries; it has been employed in cancer registries and to assess the quality of data in statewide stroke registries. Other methods, such as the Bland and Altman method,[208] may also be chosen, depending upon the type of data and registry purpose. Overall, the choice of data elements should be guided by parsimony, validity, and consistent focus on achieving the purpose for which the registry was created.

Case Example 14: Selecting data elements for a registry

Description:	The Dosing and Outcomes Study of Erythropoiesis-stimulating Therapies (DOSE) Registry was designed to understand anemia management patterns and clinical, economic, and patient-reported outcomes in oncology patients treated in outpatient oncology practice settings across the United States. The prospective design of the DOSE Registry enabled data capture from oncology patients treated with erythropoiesis-stimulating therapies.
Sponsor:	Centocor Ortho Biotech Services, LLC
Year Started:	2003
Year Ended:	2009
No. of Sites	71
No. of Patients:	2,354

Challenge

Epoetin alfa was approved for patients with chemotherapy-induced anemia in 1994. In 2002, the U.S. Food and Drug Administration approved a second erythropoiesis-stimulating therapy (EST), darbepoetin alfa, for a similar indication. While multiple clinical trials described outcomes following intervention with ESTs, little information was available on real-world practice patterns and outcomes in oncology patients. To gain this information, the registry team determined that a prospective observational effectiveness study in this therapeutic area was needed. The three key challenges were to make the study representative of real-world practices and settings (e.g., hospital-based clinics, community oncology clinics); to collect data elements that were straightforward so as to minimize potential data collection errors; and to collect sufficient data to study effectiveness, while ensuring that the data collection remained feasible and time efficient for outpatient oncology clinics.

Proposed Solution

The registry team began selecting data elements by completing a thorough literature review. Because this would be one of the first prospective observational studies in this therapeutic area, the team wanted to ensure that study results could be presented to health care professionals and decisionmakers in a manner consistent with clinical trials, of which there were many. The team also intended to make the data reports from this study comparable with clinical trial reports. To meet these objectives, data elements (e.g., baseline demographics, dosing patterns, hemoglobin levels) similar to those in clinical trials were selected whenever possible, based on a thorough literature review.

For the patient-reported outcomes component of the registry, the team incorporated standard, validated instruments. This decision allowed the team to avoid developing and validating new instruments and supported consistency with clinical trial literature, as many trials had incorporated these instruments. To capture patient-reported data, the team selected two instruments, the Functional Assessment of Cancer Therapy–Anemia (FACT-An) and the Linear Analog Scale Assessment (LASA) tool. The FACT-An tool, developed from the FACT-General scale, had been designed and validated to measure the impact of anemia in cancer patients. The LASA enables patients to report their energy level, activity level, and overall quality of life on a scale of zero to 100. Both tools are commonly used to gather patient-reported outcomes data for cancer patients.

Following the literature review, an advisory board was convened to discuss the registry objectives, data

elements, and study execution. The advisory board included representatives from the medical and nursing professions. The multidisciplinary board provided insights on both the practical and clinical aspects of the registry procedures and data elements. Throughout the entire process, the registry team remained focused on both the overall registry objectives and user-friendly data collection. In particular, the team worked to make each question clear and unambiguous in order to minimize confusion and to enable a variety of site personnel, as well as the patients, to complete the registry data collection.

Results

The registry was launched in 2003 as one of the first prospective observational effectiveness studies in this therapeutic area. Seventy-one sites and 2,354 patients enrolled in the study. The sites participating in the registry represented a wide geographic distribution and a mixture of outpatient practice settings.

Key Point

Use of common data elements, guided by a literature review, and validated patient-reported outcomes instruments enhanced data generalizability and comparability with clinical trial data. A multidisciplinary advisory board also helped to ensure collection of key data elements in an appropriate manner from both a clinical and practical standpoint.

For More Information

Larholt K, Burton TM, Hoaglin DC, et al. Clinical and patient-reported outcomes based on achieved hemoglobin levels in chemotherapy-treated cancer patients receiving erythropoiesis-stimulating agents. Community Oncology 2009, In press.

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Case Example 15: Using performance measures to develop a data set

Description:	Get With The Guidelines℠ is the flagship program for in-hospital quality improvement of the American Heart Association (AHA) and American Stroke Association (ASA). The Get With The Guidelines – Stroke program uses the experience of the ASA to ensure the care that hospitals provide for stroke is aligned with the latest evidence-based guidelines.
Sponsor:	American Stroke Association
Year Started:	2003
Year Ended:	Ongoing
No. of Sites	1,651
No. of Patients:	1,134,076

Challenge

The primary purpose of the program is to improve the quality of in-hospital care for stroke patients. The program uses the PDSA (Plan, Do, Study, Act) quality improvement cycle, in which hospitals plan quality improvement initiatives, implement them, study the results, and then make adjustments to the initiatives. To help hospitals implement this cycle, the program uses a registry to collect data on stroke patients and generate real-time reports showing compliance with a set of standardized stroke performance

and quality measures. The reports also include benchmarking capabilities, enabling hospitals to compare themselves with other hospitals at a national and regional level, as well as with similar hospitals based on size or type of institution.
In developing the registry, the team faced the challenge of creating a data set that would be comprehensive enough to satisfy evidence-based medicine but manageable by hospitals participating in the program. The program does not provide reimbursements to hospitals entering data, so it needed to keep the data set as small as possible while still maintaining the ability to measure quality improvement.

Proposed Solution

The team began developing the data set by working backward from the performance measures. Performance measures, based on the sponsor's guidelines for stroke care, contain detailed inclusion and exclusion criteria to determine the measure population, and they group patients into the denominator and numerator groups. Using these criteria, the team developed a data set that asked the questions necessary to determine compliance with each of the guidelines. The team then added additional questions to gather information on the patient population characteristics. Since the inception of the program, additional data elements and measure reports have been added to maintain alignment with the current stroke performance and quality measures.

Results

By using this approach, the registry team was able to create the necessary data set for measuring compliance with stroke guidelines. The program launched in 2003 and now has 1,651 hospitals and 1,134,076 stroke patient records. The data from the program have been used in several abstracts and resulted in 11 manuscripts since 2007.

Key Point

Registry teams should focus on the outcomes or endpoints of interest when selecting data elements. In cases where compliance with guidelines or quality measures is the outcome of interest, teams can work backward from the guidelines or measures to develop the minimum necessary data set for their registry.

For More Information

Get With The Guidelines® Web site. Available at: http://www.americanheart.org/getwiththeguidelines.

Schwamm L, Fonarow G, Reeves M, Pan W, Frankel M, Smith E, Ellrodt G, Cannon C, Liang L, Peterson E, LaBresh K. Get With the Guidelines-Stroke is Associated with Sustained Improvement in Care for Patients Hospitalized with Acute Stroke or Transient Ischemic Attack. Circulation 2009;119;107-11.

Schwamm LH, LaBresh KA, Albright D et al. Does Get With the Guidelines improve secondary prevention in patients hospitalized with ischemic stroke or TIA? [abstract]. *Stroke* 2005 Feb;36(2):416-P84.

LaBresh KA, Schwamm LH, Pan W et al. Healthcare disparities in acute intervention for patients hospitalized with ischemic stroke or TIA in Get With the Guidelines-Stroke [abstract]. *Stroke* 2005 Feb;36(2):416-P275.

Case Example 16: Developing and validating a patient-administered questionnaire

Description:	The Benign Prostatic Hypertrophy (BPH) Registry & Patient Survey was a multicenter, prospective, observational registry examining the patient management practices of primary care providers and urologists, and assessing patient outcomes, including symptom amelioration and disease progress. The registry collected patient-reported and clinician-reported data at multiple clinical visits.
Sponsor:	Sanofi-Aventis
Year Started:	2004
Year Ended:	2007
No. of Sites	403
No. of Patients:	6,928

Challenge

Lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH) have a strong relationship to sexual dysfunction in aging males. Sexual dysfunction includes both erectile dysfunction (ED) and ejaculatory dysfunction (EjD), and health care providers treating patients with symptoms of BPH should evaluate men for both types of dysfunction. Providers can use the Male Sexual Health Questionnaire (MSHQ), a validated, self-administered, sexual function scale to assess dysfunction, but the 25-item scale can be perceived as too long. To assess EjD more efficiently, it was necessary to develop a brief, patient-administered, validated questionnaire.

Proposed Solution

The team used representative, population-based samples to develop a short-form scale for assessing EjD. The team administered the 25-item MSHQ to three populations: a sample of men from the Men's Sexual Health Population Survey, a subsample of men from the Urban Men's Health Study, and a sample of men enrolled in the observational registry.

Using the data from the sample populations, the team conducted a series of analyses to develop the scale. The team used factor analysis to help select the items from the scale that had the highest correlations with the principal factors. Using conventional validation, the team examined reliability (both internal consistency and test-retest repeatability). To assess validity, tests of repeatability and discriminant/ convergent validity were used to determine that the short form successfully discriminated between men with no to mild LUTS/BPH and those with moderate to severe LUTS/BPH. Lastly, the team examined the correlation between the 7-item ejaculation domain of the 25-item MSHQ and the new short-form scale using data from the observational registry.

Results

Based on the results of these analyses, the team selected three ejaculatory function items and one ejaculation bother item for inclusion in the new MSHQ-EjD Short Form. The new scale demonstrates a high degree of internal consistency and reliability, and it provides information to identify men with no to mild LUTS/BPH and those with moderate to severe LUTS/BPH.

Key Point

Developing new instruments for collecting patient-reported outcomes requires careful testing of the new tool in representative populations to ensure validity and reliability. Registries can provide a large sample population for validating new instruments.

For More Information

Rosen RC, Catania JA, Althof SE, Pollack LM, O'Leary M, Seftel AD, Coon DW. Development and validation of four-item version of Male Sexual Health Questionnaire to assess ejaculatory dysfunction. Urology 2007;69(5):805-9.

Rosen R, Altwein J, Boyle P et al. Lower urinary tract symptoms and male sexual dysfunction: the Multinational Survey of the Aging Male. *Eur Urol* 2003;44:637-49.

Case Example 17: Understanding the needs and goals of the registry participants

Description:	The Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) studied the health status of patients for 1 year after discharge for a myocardial infarction. The registry focused on developing a rich understanding of the patients' symptoms, functional status, and quality of life by collecting extensive baseline data in the hospital and completing followup interviews at 1, 6, and 12 months.
Sponsor:	CV Therapeutics and CV Outcomes
Year Started:	2003
Year Ended:	2004
No. of Sites	19
No. of Patients:	2,498

Challenge

With the significant advances in myocardial infarction (MI) care over the past 20 years, many studies have documented the improved mortality and morbidity associated with these new treatments. These studies typically have focused on in-hospital care, with little to no followup component. As a result, information on the transition from inpatient to outpatient care was lacking, as were data on health status outcomes.

PREMIER was designed to address these gaps by collecting detailed information on MI patients during the hospital stay and through followup telephone interviews conducted at 1, 6, and 12 months. The goal of the registry was to provide a rich understanding of patients' health status (their symptoms, function, and quality of life) 1 year after an acute MI. The registry also proposed to quantify the prevalence, determinants, and consequences of patient and clinical factors in order to understand how the structures and processes of MI care affect patients' health status.

To develop the registry data set, the team began by clearly defining the phases of care and recovery and identifying the clinical characteristics that were important in each of these phases. These included patient characteristics upon hospital arrival, details on inpatient care, and details on outpatient care. The team felt that information on each of these phases was necessary, since the variability of any outcome over 1 year may be explained by patient, inpatient treatment, or outpatient factors. Health status also includes

many determinants beyond the clinical status of disease, such as access to care, socioeconomic status, and social support; the registry needed to collect these additional data in order to fully understand the health status outcomes.

Proposed Solution

While registries often try to include as many eligible patients and sites as possible by reducing the burden of data entry, this registry took an alternative approach. The team designed a data set that included over 650 baseline data elements and over 200 followup interview-assessed data elements. Instead of allowing retrospective chart abstraction, the registry required hospitals to complete a five-page patient interview while the patient was in the hospital. The registry demanded significant resources from the participating sites. For each patient, the registry required about 4 hours of time, with 15 minutes for screening, 2 hours for chart abstraction, 45 minutes for interviews, 45 minutes for data entry, and 15 minutes of a cardiologist's time to interpret the electrocardiograms and angiograms. A detailed, pre-specified sampling plan was developed by each site and approved by the data-coordinating center to ensure that the patients enrolled at each center were representative of all of the patients seen by that site.

The registry team developed this extremely detailed data set and data collection process through extensive consultations with the registry participants. The coordinators and steering committees reviewed the data set multiple times, with some sites giving extensive feedback. Throughout the development process, there was an ongoing dialog among the registry designers, the steering committee, and the registry sites.

The registry team also used standard definitions and established instruments whenever possible to enable the registry data to be cross-referenced to other studies and to minimize the training burden. The team used the American College of Cardiology Data Standards for Acute Coronary Syndromes for data definitions of any overlapping fields. To measure other areas of the patient experience, the team used the Patient Health Questionnaire to examine depression, the ENRICHD Social Support Inventory to measure social support, the Short Form-12 to quantify overall mental and physical health, and the Seattle Angina Questionnaire (SAQ) to understand the patients' perspective on how coronary disease affects their life.

Results

The data collection burden posed some challenges. Two of the 19 sites dropped out of the registry early on. Two other sites fell behind on their chart abstractions. Turnover of personnel and multiple commitments at participating sites also delayed the study.

Despite these challenges, the registry experienced very little loss of enthusiasm or loss of sites once it was up and running. The remaining 17 sites completed the registry and collected data on nearly 2,500 patients. In return for this data collection, sites enjoyed the academic productivity and collaborative nature of the study. The data-coordinating center created a Web site that offered private groups for the principal investigators, so each investigator had access to all of the abstract ideas and all of the research that was being done. This structure provided nurturing and support for the investigators, and they viewed the registry as a way to engage themselves and their institution in research with a prominent, highly respected team.

On the patient side, the registry met followup goals. Over 85 percent of participants provided 12-month followup information. The registry team attributed this followup rate to the strong rapport that the interviewers developed with the patients during the course of the followup period.

Key Point

This example illustrates that there is no maximum or minimum number of data elements for a successful registry. Instead, a registry can best achieve its goals by ensuring that sufficient information is collected

to achieve the purpose of the registry while remaining feasible for the participants. An open, ongoing dialog with the participants or a subgroup of participants can help to determine what is feasible for a particular registry and to ensure that the registry will retain the participants for the life of the study.

For More Information

Spertus JA, Peterson E, Rumsfeld JS et al. The Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER)–evaluating the impact of myocardial infarction on patient outcomes. Am Heart J 2006 Mar;151(3):589-97.

Case Example 18: Using validated measures to collect patient reported outcomes

Description:	The Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD) is a household panel registry designed to assess the prevalence and incidence of diabetes mellitus and cardiovascular disease, disease burden and progression, risk predictors, and knowledge, attitudes, and behaviors regarding health in the United States population. The study involves three distinct phases: 1) an initial screening survey, 2) a baseline survey, and 3) yearly followup surveys for 5 years.
Sponsor:	AstraZeneca Pharmaceuticals LP
Year Started:	2004
Year Ended:	Ongoing (data collection expected to end in 2010).
No. of Sites	N/A
No. of Patients:	Over 211,000 individuals were included in screening survey; approximately 15,000 individuals are being followed for 5 years.

Challenge

The SHIELD registry uses survey methodologies to collect health information from a large sample of adults. The goal of the study is to capture participants' perspectives and views on diabetes and cardiovascular disease, risk factors for the diseases, and burden of the diseases. The study investigators, noting that treatment for diabetes and cardiovascular disease relies heavily on patient self-management, felt that it was particularly important to gather information on activities, weight control, health attitudes, quality of life, and other topics directly from the participant, without a physician as an intermediary. The investigators also wanted to follow participants over time to better understand disease progression and changes in health behaviors or activities.

To achieve the study goals, the registry needed to collect health-related data directly from participants in such a way that the data would be reliable, valid, and comparable across participant groups and over time.

Proposed Solution

The study investigators decided to use validated, patient reported outcomes measures (PROs) to collect information on health status and behaviors. The PROs allowed the data from the SHIELD study to be compared to data collected in other registries to assess the generalizability of the study population. In addition, the PROs already took into account issues such as recall bias and interpretability of the questions, and self-administered instruments eliminated the possibility of introducing interviewer bias.

The registry includes seven PROs: 1) the 12-item Short Form Health Survey and European Quality of Life (EuroQoL) EQ-5D instrument to assess health-related quality of life; 2) the Sheehan Disability Scale to assess the level of disruption in work, social life, and family/home life; 3) the 9-item Patient Health Questionnaire to assess depression; 4) the Work Productivity and Activity Impairment Questionnaire: General Health to assess work productivity and absenteeism; 5) the Diet and Health Knowledge Survey; 6) the Press-Ganey Satisfaction questionnaire; and 7) the International Physical Activity Questionnaire to assess health-related physical activity and sedentary behaviors.

The investigators considered many factors, such as length, ease of use, format, and scoring system, when selecting the PROs to include in the survey. For example, a major reason for selecting the SF-12 rather than the SF-36 as a measure of quality of life was the length of the forms (12 versus 36 items). The survey is entirely paper-based, with participants mailing back completed forms. The validated scoring algorithms are used to account for missing or illegible values on the completed forms. All participants must be able to read and write in English.

Results

The registry has had a generally high response rate for the surveys. The response rates were 63.7% for the screening survey, 71.8% for the baseline survey, and between 71 and 75% for the annual surveys. In terms of missing data, participants who return the survey forms tend to complete all of the questions in the appropriate manner. However, the registry is missing longitudinal data from some participants. For example, a participant may have returned the completed form in 2005, failed to return the form in 2006, and returned the form again in 2007. The investigators must account for the missing 2006 values when conducting longitudinal analyses. To date, the data from the survey have been sufficient to support comparisons over time and across participant groups, leading to several publications.

Key Point

Utilization of standardized, validated instruments in a registry can offer many benefits, including enhanced scientific rigor, the ability to compare patient views over time, and the ability to compare registry data against other data sources to assess the representativeness of the registry population. It should be noted that significant initial planning is necessary to identify appropriate PROs, obtain the necessary permissions, and include them in a registry. Issues with missing data must be considered in the planning phases for a registry. This registry considered missing data within returned surveys. In addition, an acceptable followup rate may have been stated a priori so that response rates could be better interpreted with respect to their potential for introducing bias.

For More Information

Grandy S, Chapman RH, Fox KM, for the SHIELD Study Group. Quality of life and depression of people living with type 2 diabetes mellitus and those at low and high risk for type 2 diabetes: findings from the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD). International Journal of Clinical Practice 2008;62:562-568.

Grandy S, Fox KM. EQ-5D visual analog scale and utility index values in individuals with diabetes and at risk for diabetes: findings from the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD). Health and Quality of Life Outcomes 2008;6:18.

Fox KM, Grandy S, for the SHIELD Study Group. Out-of-pocket expenses and healthcare resource utilization among individuals with or at risk of diabetes mellitus. Current Medical Research and Opinion 2008;24:3323-3329.

Chapter 6: Data Sources for Registries

Identification and evaluation of suitable data sources should be done within the context of the registry purpose and availability of the data of interest. A single registry may have multiple purposes and integrate data from various sources. While some data in a registry is collected directly for registry purposes (primary data collection), important information also can be transferred into the registry from existing databases. Examples include demographic information from a hospital admission, discharge, and transfer system; medication use from a pharmacy database; and disease and treatment information, such as details of the coronary anatomy and percutaneous coronary intervention from a (catheterization) laboratory information system, electronic medical record, or medical claims databases. In addition, observational studies can generate as many hypotheses as they test, and secondary sources of data can be merged with the primary data collection to allow for analyses of questions that were unanticipated when the registry was conceived.

This chapter will review the various sources of both primary and secondary data, comment on their strengths and weaknesses, and provide some examples of how data collected from different sources can be integrated to help answer important questions.

Types of Data

The types of data to be collected are guided by the registry design and data collection methods. The form, organization, and timing of required data are important components in determining appropriate data sources. Data elements can be grouped into categories identifying the specific variable or construct they are intended to describe. One framework for grouping data elements into categories follows:

- *Patient identifiers:* Patient identifiers are critical to linkage of all data elements in some registries. Registry data elements are linked to the specific patient through a unique patient identifier or registry identification number.
- *Patient selection criteria:* The eligibility criteria in a registry protocol (or study plan) determine the group that will be included in the registry. These criteria may be very broad or restrictive, depending on the purpose. Criteria often include demographics (e.g., target age group), a disease diagnosis, a treatment, or diagnostic procedures and laboratory tests. Health care provider, health care facility or system, and insurance criteria may also be included in certain types of registries (e.g., following care patterns of specific conditions at large medical centers compared with small private clinics).
- *Treatments and tests:* Treatments and tests are necessary to describe the natural history of patients. Treatments can include pharmaceutical, biotechnology, or device therapies or procedures, such as surgery or radiation. Evaluation of the treatment itself is often a primary focus of registries (e.g., treatment safety and effectiveness over 5 years). Results of laboratory testing or diagnostic procedures may be included as registry outcomes and may also be used in defining a diagnosis or condition of interest.
- *Confounders:* Confounders are elements or factors that have an independent association with the outcomes of interest. These are particularly important because patients are typically not randomized to therapies in registries. Confounders such as comorbidities (disease diagnoses and conditions) can confuse analysis results and interpretation of causality. Information on the health care provider, treatment facility, concomitant therapies, or insurance may also be considered.

- *Outcomes:* The focus of this document is on patient outcomes. Outcomes are end results and are defined for each condition, including patient reported information. In some registries, surrogate markers, such as biomarkers or other interim outcomes (e.g., hemoglobin A1C levels in diabetes), that are highly reflective of the longer-term end results are used.

Cost/Resource Utilization: Cost and/or resource utilization data may be necessary to examine the cost effectiveness of a treatment. Resource utilization data reflect the resources consumed (both services and products), while cost data reflects a monetary value assigned to those resources. Examples include the actual cost of the treatment (e.g., the medication, screening, procedure, etc.) and the associated costs of the intervention (e.g., treatment of side effects, expenses incurred traveling to and from doctors' appointments, etc.). Costs that are avoided due to the treatment (i.e., the cost to treat the avoided disease) and costs related to lost work days may also be important to collect, depending on the objectives of the study. The types of data elements included in this framework are further described in Chapter 5 and below, with respect to their source or the utility of the data for linking to other sources. Many of these may be available through data sources outside of the registry system.

Patient identifiers—Depending on the data sources required, registries may utilize certain personal identifiers for patients in order to locate these same patients in other databases and link the data. For example, Social Security Numbers (SSNs), as well as a combination of other personal identifiers, can be utilized to identify individuals in the National Death Index (NDI). Patient contact information, such as address and phone numbers, may be collected to support tracking of participants over time. Information for additional contacts (e.g., family members) may be collected to support followup in cases where the patient cannot be reached. In many cases, patient informed consent and appropriate privacy authorizations are required to utilize personal identifiers for registry purposes; Chapter 8 discusses the legal requirements for including patient identifiers. Systems and processes must be in place to manage security and confidentiality of these data. Confidentiality can be enhanced by assigning a registry-specific identifier via a crosswalk algorithm, as discussed below. Demographics, such as date of birth (to calculate age at any time point), gender, and ethnicity, are typically collected and may be used to stratify the registry population.

Disease/condition—Disease or condition data include those related to the disease or condition of focus for the registry and may incorporate comorbidities. Elements of interest related to the confirmation of a diagnosis or condition could be date of diagnosis and the specific diagnostic results that were used to make the diagnosis, depending on the purpose of the registry. Disease or condition is often a primary eligibility or outcome variable in registries, whether the intent is to answer specified treatment questions (e.g., measure effectiveness or safety) or to describe the natural history. This information may also be collected in constructing a medical history for a patient. In addition to "yes" or "no" to indicate presence or absence of the diagnosis, it may be important to capture responses such as "missing" or "unknown."

Treatment/therapy—Treatment or therapy data include specific identifying information for the primary treatment (e.g., drug name or code, biologic, device product or component parts, or surgical intervention, such as organ transplant or coronary artery bypass graft), and may include information on concomitant treatments. Dosage (or parameters for devices), route of administration, and prescribed exposure time, such as daily or three times weekly for 4 weeks, should be collected. Pharmacy data may include dispensing information, such as the primary date of dispensation and subsequent refill dates. Data in device registries can include the initial date of dispensation or implantation and subsequent dates and

specifics of required evaluations or modifications. Compliance data may also be collected if pharmacy representatives or clinic personnel are engaged to conduct and report pill counts or volume measurements on refill visits or return visits for device evaluations and modifications.

Laboratory/procedures—Laboratory data include a broad range of testing, such as blood, tissue, catheterization, and radiology. Specific test results, units of measure, and laboratory reference ranges or parameters are typically collected. Laboratory databases are becoming increasingly accessible for electronic transfer of data, whether through a system-wide institutional database or a private laboratory database. Diagnostic testing or evaluation may include procedures such as psychological or behavioral assessments. Results of these procedures and physician exam procedures may be difficult to obtain through data sources other than the patient medical record.

Biosamples—The increased collection, testing and storage of biological specimens as part of a registry (or independently as a potential secondary data source such as those described further below) provides another source of information that includes both information from genetic testing (such as genetic markers) and actual specimens.

Health care provider characteristics—Information on the health care provider (e.g., physician, nurse, or pharmacist) may be collected, depending on the purpose of the registry. Training, education, or specialization may account for differences in care patterns. Geographic location has also been used as an indicator of differences in care or medical practice.

Hospital/clinic/health plans—System interactions include office visits, outpatient clinic visits, emergency room visits, inpatient hospitalizations, procedures, and pharmacy visits, as well as associated dates. Data on all procedures as defined by the registry protocol or plan (e.g., physical exam, psychological evaluation, chest x-ray, CAT scan), including measurements, results, and units of measure where applicable, should be collected. Cost accounting data may also be available to match these interactions and procedures. Descriptive information related to the points of care may be useful in capturing differences in care patterns and can also be used to track patterns of referral of care (e.g., outpatient clinic, inpatient hospital, academic center, emergency room, pharmacy).

Insurance—The insurance system or payer claims data can provide useful information on interactions with the health care systems, including visits, procedures, inpatient stays, and costs associated with these events.

Cost/Resource Utilization— Resource consumption (e.g. hospitalizations, office visits, medications) can be important endpoints in a registry. Costs reflect resources consumed and may be gathered from administrative databases (e.g., claims data from payers reflecting actual costs) or determined by assigning standard monetary values (e.g. based on national CMS payment schedules) to resource consumption gathered through other methods (e.g. chart review, patient questionnaires). When using data from payers, it is important to understand what is covered under various plans, as this may affect utilization patterns. Registries that collect cost data over long periods of time (i.e., many years) may need to adjust costs for inflation during the analysis phase of the study.

Data Sources

Data sources are classified as primary or secondary based on the relationship of the data to the registry purpose. Primary data sources incorporate data collected for direct purposes of the registry (i.e., primarily for the registry). Primary data sources are typically used when the data of interest are not available or, if available, are unlikely to be of sufficient accuracy and reliability for the planned analyses and uses. Primary data collection increases the probability of completeness, validity, and reliability (see Chapter 5) because the registry drives the methods of measurement and data collection. These data are prospectively planned and collected under the direction of a protocol or study plan, using common procedures and the same format across all registry sites and patients. The data are readily integrated for tracking and analyses. Since the data entered can be traced to the individual who collected them, primary data sources are more readily reviewed through automated checks or followup queries from a data manager than is possible with many secondary data sources.

Secondary data sources are comprised of data originally collected for purposes other than the registry under consideration (e.g., standard medical care, insurance claims processing). Data that are collected as primary data for one registry would be considered secondary data from the perspective of a second registry if linking were done. These data are often stored in electronic format and may be available for use with appropriate permissions. Data from secondary sources may be used in two ways: 1) the data may be transferred and imported into the registry, becoming part of the registry database, or 2) the secondary data and the registry data may be linked to create a new, larger data set for analysis. This chapter primarily focuses on the first use for secondary data, while Chapter 7 discusses the complexities of linking registries with other databases.

When considering secondary data sources, it is important to note that health professionals are accustomed to entering the data for defined purposes, and additional training and support for data collection are not required. Often, these data are not constrained by a data collection protocol and they represent the diversity observed in real-world practice. However, there may be increased probability of errors and underreporting because of inconsistencies in measurement, reporting, and collection. Staff changes can further complicate data collection and may affect data quality. There may also be increased costs for linking the data from the secondary source to the primary source and dealing with any potential duplicate or unmatched patients.

Sufficient identifiers are also necessary to accurately match data between the secondary sources and registry patients. The potential for mismatch errors and duplications must be managed. (See Case Example 19.) The complexity and obligations inherent in the collection and handling of personal identifiers have previously been mentioned (e.g., obligations for informed consent, appropriate data privacy, and confidentiality procedures).

Some of the secondary data sources do not collect information at a specific patient level but are anonymous and intended to reflect group or population estimates. For example, census tract or ZIP-Code-level data are available from the Census Bureau and can be merged with registry data. These data can be used as "ecological variables" to support analyses of income or education when such socioeconomic data are missing from registry primary data collection. The intended use of the data elements will determine whether patient-level information is required.

The potential for data completeness, variation, and specificity must be evaluated in the context of the registry and intended use of the data. It is advisable to have a solid understanding of the original purpose of the secondary data collection, including processes for collection and submission, and verification and validation practices. Questions to ask include: Is data collection passive or active? Are standard definitions or codes used in reporting data? Are standard measurement criteria or instruments utilized (e.g., diagnoses, symptoms, quality of life)? The existence and completeness of claims data, for example, will depend on insurance company coverage policies. One company may cover many preventive services, whereas another may have more restricted coverage. Also, coverage policies can change over time. These variations must be known and carefully documented so as not to misinterpret use rates. Additionally, secondary data may not all be collected in the format required for registry purposes (e.g., units of measure) and may require transformation for integration and analyses.

An overview of secondary data sources that may be used for registries is given below. Table 8 identifies some key strengths and limitations of the identified data sources.

Medical chart abstraction—Medical charts primarily contain information collected as a part of routine medical care. These data reflect the practice of medicine or health care in general and at a specific level (e.g., geographical, by specialty care provider). Charts also reflect uncontrolled patient behavior (e.g., noncompliance). Collection of standard medical practice data is useful in looking at treatments and outcomes in the real world, including all of the confounders that affect the measurement of effectiveness (vs. efficacy) and safety outside of the controlled conditions of a clinical trial. Chart documentation is often much poorer than one might expect, and there may be more than one patient-specific medical record (e.g., hospital and clinical records). A pilot collection is recommended for this labor-intensive method of data collection to explore the availability and reproducibility of the data of interest. It is important to recognize that physicians and other clinicians do not generally use standardized data definitions in entering information into medical charts, meaning that one clinician's documented diagnosis of "chronic sinusitis" or "osteoarthritis" or description of "pedal edema" may differ from that of another clinician.

Electronic health records.—The use of electronic health records (EHRs), sometimes called electronic medical records, or EMRs, is increasing. EHRs have an advantage over paper medical records because the data in some EHRs can be readily searched and integrated with other information (e.g., laboratory data). The ease with which this is accomplished depends on whether the information is in a relational database or exists as scanned documents. An additional challenge relates to terminology and relationships. For example, including the term "fit" in a search for patients with epilepsy can yield a record for someone who was noted as "fit," as in healthy. Relationships can also be difficult to identify through searches (e.g., patient had breast cancer vs. patient's mother had breast cancer). The quality of the information has the same limitations as described in the paragraph above. Both the availability and standardization of EHR data is expected to grow significantly in the near future. The Veteran's Administration Computerized Patient Record System (CPRS) is already estimated to cover 4.2 million lives, and some data suppliers cite individual data sets exceeding 10 million lives.[209] Further, it is anticipated that more significant standardization of EHR data will result from the "EHR certification" requirements anticipated under the American Recovery and Reinvestment Act of 2009 (ARRA). Such standardization should increase not only the availability and utility of EHR records, but also the ability to aggregate them into larger data sources.

Institutional or organizational databases— Institutional or organizational databases may be evaluated as a potential source of a wide variety of data. System-wide institutional or hospital databases are central data repositories, or data warehouses, that are highly variable from institution to institution. They may include a portion of everything from admission, discharge, and transfer information to data reflecting diagnoses and treatment, pharmacy prescriptions, and specific laboratory tests. The latter might be chemistry or histology laboratory data, including patient identifiers with associated dates of specimen collection and measurement, results, and standard "normal" or reference ranges. Catheterization laboratory data for cardiac registries may be accessible and may include details on the coronary anatomy and percutaneous coronary intervention. Other organizational examples are computerized order entry systems, pharmacies, blood banks, and radiology departments.

Table 8. Key Data Sources—Strengths and Limitations

Data source	Strengths and uses	Limitations
Direct patient reports	• Patient and/or caregiver outcomes. • Unique perspective. • Obtaining information on treatments not necessarily prescribed by clinicians (e.g., over-the-counter drugs, herbal medications). • Obtaining intended compliance information. • Useful when timing of followup may not be concordant with timing of clinical encounter.	• Literacy, language, or other barriers that may lead to underenrollment of some subgroups. • Validated data collection instruments may need to be developed. • Loss to followup or refusal to continue participation. • Limited confidence in reporting clinical information and utilization information.
Direct clinician reports	• More specific information than available from coded data or medical record.	• Clinicians are highly sensitive to burden. • Consistency in capture of patient signs, symptoms, use of nonprescribed therapy.
Medical chart abstraction	• Information on routine medical care and practice, with more clinical context than coded claims. • Potential for comprehensive view of patient medical and clinical history. • Use of abstraction and strict coding standards (including handling of missing data) increases the quality and interpretation of data abstracted.	• The underlying information is not collected in a systematic way. For example, a diagnosis of bacterial pneumonia by one physician may be based on a physical exam and patient report of symptoms, while another physician may record the diagnosis only in the presence of a confirmed laboratory test. • It is difficult to interpret missing data. For example, does absence of a specific symptom in the visit record indicate that

Data source	Strengths and uses	Limitations
		the symptom was not present or that the physician did not actively inquire about this specific symptom or set of symptoms? • Data abstraction is resource intensive. • Complete medical and clinical history may not be available (e.g., new patient to clinic).
Electronic health records (EHRs)	• Information on routine medical care and practice, with more clinical context than coded claims. • Potential for comprehensive view of patient medical and clinical history. • Efficient access to medical and clinical data. • Use of data transfer and coding standards (including handling of missing data) will increase the quality of data abstracted.	• Underlying information from physicians was not collected using uniform decision rules. (See example under "Medical chart abstraction.") • Consistency of data quality and breadth of data collected varies across sites. • Difficult to handle information uploaded as text files into the EHRs (e.g., scanned physician reports) vs. direct entry into data fields. • Historical data capture may require manual chart abstraction prior to implementation date of medical records system. • Complete medical and clinical history may not be available (e.g., new patient to clinic). • EHR systems vary widely. If data come from multiple systems, the registry should plan to work with each system individually to understand the requirements of the transfer.
Institutional or organizational databases	• Diagnostic and treatment information (e.g., pharmacy, laboratory, blood bank, radiology). • Resource utilization (e.g., days in hospital). • May incorporate cost data (e.g., billed and/or paid amounts from	• Important to be knowledgeable on coding systems used in entering data into the original systems. • Institutional or organizational databases vary widely. The registry should plan to work

Data source	Strengths and uses	Limitations
	insurance claims submissions).	with each system individually to understand the requirements of the transfer.
Administrative databases	• Useful for tracking health care resource utilization and cost-related information. • Range of data includes anything that is reimbursed by health insurance (generally including visits to physicians and allied health providers, most prescription drugs, many devices, hospitalization(s), if a lab test was performed, and in some cases, actual lab test results for selected tests (e.g., blood test results for cholesterol, diabetes). • In some cases, demographic information (e.g., gender, date of birth from billing files) can be uploaded. • Potential for efficient capture of large populations.	• Represents clinical cost drivers vs. complete clinical diagnostic and treatment information. • Important to be knowledgeable on the process and standards used in claims submission. For example, only primary diagnosis may be coded and secondary diagnoses not captured. In other situations, value-laden claims may not be used (e.g., an event may be coded as a "nonspecific gynecologic infection" rather than a "sexually transmitted disease"). • Important to be knowledgeable on data handling and coding systems used when incorporating the claims data into the administrative systems. • Can be difficult to gain the cooperation of partner groups, particularly in regard to receiving the submissions in a timely manner.
Death indexes	• Completeness—death reporting is mandated by law in the United States. • Strong backup source for mortality tracking (e.g., patient lost to followup). • National Death Index (NDI)—centralized database of death records from State vital statistics offices, database updated annually. • NDI causes of death relatively reliable (93-96 percent) compared with State death certificates. • Social Security Administration's (SSA) Death Master File—database	• Time delay—indexes depend on information from other data sources (e.g., State vital statistics offices), with delays of 12 to 18 months or longer (NDI). It is important to understand the frequency of updates of specific indexes that may be utilized. • Absence of information in death indexes does not necessarily indicate "alive" status at a given point in time. • Most data sources are country-specific, and thus do not

Data source	Strengths and uses	Limitations
	of deaths reported to SSA, database updated weekly.	include deaths that occurred outside of the country.
U.S. Census Bureau databases	• Population data. • Core census survey conducted every decade. • Wide range in specificity of information from U.S. population down to neighborhood and household level. • Useful in determining population estimates (e.g., numbers, age, family size, education, employment status).	• Targets participants via survey sampling methodology and estimates. • Does not provide subject-level data.
Existing registries	• Can be merged with another data source to answer additional questions not considered in the original registry protocol or plan. • May include specific data not generally collected in routine medical practice. • Can provide historical comparison data. • Reduces data collection burden for sites, thereby encouraging participation.	• Important to understand the existing registry protocol or plan to evaluate data collected for element definitions, timing, and format. • Creates a reliance on the other registry. • Other registry may end. • Other registry may change data elements (which highlights the need for regular communication). • Some sites may not participate in both. • Must rely on the data quality of the other registry.

Administrative databases—Private and public medical insurers collect a wealth of information in the process of tracking health care, evaluating coverage, and managing billing and payment. Information in the databases includes patient specific information (e.g., insurance coverage and copays; identifiers such as name, demographics, Social Security Numbers, or plan numbers; and dates of birth) and health care provider descriptive data (e.g., identifiers, specialty characteristics, locations). Typically, private insurance companies organize health care data by physician care (e.g., physician office visits) and hospital care (e.g., emergency room visits, hospital stays). Data include procedures and associated dates, as well as costs charged by the provider and paid by the insurers. Amounts paid by insurers are often considered proprietary and unavailable. Standard coding conventions are utilized in the reporting of diagnoses, procedures, and other information. Coding conventions include the Current Procedure Terminology (CPT) for physician services and International Classification of Diseases (ICD) for

diagnoses. The databases serve the primary function of managing and implementing insurance coverage, processing, and payment.

Medicare and Medicaid claims files are two examples of commonly used administrative databases. The Medicare program covers nearly 45 million people in the United States, including almost everyone over the age of 65, people under the age of 65 who qualify for Social Security Disability, and people with end-stage renal disease.[210] The Medicaid program covers low-income children and their mothers, pregnant women, the blind, aged, or disabled. As of 2007, approximately 40 million people were covered by Medicaid.[211] Medicare and Medicaid claims files, maintained by the Centers for Medicare & Medicaid Services (CMS), can be obtained for inpatient, outpatient, physician, skilled nursing facility, durable medical equipment, and hospital services. As of 2006, Medicare claim files for prescription drugs can also be obtained. The claims files generally contain person-specific data on providers, beneficiaries, and recipients, including individual identifiers that would permit the identity of a beneficiary or physician to be deduced. Data with personal identifiers are clearly subject to privacy rules and regulations. As such, the information is confidential and is to be used only for reasons compatible with the purpose(s) for which the data are collected. The Research Data Assistance Center (ResDAC), a CMS contractor at the University of Minnesota, provides assistance to academic, government, and nonprofit researchers interested in using Medicare and/or Medicaid data for their research.[212]

Death and birth records—Death indexes are national databases tracking population death data (e.g., NDI[213] and the Death Master File [DMF] of the Social Security Administration [SSA][214]). Data include patient identifiers, date of death, and attributed causes of death. These indexes are populated through a variety of sources. For example, the DMF includes death information on individuals who had an SSN and had their death reported to the SSA. Reports may come in to the SSA by different paths, including from survivors or family members requesting benefits or from funeral homes. However, because of the importance of tracking Social Security benefits, all States, nursing homes, and mortuaries are required to report all deaths to the SSA, thus ensuring virtually 100 percent complete mortality ascertainment for those eligible for SSA benefits. The NDI is updated annually with computer death records submitted by State vital statistics offices and has all, or nearly all, deaths in the United States. The NDI can be used to provide both fact of death and cause of death, as recorded on the death certificate. Cause-of-death data in the NDI are relatively reliable (93-96 percent) compared with death certificates.[215,216] Time delays in death reporting should be considered when using these sources, and vital status should not be assumed to be alive by the absence of information at a recent point in time. These indexes are a valuable source of data for death tracking. Of course, mortality data can be accessed directly through queries of State vital statistics offices and health departments when targeting information on a specific patient or within a State. Likewise, birth certificates are available through State departments and may be useful in registries of children or births.

Area level databases—Two sources of area level data are the U.S. Census and the Area resource file (ARF). The U.S. Census Bureau databases[217] provide population-level data utilizing survey sampling methodology. The Census Bureau conducts many different surveys, the main one being the population census. The primary use of the data is to determine the number of seats assigned to each State in the House of Representatives, although the data are used for many other purposes. These surveys calculate estimates through statistical processing of the sampled data. Estimates can be provided with a broad range of granularity, from population numbers for large regions (e.g., specific States), to ZIP Codes, all

the way down to a household level (e.g., neighborhoods identified by street addresses). Information collected includes demographic, gender, age, education, economic, housing, and work data. The data are not collected at an individual level but may serve other registry purposes, such as understanding population numbers in a specific region or by specific demographics. The ARF is maintained by the Health Resources and Services Administration, which is part of the Department of Health and Human Services. The ARF includes county-level data on health facilities, health professions, measures of resource scarcity, health status, economic activity, health training programs, and socioeconomic and environmental characteristics.[218]

Provider-level databases—Data on medical facilities and physicians may be important for categorizing registry data or conducting subanalyses. Two sources of such data are the American Hospital Association's Annual Survey Data and the American Medical Association's Physician Masterfile Data Collection. The Annual Survey Data is a longitudinal database that collects 700 data elements, covering organizational structure, personnel, hospital facilities and services, and financial performance , from over 6,000 hospitals in the United States.[219] Hospitals in the database each have a unique ID, allowing the data to be linked to other sources; however, there is a data lag of about 2 years, and the data may not provide enough nuanced detail to support some analyses of cost or quality of care. The Physician Masterfile Data Collection contains current and historic data on nearly one million physicians and residents in the United States. Data on physician professional medical activities, hospital and group affiliations, and practice specialties are collected each year.

Existing registry and other databases—There are numerous national and regional registries and other databases that may be leveraged for incorporation into other registries (e.g., disease-specific registries managed by nonprofit organizations, professional societies, or other entities). An example is the National Marrow Donor Program (NMDP),[220] a global database of cord blood units and volunteers who have consented to donate marrow and blood cells. Databases maintained by the NMDP include identifiers and locators in addition to information on the transplants, such as samples from the donor and recipient, histocompatibility, and outcomes. NMDP actively encourages research and utilization of registry data through a data application process and submission of research proposals. In accessing data from one registry for the purposes of another, it is important to recognize that data may have changed during the course of the source registry, and this may or may not have been well documented by the providers of the data. For example, in the United States Renal Data System (USRDS),[221] a vital part of personal identification is CMS 2728, an enrollment form that identifies the incident data for each patient as well as other pertinent information, such as the cause of renal failure, initial therapy, and comorbid conditions. Originally created in 1973, this form is in its third version, having been revised in 1995 and again in 2005. Consequently, there are data elements that exist in some versions and not others. The coding for some variables has changed over time. For example, race has been redefined to correspond with Office of Management and Budget directives and Census categories. Furthermore, in the early years of the registry, this form was optional, so until 1983, it was only filled out for about one-half of the subjects. Since 1995, it has been mandatory for all persons with end-stage renal disease. These changes in form content, data coding, and completeness would not be evident to most researchers trying to access the data.

Other Considerations for Secondary Data Sources

The discussion below focuses on logistical and data issues to consider when incorporating data from other sources. Chapter 10 fully explores data collection, management, and quality assurance for registries.

Before incorporating a secondary data source into a registry, it is critical to consider the potential impact of the data quality of the secondary data source on the overall data quality of the registry. The potential impact of quality issues in the secondary data sources depends on how the data is used in the primary registry. For example, quality would be significant for secondary data that will be populated throughout the registry (i.e., used to populate specific data elements in the entire registry over time), particularly if these populated data elements are critical to determining a primary outcome. Quality of the secondary data would have less of an effect on overall registry quality if the secondary data are only linked to registry data for a specific analytic study. Before incorporating any secondary data source, registry sponsors should assess the quality of the secondary data source and the potential impact of that data source's quality on the primary registry. For more information on data quality, see Chapter 10.

The importance of patient identifiers for linking to secondary data sources cannot be overstated. Multiple patient identifiers should be used, and primary data for these identifiers should not be entered into the registry unless the identifying information is complete and clear. While an SSN is very useful, high-quality probabilistic linkages can be made to secondary data sources using various combinations of such information as name (last, middle initial, and first), date of birth, and gender. For example, the NDI will make possible matches based on any of seven conditions. As noted earlier, the various types of data (e.g., personal history, adverse events, hospitalization, and drug use) have to be linked through a common identifier. It is common in clinical trials to embed some intelligence into that identifier, such as SSN, initials, or site identifiers. While this may make sense for a closed system, it raises privacy concerns. A more complete discussion of both statistical and privacy issues in linkage is provided in Chapter 7. The best identifier is one that not only is unique, but has no embedded personal identification, unless that information is scrambled and the key for unscrambling it is stored remotely and securely. The group operating the registry should have a process by which each new entry to the registry is assigned a unique code and there is a crosswalk file(s) to enable the system to append this identifier to all new data as they are accrued. The crosswalk file should not be accessible by persons or entities outside the management group.

In addition, consideration should be given to the fact that a registry may need to accept and link data sets from more than one outside organization. Each institution contributing data to the registry will have unique requirements for patient data, access, privacy, and duration of use. While having identical agreements with all institutions would be ideal, this may not always be possible from a practical perspective. Yet all registries have resource constraints, and decisions about including certain institutions have to be determined based on the resources available in order to negotiate specialized agreements or to maintain specialized requirements. To the extent that some variability is allowed, agreements should be coordinated as much as possible so that the function of the registry is not greatly impaired. All organizations participating in the registry should have a common understanding of the rules regarding access to the data. Although exceptions can be made, it should be agreed that access to data will be based on independent assessment of research protocols and that participating organizations will not have veto power over access.

When data from secondary sources are utilized, agreements should specify ownership of the source data and clearly permit data use by the recipient registry. The agreements should also specify the roles of each institution, its legal responsibilities, and any oversight issues. It is critical that these issues and

agreements be put in place before data are transferred so that there are no ambiguities or unforeseen restrictions on the recipient registry later on.

Some registries may wish to incorporate data from more than one country. In these cases, it is important to ensure that the data are being collected in the same manner in each country, or to plan for any necessary conversion. For example, height and weight data collected from sites in Europe will likely be in different units than height and weight data collected from sites in the U.S. Laboratory test results may also be reported in different units, and there may be variations in the types of pharmaceutical products and medical devices that are approved for use in the participating countries. Understanding these issues prior to incorporating secondary data sources from other countries is extremely important to maintain the integrity and usefulness of the registry database.

When incorporating other data sources, consideration should also be given to the registry update schedule. A mature registry will usually have a mix of data update schedules. The registry may receive an annual update of large amounts of data, or there could be monthly, weekly, or even daily transfers of data. Regardless of the schedule of data transfer, routine data checks should be in place to ensure proper transfer of data. These should include simple counts of records as well as predefined distributions of key variables. Conference calls or even routine meetings to go over recent transfers will help avoid mistakes that might not otherwise be picked up until much later. An example of the need for regular communication is a situation that arose with the United Network for Organ Sharing (UNOS) data a few years ago. UNOS changed the coding for donor type in their transplant records. This resulted in an apparent 100-percent loss of living donors in a calendar year. This was not conveyed to USRDS and was not detected by USRDS staff. Standard analysis files that had been sent to researchers with the errors had to be replaced.

Distributed data networks are another model for sharing data. In a distributed data network, data sharing may be limited to the results of analyses or aggregated data only. There is much interest in the potential of distributed data networks, particularly for safety monitoring or public health surveillance. However, the complexities of data sharing within a distributed data network are still being addressed, and it is premature to discuss good practice for this area.

Summary

In summary, a registry is not a static enterprise. The management of registry data sources requires attention to detail, constant feedback to all participants, and a willingness to make adjustments to the operation as dictated by changing times.

Case Example 19: Integrating data from multiple sources with patient ID matching

Description:	KIDSNET is Rhode Island's computerized registry to track children's use of preventive health services. The program collects data from multiple sources and uses those data to help providers and public health professionals identify children in need of services. The purpose of the program is to ensure that all children in the State receive the appropriate preventive care measures in a timely manner.
Sponsor:	State of Rhode Island, Centers for Disease Control and Prevention, and others
Year Started:	1997
Year Ended:	Ongoing
No. of Sites	228 participating practices plus other authorized users
No. of Patients:	289,120

Challenge

In the 1990s, the Rhode Island Department of Health recognized that its data on children's health were fragmented and program specific. The State had many children's health initiatives, such as programs for hearing assessment and lead prevention, but these programs collected data separately and did not attempt to link the information. This type of fragmented structure is common in public health agencies, as many programs receive funding to fulfill a specific need but no funding to link that information with other programs. This type of linkage would benefit the department's activities, as children who are at risk for one health issue are often at risk for other health issues. By integrating the data, the department would be able to better integrate services and provide better service.

To integrate the data from these multiple sources and to allow new data to be entered directly into the program, the department implemented a computerized registry. The registry consolidates data from 11 different sources to provide an overall picture of a child's use of preventive health care services. The sources include newborn developmental risk screening; the immunization registry; lead screening; hearing assessment; Women, Infants, and Children (WIC); home visiting; early intervention; blood spot screening; foster care; birth defects; and vital records data. The goals of the registry are to monitor and assure the use of preventive health services, provide decision support for immunization administration, give providers reporting capacity to identify children who are behind in services, and provide recall services and quality assurance.

After launching in 1997, the registry began accumulating data on children who were born in the State or receiving preventive health care services in the State. Some of the 11 data sources entered data directly into the registry, and some of the data sources sent data from another database to the registry. The registry then consolidated data from these 11 sources into a single patient record for each child by matching the records using simple deterministic logic. As the registry began importing records, the system held some records as questionable matches, since it could not determine if the record was new or a match to an existing record. These records required manual review to resolve the issue, which was time consuming, at approximately 3 minutes per record.

Without resources to devote to the manual review, the number of records held as questionable matches increased to 48,685 by 2004. The time to resolve these records manually was estimated at 17 months, and the registry did not have the resources to devote to that task. However, the incomplete data resulting from

so many held records made the registry less successful at tracking children's health and less utilized by providers.

Proposed Solution

To resolve the issue of patient matching, the sponsor implemented an automated solution to the matching problem after evaluating several options, including probabilistic and deterministic matching strategies and commercial and open-source options for matching software. Since the State had limited funds for the project, an open-source product, Febrl, was selected.

A set of rules to process incoming records was developed, and an interface was created for the manual review of questionable records. Using the rules, the software determines the probability of a match for each record. The registry then sets probability thresholds above which a record is considered a certain match and below which a record is considered a new record. All of the records that fall into the middle ground require manual review.

Results

After considerable testing, the new system launched in spring 2004. Immediately upon implementation, 95 percent of the held records were processed and removed from the holding category, resulting in the addition of approximately 11,000 new patient records to the registry. The new interface for manual review reduced the time to resolve an error from 3 minutes to 40 seconds. With these improvements, the registry now imports 95 percent of the data sent to the database and is able to process the questionable records through the improved interface.

Key Point

Many strategies and products exist to deal with matching patients from multiple data sources. Once a product has been selected, careful consideration must be given to the probability thresholds for establishing a match. Setting the threshold for matches too high may result in an unmanageable burden of manual review. However, setting the threshold too low could affect data quality, as records may be merged inappropriately. A careful balance must be found between resources and data quality in order for matching software to help the registry. In addition, matching quality should be monitored over time, as matching rules and probability thresholds may need to be adjusted if the underlying data quality issues change.

For More Information

Wild EL, Hastings TM, Gubernick R et al. Key elements for successful integrated health information systems: lessons learned from the states. J Public Health Manag Pract 2004 Nov 10 Suppl:S36-S47.

Chapter 7: Linking Registry Data: Technical and Legal Considerations

The purpose of this chapter is to identify important technical and legal considerations and provide guidance to researchers and research sponsors who are interested in linking data held in a health information registry with additional data, such as from claims or other administrative files, or another registry. The chapter is designed to help investigators find an appropriate way to address their critical research questions, remain faithful to the conditions under which the data was originally collected, and protect individual patients by safeguarding their privacy and maintaining the confidentiality of the data under applicable law.

There are two equally weighted and important sets of questions to address in the planning process: (1) what is a feasible technical approach to linking the data, and (2) whether the linkage is legally feasible under the permissions, terms, and conditions that applied to the original compilations of each data set. Legal feasibility depends on the applicability of federal and state legal protections for the confidentiality of health information and participation in human research to the specific purpose of the data linkage, as well as any specific permissions obtained from individual patients for the use of their health information. Indeed, there is a great deal of analysis and planning for such projects, as the technical approach may be influenced by permitted uses of the data under applicable regulations, while the legal assessment may change depending on how the linkage needs to be performed and the nature and purpose of the resulting linked data set. Tables 1 and 2 comprise a list of technical and regulatory questions, respectively, for the consideration of data linkage project leaders during the planning of a project. The questions are intended to assist in organizing the resources needed to implement the project, including the statistical, regulatory, and collegial advice that might prove helpful in navigating the complexities of data linkage projects. This chapter presumes the investigators have identified an explicit purpose for the data linkage in the form of a scientific question they are trying to answer. The nature of this objective is critical to assessing the applicable regulatory requirements for uses of the data. Investigators should assign the goal of the data linkage project to one of the following categories of health care operations as defined by the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule, including: health care quality-related activities, public health practice, research, or some combination of these purposes. If research is one purpose of the project, then the Common Rule (human subjects protection regulations) is likely to apply to the project. More information on HIPAA and the Common Rule is provided in Chapter 8.

The application of the HIPAA Privacy and Security Rules depends on the origins of the data sets being linked, and such origins may also influence the feasibility of making the data linkage. Investigators should know the source for the original data, the conditions under which it was compiled, and what kinds of permissions apply to it, from both individual patients and the custodial institutions. Health information is most often data that has two sources: individual and institutional; these sources may have legal rights and continuing interests in the use of the data.

It is important to be aware that the legal requirements may not remain stable and the protections for the research use of health information is likely to change in response to continued development of electronic health information technologies.

This chapter provides eight sections focusing on core issues in three major parts: Technical Aspects of Data Linkage Projects, Legal Aspects of Data Linkage Projects, and Risk Mitigation for Data Linkage Projects. The Technical Aspects of Data Linkage Projects section discusses the reasons and technical methods for linking datasets containing health information, including data held in registries. The Legal Aspects of Data Linkage Projects section defines important concepts, including the different definitions of "disclosure" as used by statisticians and in the HIPAA Privacy Rule. This section also discusses the risks of identification for individuals inherent in data linkage projects and describes the legal standards of the HIPAA Privacy Rule that pertain to these risks. Finally, the Risk Mitigation for Data Linkage Projects section summarizes both recognized and developing technical methods for mitigating the risks of identification. In addition, Appendix D consists of a hypothetical data linkage project that is intended to provide context for the technical and legal information presented below. Case Examples 20, 21, and 22 describe registry-related data linkage activities. While some of the concepts presented are applicable to other important non-patient identities that might be at risk in data linkage, such as provider identities, those issues are beyond the scope of the discussion below.

Technical Aspects of Data Linkage Projects

Linking Records for Research and Improving Public Health

Data regarding the health of individuals included in registries come in a wide variety of forms, most of which have been gathered originally for the delivery of clinical services or payment for those services, and under promises or legal guarantees of confidentiality, privacy, and security. These sources of data may include individual doctor's records, billing information, vital statistics on births and deaths, health surveys, and data associated with biospecimens, among other sources.

The broad goals of registries are to amass data from potentially diverse sources to allow researchers to explore and evaluate alternative health outcomes in a systematic fashion. These goals are usually accomplished by gathering data from multiple sources and linking the data across sources, either with explicit identifiers designed for linking, or in a probabilistic fashion via the characteristics of the individuals to whom the data correspond. From the research perspective, the more data included, the better, both in the number of cases and in the details and the extent of the health information. The richer the database, the more likely it is that data analysts will be able to discover relationships that might affect or improve health care. Notably, many discussions about privacy protection focus on limiting the level of detail available in data to which others have access.

There is an ethical obligation to protect patient interests when collecting, sharing, and studying person-specific biomedical information.[222] Many people fear that information derived from their medical or biological records will be used against them in employment decisions, limit access to health or life insurance, or cause social stigma.[223] These fears are not unfounded, and various cases have transpired in which it was found that an individual's genetic characteristics or clinical manifestations were used in a manner inconsistent with an individual's expectations of privacy and fair use.[224] If individuals fear that their health-related information could be associated with, or used against them, they may be less likely to seek treatment in a clinical context or participate in research studies.[225]

A tension exists between the broad goals of registries, and regulations protecting individually identifiable information. Approaches and formal methodologies that help mediate this tension are the principal technical focus of this chapter. To understand the extent to which these tools can assist data linkages involving registry data, one needs to understand the risks of identification in different types of data.

A large body of federal law applies to privacy. A recent comprehensive review of privacy law and its effects on biomedical research identified no fewer than 15 separate federal laws pertaining to health information privacy.[226] Special federal laws also apply to health information related to substance abuse.[227] A full review of all laws related to privacy, confidentiality, and security of health information also would consider separate state privacy protections, as well as state laws pertaining to the confidentiality of data. Nevertheless, the legal aspects of this chapter only focus on the federal regulations commonly referred to as the HIPAA Privacy Rule.

What Do Privacy, Disclosure, and Confidentiality Mean?

Privacy is a term whose definition varies with context.[228] As used in the HIPAA Privacy Rule, the term applies to protected health information (PHI). In this context, the concept of privacy relates to permitted uses and disclosures of individually identifiable health information. The HIPAA Privacy Rule addresses to whom the custodian of PHI, a "covered entity," may transmit it and under what conditions. The HIPAA Privacy Rule establishes three basic concepts of health information: data that are identifiable; data that lack certain direct identifiers, otherwise known as a "limited data set"; and data that are de-identified. Registries commonly acquire identifiable data and may create the last two categories of data. Along this spectrum of data, the HIPAA Privacy Rule applies different legal standards and protections.[229]

Disclosure has two different meanings: one is technical and the other is a HIPAA Privacy Rule definition.

Technical definition

Disclosure relates to the attribution of information to the source of the data, regardless of whether the data source is an individual or an organization. There are basically three types of disclosure of data that possess the capacity to make the identity of particular individuals known: identity, attribute, and inferential.

Identity disclosure occurs when the data source becomes known from the data release itself.[230] [231]

Attribute disclosure occurs when the released data make it possible to infer the characteristics of an individual data source more accurately than would have otherwise been possible.[232] [233] The usual way to achieve attribute disclosure is through identity disclosure. First, one identifies an individual through some combination of variables and then learns about the values of additional variables included in the released data. Attribute disclosure may occur, however, without identity disclosure, such as when all people from a population subgroup share a characteristic and this quantity becomes known for any individual in the subgroup.

Inferential disclosure relates to the probability of identifying a particular attribute of a data source. Because almost any data release can be expected to increase the likelihood of an attribute being associated with a data source, the only way to guarantee protection is to release no data at all. It is for this reason that researchers use certain methods not to prevent disclosure, but to limit or control the nature of the disclosure. These methods are known as disclosure limitation methods or statistical disclosure control.[234]

HIPAA Privacy Rule definition

Disclosure means the release, transfer, provision of, access to, or divulging in any other manner of information outside of the entity holding the information.[235]

Confidentiality broadly refers to a quality or condition of protection accorded to statistical information as an obligation not to permit the transfer of that information to an unauthorized party.[236] Confidentiality can be owed to both individuals and health care organizations. A different notion of confidentiality arises from the special relationship between a clinician and patient. It relates to the ethical, legal, and professional obligation of those who receive information in the context of a clinical relationship to respect the privacy interests of their patients. Most often, the term is used in the former sense and not in the latter, but these two meanings inevitably overlap in a discussion of health information as data. The methods for disclosure limitation described here have been developed largely in the context of confidentiality protection, as defined by laws, regulations, and especially by the practices of statistical agencies.

Linking Records and Probabilistic Matching

Computer-assisted record linkage goes back to the 1950s and was put on a firm statistical foundation by Fellegi and Sunter.[237] Most common techniques for record linkage either rely on the existence of unique identifiers or they utilize a structure similar to the one Fellegi and Sunter described with the incorporation of formal statistical modeling and methods, as well as new and efficient computational tools.[238, 239] The simplest way to match records from separate databases is to use a so-called deterministic method of linking the databases employing unique identifiers contained in each record. These identifiers might be names or social security numbers in the U.S., but these particular identifiers may not, in fact, be unique. As a result, some form of probabilistic approach is typically used to match the records. Thus, there is little distinction between methods using deterministic linkage as opposed to probabilistic linkage, except for the explicit representation of uncertainty in the matching process in the latter.

The now-standard approach is built on five key components for identifying matching pairs of records across two databases:[240]

1. Represent every pair of records using a vector of features (variables) which describe similarity between individual record fields. Features can be Boolean, discrete, or continuous.

2. Place feature vectors for record pairs into three classes: matches (M), non-matches (U), and possible matches *(P)*. These correspond to "equivalent", "nonequivalent," and "possibly equivalent" (e.g., requiring human review) record pairs, respectively.

3. Perform record-pair classification by calculating the ratio $(P(\gamma \mid M)) / (P(\gamma \mid U))$ for each candidate record pair, where γ is a feature vector for the pair and $P(\gamma \mid M)$ and $P(\gamma \mid U)$ are the probabilities of observing that feature vector for a matched and non-matched pair, respectively. Two thresholds based on desired error levels—T_μ and T_λ—optimally separate the ratio values for equivalent, possibly equivalent, and nonequivalent record pairs.

4. When no training data in the form of duplicate and non-duplicate record pairs is available, matching can be unsupervised; that is, conditional probabilities for feature values are estimated using observed frequencies in the records to be linked.

5. Most record pairs are clearly non-matches, so one need not consider them for matching. This situation is managed by "blocking," or partitioning the databases, for example, based on geography or some other variable in both databases, so that only records in comparable blocks are compared. Such a strategy significantly improves efficiency.

The first four components lay the groundwork for accuracy of record-pair matching using statistical or machine learning prediction models, such as logistic regression. The fewer near identifiers used in steps 1 and 2, the poorer the match is likely to be. Accuracy is well known to be high when there is a 1–1 match between records in the two databases, and accuracy deteriorates as the overlap between the files decreases and the measurement error in the feature values consequently increases. The fifth component provides for efficiently processing large databases, but to the extent that blocking is approximate and possibly inaccurate, its use decreases the accuracy of record-pair matching. The less accurate the matching, the more "error" there will be in the merged registry files. This error will impede quality analyses and findings from the resulting data.[241, 242]

This standard approach has problems when there are lists or files with little overlap, when there are undetected duplications within files, and when one needs to link three or more lists. In the latter case, one essentially matches all lists in pairs, and then resolves discrepancies. Unfortunately, there is no unique way to do this.

Record linkage methodology has been widely used by statistical agencies, especially in the U.S. Bureau of the Census. The methodology has been combined with disclosure limitation techniques, such as the addition of "noise" to variables in order to produce public use files that the agencies believe cannot necessarily be linked back to the original databases used for the record linkage. Another technique involves protecting individual databases by stripping out identifiers and then attempting record linkage. This procedure has two disadvantages. First, the quality of matches is likely to decrease markedly, and second, the resulting merged records will still need to be protected by some form of disclosure limitation. Therefore, as long as there are not legal restrictions against the use of identifiers for record linkage purposes, it is preferable to use detailed identifiers to the extent possible and to remove them following matching procedure.

Currently there are not any special features of registry data that are known to enhance or inhibit matching. Registry data may be easier targets for re-identification because the specifics of diseases or conditions help to define the registries. In the United States, efforts are often made to match records using social security numbers. There are large numbers of entry errors for these numbers in many databases, as well as the problems associated with multiple people using one number and some people using multiple numbers.[243] Lyons et al. describe a very large-scale matching exercise in the United Kingdom linking multiple health care and social services datasets using National Health Service numbers and various alternative sets of matching variables in the spirit of the record linkage methods described above. They report achieving accurate matching at rates of only about 95 percent.[244]

Procedural Issues in Linking Datasets

It is important to understand that neither "data" nor "link" can be unambiguously defined. For instance, a dataset may be altered by the application of tools for statistical disclosure limitation, in which case it is no longer the same dataset. Linkage need not mean, as it is customarily construed, 'bring(ing) the two (or more) datasets together on a single computer.' Many analyses of interest can be performed using technologies that do not require literal integration of the datasets. Even the relationship between datasets can vary. Two datasets can hold the same attributes for different individuals ("horizontal partitioning"), different attributes for the same individuals ("vertical partitioning"), or a complex combination of the two.

The process of linking horizontally partitioned datasets engenders little incremental risk of re-identification. There is, in almost all cases, no more information about a record on the combined dataset than was present in the individual dataset containing it. Moreover, any analysis requiring only data summaries (e.g., in technical terms, sufficient statistics) that are additive across the datasets can be performed using tools based on the computer science concept of secure summation.[245] Examples of analyses for which this approach works include creation of contingency tables, linear regression, and some forms of maximum likelihood estimation.

Only in a few cases have comparable techniques for vertically partitioned data been well enough understood to be employed in practice.[246] Instead, it is necessary to actually link individual subjects' records that are contained in two or more datasets. This process is inherently and unavoidably risky because the combined dataset contains more information about each subject than either of the components.

Discussed below is a preferred approach that is complex, but it attenuates or can even obviate other problems. Suppose that each of the two datasets to be linked contains the same unique identifiers (for individuals, an example is social security numbers) in all of the records. In this case, there exist techniques based on cryptography (homomorphic encryption[247] and hash functions) that enable secure determination of which individuals are common to both datasets and assignment of unique but uninformative identifiers to the shared records. Each dataset can then be purged of individual identifiers and altered to further limit re-identification, following which error-free and risk-free linkage can be performed.

Such techniques are computationally very complex, and may involve trusted third parties, who do not, however, have access to information in either dataset other than the common identifier. Therefore, in many cases the database custodian may prefer to remove identifiers and carry out statistical disclosure limitation prior to linkage. It is important to understand that this preferred approach compromises, perhaps irrevocably, the linkage process, and may introduce errors into the linked dataset that later—perhaps dramatically—alters the results of statistical analyses.

Many techniques for record linkage depend at some level on the presence of sets of attributes in both databases that are unique to individuals but do not lead to re-identification. For instance, the combination of date-of-birth, gender, and ZIP code of residence might be present in both databases. It is estimated that this combination of attributes uniquely characterizes a significant portion of U.S. citizens, so re-identification would only require access to a suitable external database. Other techniques such as the Fellegi-Sunter record linkage methods described above are more probabilistic in nature. They can be effective, but as we noted, they also introduce data quality effects that cannot readily be characterized.

No matter how linkage is performed, a number of other issues should be addressed. For instance, comparable attributes should be expressed in the same units of measure in both datasets (e.g., English or metric values for weight). Conflicting values of attributes for each individual common to both databases need reconciliation. Another issue involves the management of records that appear in only one database; the most common decision is to drop them. Data quality provides another example; it is one of the least understood statistical problems and has multiple manifestations.[248] Even assuming some limited capability to characterize data quality, the relationship between the quality of the linked dataset and the quality of each component should be considered. The linkage itself can produce quality degradation. The best way to address these issues is not clear, and intuition can be faulty. For example, there is reason to believe that the quality of a linked dataset is strictly less than that of either component and not, as might be supposed, somewhere between the two.

Finally, it is important to understand that there exist endemic risks to data linkage. Anyone with access to one of the original datasets and the linked dataset may learn, even if imperfectly, the values of attributes in the other. It may not be possible to determine what knowledge the linkage will create without actually executing the linkage. For these reasons, strong consideration should be given to forms of data protection such as licensing and restricted access in research data centers where both analyses and results can be controlled.

Legal Aspects of Data Linkage Projects

Risks of Identification

The HIPAA Privacy Rule defines de-identification as the removal of names, addresses, telephone numbers, and other direct personal identifiers from health information; however, this removal process alone may not be sufficient. Residual data that are especially vulnerable to disclosure threats include (i) geographic detail, (ii) longitudinal information, and (iii) extreme values (e.g., income). Population health data are clearly more vulnerable than sample data, and variables that are available in other accessible databases pose special risks.

Statistical organizations such as the National Center for Health Statistics have traditionally focused on the issue of identity disclosure and thus refuse to report information in which individuals or institutions can be identified. This situation occurs, for example, when a data source is unique in the population for the characteristics under study, and is directly identifiable in the database to be released. But, such uniqueness and subsequent identity disclosure may not reveal any information other than the association of the source with the data collected in the study. In this sense, identity disclosure may only be a technical violation of a promise of confidentiality. Thus, uniqueness only raises the issue of possible confidentiality problems resulting from identification. A separate issue is whether the release of information is one that is permitted by the HIPAA Privacy Rule or is authorized by the data source.

The foregoing discussion implicitly introduces the notion of *harm*, which is not the same as a breach of confidentiality. For example, it is possible for a pledge of confidentiality to be technically violated, but produce no harm to the data source because the information is "generally known" to the public at large. In this case, some would argue that additional data protection is not required. Conversely, if one attempts to match records from one file to another file which is subject to a pledge of confidentiality, and an "incorrect" match is made, there is no breach of confidentiality, but there is the possibility of harm if the match is assumed to be correct. Furthermore, information on individuals or organizations in a release of

sample statistical data may well increase the information about characteristics of individuals or organizations not in the sample. This information may produce an inferential disclosure for such individuals or organizations and cause them harm, even though there was no confidentiality obligation. Figure 2 depicts the relationships among confidentiality, disclosure, and harm.

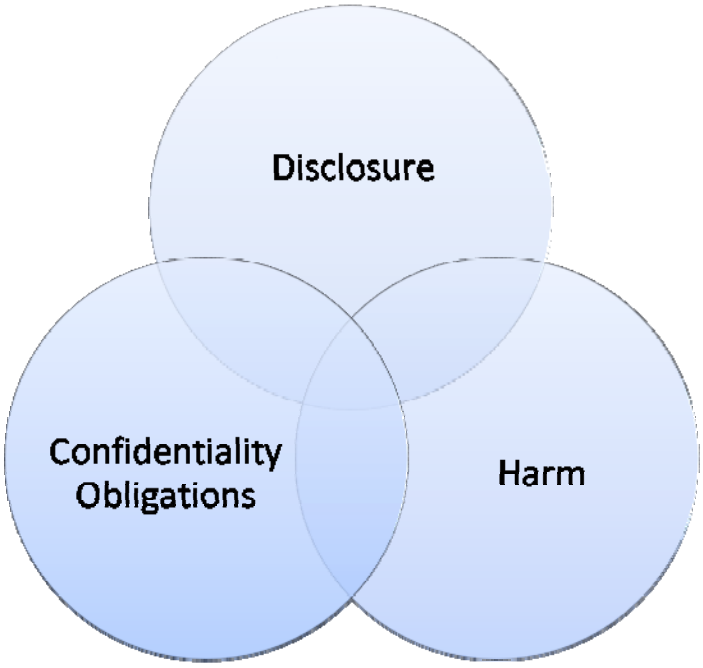

Figure 2. Relationships among confidentiality, disclosure, and harm

Some people believe that the way to assure confidentiality and prevent identity disclosure is to arrange for individuals to participate in a study anonymously. In many circumstances, such a belief is misguided, because there is a key distinction between collecting information anonymously and ensuring that personal identifiers are not inappropriately made available. Moreover, we simply do not collect clinical health care data anonymously. Not only do patient records come with multiple identifiers crucial to ensuring patient safety for clinical care, but they also contain other information that may allow the identification of the patient, even if direct identifiers are stripped from the records.

Health or medical related data may also come from sample surveys in which the participants will have been promised that their data will not be released in ways that would allow them to be individually identified. Disclosure of such data can produce substantial harm to the personal reputations or financial interests of the participants, their families, and others with whom they have personal relationships. For example, in the pilot surveys for the National Household Seroprevalence Survey, the National Center for Health Statistics moved to make responses during the data collection phase of the study anonymous because of the harm that could potentially result from information that an individual had an HIV virus infection or engaged in high-risk behavior. But, such efforts still could not guarantee that one could not identify a participant in the survey database. This example also raises an interesting question about the

confidentiality of registry data after an individual's death, in part because of the potential for harm to others. The health information of decedents is subject to the HIPAA Privacy Rule, and several statistical agencies explicitly treat the identification of a deceased individual as a violation of their confidentiality obligations.

Examples of how patients could be re-identified even if names are suppressed

For years, the confidentiality of health information has been protected through a process of "de-identification." This protection entails the removal of person-specific features, such as names, residential street addresses, phone numbers, and social security numbers. However, as discussed above, de-identification does not guarantee that individuals may not be identified from the resulting data. On multiple occasions, it has been shown that de-identified health information can be "re-identified" to a particular patient without hacking or breaking into a private health information system. For instance, in the mid-1990's Latanya Sweeney, then a graduate student at the Massachusetts Institute of Technology, showed that de-identified hospital discharge records, which were made publicly available at the state level, could be linked to identifiable public records in the form of voter registration lists. Her demonstration received notoriety, because it led to the re-identification of the medical status of the then-governor in the Commonwealth of Massachusetts.[249] This result was achieved by linking the data resources on their common fields of patient's date of birth, gender, and ZIP code. Various estimates indicate that the uniqueness of this combination of attributes in the U.S. population is somewhere between 65 and 87 percent, with certain subpopulations even more unique.[250]

High-risk identifiers

One response to the Sweeney demonstration was the HIPAA Privacy Rule de-identification standard, which requires the removal of explicit identifiers (e.g., names), dates, geocodes (for populations of less than 20,000 inhabitants), and other data elements that, in combination, could be used to ascertain an individual's identity. In all, the de-identification standard enumerates eighteen features that should be removed from patient information prior to data sharing.

Nonetheless, even the removal of these data elements may fail to prevent re-identification. In many instances, there are residual features that can lead to identification. The extent to which residual features can be used for re-identification depends on the availability of relevant data fields. Thus, one can roughly partition identifiers into "high" and relatively "low" risk features. The high-risk features are the sort that are documented in multiple environments and are publicly available. These are features that could be exploited by any recipient of such records. For instance, patient demographics are high-risk identifiers. Even de-identified health information permitted under the HIPAA Privacy Rule may leave certain individuals in a unique status, and thus, at high risk for identification through public data resources containing similar features, such as public records containing birth, death, marriage, voter registration and property assessment information.

Relatively low risk identifiers

In contrast, data elements that are lower risk do not appear in public records and are less available. For instance, clinical features, such as an individual's diagnosis and treatments, are relatively static because they are often mapped to standard codes for billing purposes. These features might appear in de-

identified information, such as hospital discharge databases, as well as in identified resources such as electronic medical records. While combinations of diagnostic and treatment codes might uniquely describe an individual patient in a population, the identifiable records are available to a much smaller group than the general public. Moreover, this select group is ordinarily considered to be trustworthy, such as the clinicians and business associates of the custodial organization for the records, because they owe independent ethical, professional, and legal duties of confidentiality to their patients.

Special issues with linkages to biospecimens

Medicine is increasingly moving towards evidence-based and personalized health care systems. In support of this trend, there is a growing focus on associations between clinical and biological phenomena. In particular, the decreasing cost of genome sequencing technology has facilitated a rapid growth in the volume of biospecimens and derived DNA sequence data. As much of this research is sponsored through federal funding, it is subject to data sharing requirements. However, biospecimens and DNA, in particular, are inherently unique and there are a number of routes by which DNA information can be identified to an individual.[251] For instance, there are over a million single nucleotide polymorphisms (SNPs) in the human genome; these little snippets of DNA are often used to make genetic correlations with clinical conditions. Yet, it is estimated that fewer than one hundred SNPs can uniquely represent an individual.[252] Thus, if de-identified biological information is tied to sensitive clinical information, it may provide a match to the identified biological information itself, (e.g., in a forensic setting).[253]

Biospecimens and derivative information are of particular concern because they can convey knowledge not only about the individual from whom they are derived, but also about other related individuals. For instance, it is possible to derive estimates about the DNA sequence of relatives.[254] If the genetic information is predictive or diagnostic, it can adversely affect the ability of family members to obtain insurance and employment, or it may cause social stigmatization.[255] The Genetic Information Nondiscrimination Act of 2008 (GINA) prohibits health insurers from using genetic information about individuals or their family members, whether collected intentionally or incidentally, in determining eligibility and coverage, or in underwriting and premium setting. Insurers may, however, in collaboration with external research entities, request that policy holders undergo genetic testing, but a refusal to do so cannot be permitted to affect the premium or result in medical underwriting.[256]

Risk Mitigation for Data Linkage Projects

Methodology for Mitigating the Risk of Re-Identification

The disclosure limitation methods briefly described here are designed to protect against identification of individuals in statistical databases, and are among the techniques that data linkage projects involving registries are most likely to use. One problem these methods do not address is the simultaneous protection of individual and institutional data sources. The discussion here also relates to the problems addressed by secure computation methodologies, which are explored in the next section.

Basic methodology for statistical disclosure limitation

Duncan[257] categorizes the methodologies used for disclosure limitation in terms of disclosure limiting masks, i.e., transformations of the data where there is a specific functional relationship (possibly stochastic) between the masked values and the original data. The basic idea of masking involves data

transformations. The goal is to transform an $n \times p$ data matrix Z through pre- and post-multiplication and the possible addition of noise, such as depicted in Equation (1):

$$Z \rightarrow AZB + C \qquad (1)$$

where A is a matrix that operates on cases, B is a matrix that operates on variables, and C is a matrix that adds perturbations or noise to the original information. Matrix masking includes a wide variety of standard approaches to disclosure limitation:

- Adding noise,
- Releasing a subset of observations (delete rows from Z),
- Cell suppression for cross-classifications,
- Including simulated data (add rows to Z),
- Releasing a subset of variables (delete columns from Z), and
- Switching selected column values for pairs of rows (data swapping).

This list also omits some methods, such as micro-aggregation and doubly random swapping, but it provides a general idea of the types of techniques being developed and applied in a variety of contexts, including to medical and public health data.

The possibilities of both identity and attribute disclosure remain, even when a mask is applied to a dataset, although the risks may be substantially diminished.

Duncan suggests that we can categorize most disclosure limiting masks as suppressions (e.g., cell suppression), re-codings (e.g., collapsing rows or columns, or swapping), or samplings (e.g., releasing subsets), although he also allows for simulations as discussed below. Further, some masking methods alter the data in systematic ways (e.g., through aggregation or through cell suppression), whereas others do it through random perturbations, often subject to constraints for aggregates. Examples of perturbation methods are controlled random rounding, data swapping, and the post-randomization method (PRAM) of Gouweleeuw, [258] which has been generalized by Duncan and others. One way to think about random perturbation methods is as a restricted simulation tool that connects them to other types of simulation approaches.

Various authors pursue simulation strategies and present general approaches to "simulating" from a constrained version of the cumulative, empirical distribution function of the data. In 1993, Rubin asserted that the risk of identity disclosure could be eliminated by the use of synthetic data (in his case using Bayesian methodology and multiple imputation techniques) because there is no direct function link between the original data and the released data.[259] Said another way, the data remain confidential because simulated individuals have replaced all of the real ones. Raghunathan, Reiter, and Rubin [260] provide

details on the implementation of this approach. Abowd and Woodcock (for their chapter in Doyle et al., 2001) [261] describe a detailed application of multiple imputation and related simulation technology for a longitudinally linked individual and work history dataset. With both simulation or multiple-imputation methodology, however, it is still possible that the data values of some simulated individuals remain virtually identical to those in the original sample, or at least close enough that the possibility of both identity and attribute disclosure remain. As a result, checks for the possibility of unacceptable disclosure risk should be made.

Another important feature of the statistical simulation approach is that information on the variability is directly accessible to the user. For example, in the Fienberg, Makov, and Steele [262] approach for categorical data, the data user can begin with the reported table and information about the margins that are held fixed, and then run the Diaconis-Sturmfels Monte Carlo Markov chain algorithm to regenerate the full distribution of all possible tables with those margins. This technique allows the user to make inferences about the added variability in a modeling context that is similar to the approach to inference in Gouweleeuw, et al.[263] Similarly, Raghunathan and colleagues proposed the use of multiple imputations to directly measure the variability associated with the posterior distribution of the quantities of interest.[264] As a consequence, Rubin showed that simulation and perturbation methods represent a major improvement in access to data without sacrificing confidentiality over cell suppression and data swapping. These methods also conform to the statistical principle allowing the user of released data to apply standard statistical operations without being misled.

There has been considerable research on disclosure limitation methods for tabular data, especially in the form of multi-way tables of counts (contingency tables). The most popular methods include a process known as cell suppression, which systematically deletes the values in selected cells in the table and collapses categories. This process is a form of aggregation. While cell suppression methods have been very popular among the U.S. government statistical agencies, and are useful for tables with non-negative entries rather than simply counts, they also have major drawbacks. First, good algorithms do not yet exist for the methodology when it is associated with high dimensional tables. More importantly, the methodology systematically distorts the information about the cells in the table for users and, as a consequence, makes it difficult for secondary users to draw correct statistical inferences about the relationships among the variables in the table. For further discussion on cell suppression and extensive references, see the various chapters in Doyle et al.,[265] notably the one by Duncan and his collaborators.

A special example of collapsing categories involves summing over variables to produce marginal tables. Instead of reporting the full multi-way contingency table, one or more collapsed versions of it might be reported. The release of multiple sets of marginal totals has the virtue of allowing statistical inferences about the relationships among the variables in the original table using log-linear model methods (e.g., see Bishop, Fienberg, and Holland).[266] With multiple collapsed versions, statistical theory makes it clear that one may have highly accurate information about the actual cell entries in the original table. As a result, the possibility of disclosures still requires investigation. In part to address this problem, a number of researchers have recently worked on the problem of determining upper and lower bounds for the cells of a multi-way table given a set of margins, although other measures of risk may clearly be of interest. The problem of computing bounds is in one sense an old one, at least for two-way tables, but it is also deeply linked to recent mathematical developments in statistics and has generated a flurry of new research.[267] [268]

The risk-utility tradeoff

Common to virtually all of the methodologies discussed in the preceding section is the notion of a risk-utility tradeoff, in which the risk of disclosure is balanced with the utility of the released data, e.g., see Duncan[269], Fienberg[270], and their chapter with others in Doyle et al.[271] To keep this risk at a low level requires applying more extensive data masking, which limits the utility of what is released. Advocates for the use of simulated data often claim that this use eliminates the risk of disclosure, but still others dispute this claim.

Privacy-preserving data mining methodologies

With the rise in the data mining and machine learning literature over the past two decades, there have been a large number of methods introduced under the banner of privacy-preserving computation. The methodologies vary, and many of them focus on standard tools such as the addition of noise or data swapping of one sort or another. But, the claims of identity protection in this literature are often exaggerated or unverifiable. For a discussion of some of these ideas and methods, see Fienberg and Slavkovic.[272] For two recent interesting examples explicitly set in the context of medical data, see Malin and Sweeney[273] and Boyens, Krishnan, and Padman.[274]

The common message of this literature is that privacy protection has costs measured in the lack of availability of research data. To increase the utility of released data for research, some measure of privacy protection, however small, needs to be sacrificed. It is nonetheless still possible to optimize utility, subject to predefined upper bounds on what is considered to be acceptable risk of identification. See a related discussion in Fienberg.[275]

Cryptographic approaches to privacy protection

While the current risks of identification in modern databases is similar for statistical agencies and biomedical researchers, there are also new challenges: contemporary information repositories that store social network data (e.g., cell phone, MySpace, and Facebook data), product preferences (e.g., Amazon), web search data, and other sources of information not previously archived in a digital format. A recent literature emanating from cryptography focuses on algorithmic aspects of the problem with an emphasis on automation and scalability of a process for conferring anonymity. Automation, in turn, presents a fundamentally different perspective on how privacy is defined and provides for both a formal definition of privacy and proofs for how it can be protected. By focusing on the properties of the algorithm for anonymity, it is possible to formally guarantee the degree of privacy protection and the quality of the outputs in advance of data collection and publication.

This new approach, known as differential privacy, limits the incremental information a data user might learn beyond that which is known before exposure to the released statistics. No matter what external information is available, the differential privacy approach guarantees the same information is learned about an individual, whether or not information about the individual is present in the database. The papers by Dwork et al.[276, 277] provide an entry point to this literature. Differential privacy, as these authors describe it, works primarily through the addition of specific forms of noise to all data elements and the summary information reported, but it does not address issues of sampling or access to individual-

level micro-data. While these methods are intriguing, their utility for data linkages with registry data remains an open issue.

Security Practices, Standards, and Technologies

In general, people adopt two different philosophical positions about the preservation of confidentiality associated with individual-level data: (1) *restricted* or *limited information*, with restrictions on the amount or format of the data released, and (2) *restricted* or *limited access*, with restrictions on the access to the information itself.

If registry data are a public health good, then restricted access is justifiable only in situations where the confidentiality of data in the possession of a researcher cannot be protected through some form of restriction on the information released. Restricted access is intended to allow use of unaltered data by imposing certain conditions on users, analyses, and results that limit disclosure risk. There are two primary forms of restricted access. Licensing legally binds users to conditions such as agreeing not to use data for re-identification and advance review of publications, but allows users to transfer data to their sites, and to use the software of their choice. Research data centers, discussed in more detail below, and remote analysis servers are conceptually similar: users, and sometimes analyses, are evaluated in advance. The results are reviewed, and often limited, in order to limit risk of disclosure. The data remain at the holder's site and computers; the difference is whether access is in person or using the World Wide Web.

Accountability

To limit the possibility of re-identification, data can be manipulated by the above techniques to mitigate risk. At the same time, it is important to ensure that researchers are accountable for the use of the datasets that are made available to them. Best practices in data security should be adopted with specific emphasis on authentication, authorization, access control, and auditing. In particular, each data recipient should be assigned a unique login ID or, if the data is made available online, through a query-response server. Prior to each session of data access, data custodians should authenticate users. Access to information should be controlled either in a role-based or information-based manner. Each user access and query to the data should be logged to enable auditing functions. If there is a breach in data protection, the data custodian can investigate the potential cause and make any required notifications.

Registries as data enclaves

To limit access to data, many statistical agencies have built enclaves, often referred to as research data centers, where users can access and use data in a regulated environment. In such settings, the security of computer systems is controlled and managed by the agency providing the data. Such environments may maximize data security. For a more extensive discussion of the benefits of restricted access, see the chapter by Dunne in Doyle, et al.[278]

These enclaves incur considerable costs associated with their establishment and upkeep. A further limitation is that the enclave may require the physical presence of the data user, which also increases the overall cost to researchers working with the data. Moreover, such environments often prevent users from

executing specialized data analyses, which may require programming and other software development beyond the scope of traditional statistical software packages made available in the enclave.

The process for access to data in enclaves or restricted centers involves an examination of the research credentials of those wishing to do so. In addition, these centers control the physical access to confidential data files and they review the materials that data users wish to take from the centers and to publish. Researchers who are accustomed to reporting residual plots and other information that allows for a partial reconstruction of the original data, at least for some variables, will encounter difficulties, because restricted data centers typically do not allow users to remove such information.

It is important to recognize, however, that query-response is not applicable to every data-sharing scenario, and data is often shared beyond the enclaves. When access logging and auditing is not possible, then a review of the security procedures and technologies employed by the recipient institution should occur. This process may be outsourced to an independent auditing agency.

Layered restricted access to databases

In many countries, the traditional arrangement for data use involves restrictions on both information and access, with only highly aggregated data and summary statistics released for public use.

One potential strategy for privacy protection for the linkage of registries to other confidential data is a form of layered restrictions that combines two approaches with differing levels of access at different levels of detail in the data. The registry might function as an enclave, similar to those described in the preceding section, and public access might be limited to only aggregate data. Between these two extremes there might be several layers of restricted access. An example is licensing that includes privacy protection, requiring greater protection as the potential for disclosure risk increases.

Such a layered approach might require a broader interpretation of the HIPAA Privacy Rule restrictions for certain kinds of medical records[279] or different forms of releases for patient records. The HIPAA Privacy Rule's detailed approach to releasing data can be shown to only partially protect individual data, and at the same time, unnecessarily restricts access to medical record data for research purposes. As a result, there is a need to develop a clearer sense of how health information subject to the HIPAA Privacy Rule might be linked with registry data and then subsequently protected. Such clarifications could allow for more complete research data while offering protection against the risks of identity disclosure to individuals and health care providers.

Summary

This chapter describes technical and current legal considerations for researchers interested in creating data linkage projects involving registry data. The discussion of the HIPAA Privacy Rule provides a basis for understanding the conditions under which the use and disclosure of protected health information (PHI) is permitted for research and other purposes relevant to registries. These conditions determine whether and how the linkage of certain datasets may be legally feasible. In addition, the chapter presents typical methods for record linkage that are likely to form the basis for the construction of data linkage projects. It also discusses both the hazards for re-identification created by data linkage projects, and the statistical methods used to minimize the risk of re-identification. Some limitations of this discussion are the exclusion of: 1) considerations about linking data from public and private sectors, where different ethical

and legal restrictions may apply, and 2) detailed information about the risks involved with identifying the health care providers that collect and provide data.

Dataset linkage entails the risks of loss of reliable confidential data management and identification or re-identification of individuals and institutions. Recognized and developing statistical methods and secure computation may limit these risks and may allow the public health the benefits that registries linked to other datasets have the potential to contribute.

Summary of Legal and Technical Planning Questions

The questions in Tables 9 and 10 are intended to assist the planning of data linkage projects that involve using registry data plus other files. Registry operators should use the answers to these questions to assemble necessary information and other resources to guide planning for their data linkage project. The questions, like the preceding discussion, are divided into regulatory and technical questions.

The assumptions listed below in Table 9 apply to the regulatory questions that follow. The application of these assumptions to the proposed data linkage project should be confirmed or determined.

- The HIPAA Privacy Rule applies to the initial data sources
- Other law may restrict access or use of the initial data sources
- The Common Rule or FDA regulations may or may not apply to data linkage
- The Common Rule or FDA regulations may or may not apply to original datasets

Different regulatory concerns arise depending on the answers to each category of the following questions. Consultation as necessary with experienced health services, social science, or statistician colleagues, and regulatory personnel (Privacy Officer) or legal counsel is recommended to clarify answers for specific data linkage projects.

Table 9: Legal Planning Questions

1. Purpose for data linkage	• Research? • Public health? • Quality improvement? • Required for post-marketing safety studies? • Determining effectiveness of a product or service? • Other purpose? • Combination of purposes?
2. Conditions under which data (plus or minus biospecimens) were originally collected	• Collected by law (e.g., regulatory purpose, public health purpose)? • For treatment, payment, or health care operations? • With documented consent to research participation and authorization for research use of protected health information from each individual?

	• With an IRB alteration or waiver of consent and authorization? • With permission of health care provider or plan? • Contractual conditions or limitations on future use or disclosure (release)? • What are the reasonable expectations, held by the original data sources and the data custodians, of privacy or confidentiality for future uses of the data?
3. Data	• Is sensitive information involved (e.g., about children, infectious disease, mental health conditions)? • Does the data contain direct identifiers? Indirect identifiers? • Is protected health information involved (PHI)? • Is a limited data set (LDS) and thus a data use agreement (DUA) involved? • Is the data de-identified in accordance with the HIPAA Privacy Rule • Does the data contain a code to identifiers? • Who holds the key to the code? • Is an honest broker involved? • Does the code to identifiers conform to the re-identification standard in the HIPAA Privacy Rule? • Is re-identification needed prior to performing the data linkage? • After the data linkage, will the risk increase that the data may be identifiable? • What is the minimally acceptable cell size to avoid identifying individuals?
4. Is the person or institution holding the data for the linkage	• A covered entity under the HIPAA Privacy Rule or the American Recovery and Reinvestment Act of 2009? • Not a covered entity?
5. Is the person or institution performing data linkage	• A covered entity under the HIPAA Privacy Rule or the American Recovery and Reinvestment Act of 2009? • Not a covered entity?
6. What other law or policies may apply to data use or disclosure (release)?	• Is governmental data involved? • Are NIH data sharing policies involved? • Does state law apply? Which state?
7. What are the terms and conditions that apply to data disclosure (release) and use under any agreement with the original source of the data?	• For individuals as the data source, the consent and authorization documents may contain limitations on data use, unless the data has been sufficiently de-identified. • For data custodians as the data source, there may be a data use agreement or other contract that applies to data use by any subsequent holder of the data.
8. What are anticipated needs for data validation and verification?	• Initially for the data linkage processes? • In the future?
9. What are future needs for privacy protection of the	• What will happen to data resulting from the linkage once the

data source or maintenance of data confidentiality?	analyses have been completed? How will it be stored?
10. Anticipated future uses of the linked data?	• Will the data resulting from the linkage be maintained for multiple analyses? For the same or different purposes? • Will the data resulting from the linkage be used for other linkages in the future? • What permissions are necessary for, or restrictions apply to, planned future uses of the data? • Are there currently requirements for tracking uses and disclosures of the data?

Table 10: Technical Planning Questions

- Who is performing the linkage? Are the individuals performing the linkage permitted access to identifiers or restricted set of identifiers? Are they an honest broker or the source of one of the datasets to be linked?
- How easy will it be to know whether a given person is in the registry? Are censuses riskier than surveys?
- Is there a common feature or pseudonym available across the datasets being linked?
- Is the registry a flat file or relational database? The latter is more difficult to manage, unless a primary key is applied.
- Is the registry relatively static or dynamic? The latter is harder to manage if data is being added over time, because the risk of identification increases.
- How many attributes are in the registry? The more attributes, the more difficult the risk of identification associated with the registry will be to manage.
- How will conflicting values of attributes, that are common to both databases, be resolved? Comparable attributes (e.g., weight) should be converted to the same units of measurement in datasets that will be linked.
- Does the registry contain information that makes the risk identification intrinsic to the registry? Other than direct identifiers such as names or social security numbers, fine-scale geography is also problematic.
- Is there a sound data dictionary?
- How many external databases will be linked to the registry data? How readily available and costly is each external database?
- How will records that appear in only one database be managed?
- How will the accuracy of the linked dataset relate to the accuracy of its components? The accuracy is only as good as that of the least accurate component.

Case Example 20: Linking registries at the international level

Description:	Psonet is an investigator-initiated, international scientific network of coordinated population-based registries; its aim is to monitor the long-term effectiveness and safety of systemic agents in the treatment of psoriasis.
Sponsor:	Supported by a grant from the Italian Drug Agency (AIFA) and coordinated by the Centro Studi GISED.
Year Started:	2005
Year Ended:	Ongoing
No. of Sites	9 different registries across Europe
No. of Patients:	20,000

Challenge

The number of options for systemic treatment of psoriasis has greatly increased in recent years. Because psoriasis is a chronic disease involving life-long treatment, data on long-term effectiveness and safety are needed for both old and new treatments. Several European countries have established patient registries for surveillance of psoriasis treatments and outcomes. However, these registries tend to have small patient populations and little geographic diversity, limiting their strength as surveillance tools for rare or delayed adverse events.

Proposed Solution

Combining the results from nation-based registries would increase statistical power and may enable investigators to conduct analyses that would not be feasible at a single country level. Psonet was established in 2005 as a network of European registries of psoriasis patients being treated with systemic agents. The goal of the network is to improve clinical knowledge of prognostic factors and patient outcomes, thus improving treatment of psoriasis patients. An International Coordinating Committee (ICC), including representatives of the national registries and some national pharmacovigilance centers, oversees the network activities, including data management, publications, and ethical or privacy issues. The ICC has appointed an International Safety Review Board whose job is to review safety data, prepare periodic safety reports, and set up procedures for the prompt identification and investigation of unexpected adverse events.

When drafting the registry protocol, member registries agreed to a common set of variables and procedures to be included and implemented in the national registries. Thus, inclusion criteria, clinical and socio-demographical characteristics, major outcomes, and followup schedules are harmonized between registries. At regular intervals, selected individual patient data are extracted from national registries and prepared in a standardized form. These data are included in a centralized database under the control of the ICC, with appropriate assurance of data confidentiality. Data checks are performed and descriptive tables are prepared and circulated among participants after each update.

Patient informed consent is obtained before their medical records are included in Psonet. For identification of case report forms in the registry, patient initials and date of birth are used.

Results

Nine European national and local registries at different stages of development are associated with the

registry to date, contributing a total of about 20,000 patients. While the registry is too new to have published results, planned activities and analyses include comparative data on treatment strategies for psoriasis in Europe; rapid alerts on newly recognized unexpected events; regular reports on effectiveness and safety data, and analyses of risk factors for lack of response as a preliminary step to identifying relevant biomarkers.

Key Point

Data from multiple registries in different countries may be combined to provide larger patient populations for study of long-term outcomes and surveillance for rare or delayed adverse events.

For More Information

www.psonet.eu

Lecluse, LLA, Naldi, L, Stern, RS & Spuls, PI. National Registries of Systemic Treatment for Psoriasis and the European 'Psonet' Initiative. *Dermatology*. Published online: Dec 11, 2008.

Naldi L: The search for effective and safe disease control in psoriasis. *Lancet* 2008; 371: 1311–1312.

Case Example 21: Linking a procedure-based registry with claims data to study long-term outcomes

Description:	The CathPCI Registry measures the quality of care delivered to patients receiving diagnostic cardiac catheterizations and percutaneous coronary interventions (PCI) in both inpatient and outpatient settings. The primary outcomes evaluated by the registry include the quality of care delivered, outcome evaluation, comparative effectiveness, and post-market surveillance.
Sponsor:	American College of Cardiology Foundation (ACCF) through the National Cardiovascular Data Registry (NCDR). Funded by participation dues from catheterization laboratories.
Year Started:	1998
Year Ended:	Ongoing
No. of Sites	1,150 catheterization laboratories
No. of Patients:	8.8 million patient records; 2.91 million PCI procedures

Challenge

The registry sponsor was interested in studying long-term patient outcomes for diagnostic cardiac catheterizations and percutaneous coronary interventions (PCI), but longitudinal data are not collected as part of the registry. Rather than create an additional registry, it was determined that the most feasible option was linking CathPCI data with available third party databases such as Medicare.
Before the linkage could occur, however, several legal questions needed to be addressed, including what identifiers could be used for the linkage and whether Institutional Review Board (IRB) approval was necessary.

Proposed Solution

The registry developers explored potential issues relating to the use of protected health information (federal HIPAA laws) to perform the linkage; the applicability of the Common Rule (protection of human subjects) to the linkage; and the contractual obligations of the individual legal agreement with each participating hospital with regard to patient privacy. The CathPCI Registry gathers existing data that is collected as part of routine health care activities. Informed consent is not required. Direct patient identifiers are collected in the registry, and the registry sponsor has business associates' agreements in place with participating catheterization laboratories.

After additional consultation from legal counsel, the registry sponsor concluded that the linkage of data could occur under two conditions: (1) that the datasets used in the merging process must be in the form of a Limited Dataset, and (2) that an institutional review board (IRB) must evaluate such linkage. The resulting decision was based on two key factors. First, the registry participant agreement includes a Data Use Agreement, which permits the registry sponsor to perform research on a Limited Dataset but also requires that no attempt be made to identify the patient. Second, since there was uncertainty as to whether the proposed data linkage would meet the definition of research on human subjects, the registry sponsor chose to seek IRB approval with a waiver of informed consent.

Results

CathPCI Registry data was linked with Medicare data, using probabilistic matching techniques to link the limited data sets. A research protocol describing the need for linkage, the linking techniques, and the research questions to be addressed was approved by an IRB. Researchers must reapply for IRB approval for any new research questions that they wish to study in the linked data.

Results of the linkage analyses were used to develop a new measure, 'Readmission following PCI,' for the Centers for Medicare & Medicaid Services hospital inpatient quality pay-for-reporting program. The new measure is currently under review.

Key Point

There are many possible interpretations of the legal requirements for linking registry data with other data sources. The interpretation of legal requirements should include careful consideration of the unique aspects of the registry, its data, and its participants. In addition, clear documentation of the way the interpretation occurred and the reasoning behind it will help to educate others about such decisions and may allay anxieties among participating institutions.

For More Information

https://www.ncdr.com/webncdr/DefaultCathPCI.aspx

Case Example 22: Linking registry data to examine long-term survival

Description:	The Yorkshire Specialist Register of Cancer in Children and Young People (YSRCCYP) is a population-based registry that collects data in children and young adults diagnosed with a malignant or certain benign neoplasm, living within the Yorkshire and Humber Strategic Health Authority (SHA). The goals of the registry are 1) to serve as a data source for research at local, national, and international levels on the causes of cancer in children, teenagers, and young people, and 2) to evaluate the delivery of care provided by clinical and other health service professionals.
Sponsor:	Primary funding is provided by the Candlelighters Trust, Leeds.
Year Started:	1974
Year Ended:	Ongoing
No. of Sites	18 National Health Service (NHS) Trusts
No. of Patients:	7,250

Challenge

In 2002, approximately 1,500 children in the United Kingdom (UK) were diagnosed with cancer. Previous estimates of malignant bone tumors in children have been approximately 5 per million person years in the UK. The registry collects data on individuals under age 30 years, living within the Yorkshire and Humber Strategic Health Authority (SHA), and diagnosed with a malignant or certain benign neoplasm from pediatric oncology and hematology clinics or teenage and young adult cancer clinics. Primary patient outcomes of the registry include length of survival, access to specialist care, late effects following cancer treatment, and hospital activity among long-term survivors. While bone cancer is ranked as the seventh most common malignancy in the UK, the relative rarity of this type of childhood cancer makes it difficult to gather sufficient data to evaluate incidence and survival trends over time.

Proposed Solution

The registry participated in a collaborative effort to combine its data with three other population-based registries – the Northern Region Young Persons' Malignant Disease Registry (YSRCCYP), the West Midlands Regional Children's Tumour Registry (WMRCTR), and the Manchester Children's Tumour Registry (MCTR). Together, the four population-based registries represented approximately 35 percent of the children in England.

Results

In a 20-year period, spanning 1981 and 2002, 374 cases of malignant bone tumors were identified in children ages 0 to 14 years. The age-standardized incidence rate for all types of bone cancers (i.e., osteosarcoma, chondrosarcoma, Ewing sarcoma, and other) was reported to be 4.84 per million per year. For the two most common types of bone cancer, osteosarcoma and Ewing sarcoma, the incidence rates were 2.63 cases per million person years (95% CI of 2.27-2.99) and 1.90 cases per million person year (95% CI of 1.58-2.21), respectively. While an improvement in survival was observed in patients with Ewing sarcoma, no survival improvement was detected in patients with osteosarcoma. The 5-year survival rate for children with all types of diagnoses observed in the study was an estimated 57.8 percent (95% CI 52.5 to 63).

Key Point

In the analysis of rare diseases, the number of cases and deaths included in the study determines the

statistical power for examining survival trends and significant risk factors, and the precision in estimating the incidence rate or other parameters of disease. In cases where it is difficult to obtain a large enough sample size within a single study, considerations should be given to combining registry data collected among similar patient populations.

For More Information

Eyre R, Feltbower RG, Mubwandarikwa E, Jenkinson HC, Parkes S, Birch JM, Eden TOB, James PW, McKinney PA, Pearce MS, McNally RJQ. Incidence and survival of childhood bone tumours in Northern England and the West Midlands, 1981-2002. Br J Cancer 2009; 100: 188-193.

Chapter 8: Principles of Registry Ethics, Data Ownership, and Privacy

This chapter covers the ethical and legal considerations that should accompany the development and use of all health information registries, including patient registries as defined in this document, for the purposes of public health activities, governmental health program oversight, quality improvement/assurance, and research. These considerations apply generally accepted ethical principles for scientific research involving human subjects to health information registries. Related topics include issues of transparency in the operation of registries, oversight of registry activities, and property rights in health care information and registries.

The purpose of this chapter is solely to provide information that will help readers understand the issues, not to provide specific legal opinion or regulatory advice. Legal advisors should always be consulted to address specific issues and to ensure that all applicable Federal, State, and local laws are followed. The discussion below about legal protections for the privacy of health information focuses solely on U.S. law. Health information is also legally protected in European and some other countries by distinctly different rules. If registry developers intend to obtain health information from outside of the United States, they should consult legal counsel early in the registry planning process for the necessary assistance. It should also be noted that the rules and regulations described here are for the protection of patients, not to prevent legitimate research. While the requirements may seem daunting, they are not insurmountable barriers to legitimate research. With careful planning and legal guidance, registries can be designed and operated in compliance with applicable rules and regulations.

In the context of this chapter, "health information" is broadly construed to include any individual patient information created or used by health care providers and insurance plans that relates to a health condition, the provision of health care services, or payment for health care services.[280] As a result, health information may include demographic information and personal characteristics, such as socioeconomic and marital status, the extent of formal education, developmental disability, cognitive capacities, emotional stability, as well as gender, age, and race, all of which may affect health status or health risks. Health information, as defined here, should be regarded as intimately connected to individual identity, and thus, intrinsically private. Typically, health information includes information about family members, so it also can have an impact on the privacy of third parties. Patients widely regard health information as a confidential communication to a health care provider and expect confidentiality to be maintained.

Serious ethical concerns have led to Federal legal requirements for prospective review of registry projects and specific permissions to use health information for research purposes. The creation and use of patient registries for a research purpose ordinarily constitute "research involving human subjects" as defined by regulations applicable to research activities funded by the U.S. Department of Health and Human Services[281] (HHS) and certain other Federal agencies. Moreover, Federal privacy regulations resulting from the Health Insurance Portability and Accountability Act of 1996 (HIPAA)[282] and the rules promulgated thereunder, specifically apply to the use and disclosure of certain individually identifiable health information for research purposes.

The term "human subjects" is used throughout this chapter for consistency with applicable Federal law. Some may prefer the term "research participants."

This chapter provides a general guide to Federal legal requirements in the United States. (Legal requirements in other countries may also be relevant and may be different from those in this country, but even a general discussion of the international situation is beyond the scope of this document.) These legal requirements may influence registry decisions involving the selection of data elements and data verification procedures, as well as affect subsequent uses of registry data for secondary research purposes. State laws also may apply to the use of health information for research purposes. The purpose of a registry, the status of its developer, and the extent to which registry data are identifiable largely determine applicable regulatory requirements. Table 11, included at the end of this chapter, provides an overview of the applicable regulatory requirements based on the type of registry developer and the extent to which registry data are identifiable. This chapter reviews the most common of these interactions. The complexity and sophistication of registry structures and operations vary widely, with equally variable processes for obtaining data. Nonetheless, common ethical and legal principles are associated with the creation and use of registries. These commonalities are the focus of this chapter.

Ethical concerns about the conduct of biomedical research, especially research involving the interaction of the clinical research community with their patients and commercial funding agencies, have produced an impetus to make financial and other arrangements more public. The discussion of transparency in this chapter includes recommendations for the public disclosure of registry operations as a means of maintaining public trust and confidence in the use of health information. Reliance on a standing advisory committee is recommended to registry developers as a way to provide expert technical guidance for registry operations and firmly establish the independence of the registry from committed or conflicted interests, as described in Chapter 2. This discussion of transparency in methods is not intended to discourage private investments in registries that produce proprietary information in some circumstances. Neither the funding source nor the generation of proprietary information from a registry determines whether a registry achieves the good practices described in this handbook.

Registry developers are likely to encounter licensing requirements, including processing and use fees, in obtaining health and claims information. Health care providers and health insurance plans have plausible claims of ownership to health and claims information, although the public response to these claims has not been tested. Registry developers should anticipate negotiating access to health and claims information, especially when it is maintained in electronic form. The processes for use of registry datasets, especially in multiple analyses by different investigators, should be publicly disclosed if the confidentiality protections required for health information are to remain credible.

The next section of this chapter discusses the ethical concerns and considerations involved with obtaining and using confidential health information in registries. The transformation of ethical concerns into the legal regulation of human subjects research and individually identifiable health information is then described. Following this topic, an overview is presented of these regulatory requirements and their interactions as they specifically relate to registries. Next, recommendations are made about registry transparency and oversight, based on the need to ensure the independence, integrity, and credibility of biomedical research, while preserving and improving the utility of registry data. In addition, this section briefly discusses property rights in health information and registries.

Ethical Concerns Relating to Health Information Registries

Application of Ethical Principles

The Belmont Report[283] is a summary of the basic principles and guidelines developed to assist in resolving ethical problems in the conduct of research with human subjects. It was the work product of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was created by the National Research Act of 1974.[284]

The Belmont Report identifies three fundamental principles for the ethical conduct of scientific research that involves human subjects. These principles are respect for persons (as autonomous agents; self-determination), beneficence (do good; do no harm; protect from harm), and justice (fairness; equitable distribution of benefits and burdens; equal treatment). Together, they provide a foundation for the ethical analysis of human subjects research, including the use of health information in registries developed for scientific purposes with a prospect of producing social benefits. These principles are substantively the same as those identified by the Council for International Organizations of Medical Sciences (CIOMS) in its international guidelines for the ethical review of epidemiologic studies.[285]

Nevertheless, the application of these principles to specific research activities can result in different conclusions about what comprises the ethical design and conduct of the research in question. These different conclusions frequently occur because the principles are assigned different values and relative importance by the person performing the ethical analysis. In most of these situations, however, a generally supported, consensus position on the ethical design and conduct of the research is a desirable and achievable goal. This goal does not preclude reanalysis as social norms or concerns about research activities change over time in response to new technologies or persistent ethical questioning.

The ethical principle of *respect for persons* supports the practice of obtaining individuals' consent to the use of their health information for research purposes that are unrelated to the clinical and insurance reasons for creating it. In connection with research registries, consent may have multiple components: (1) consent to registry creation by the compilation of patient information; (2) consent to the initial research purpose and uses of registry data; and (3) consent to subsequent use of registry data by the registry developer or others for the same or different research purposes. The consent process should adequately describe registry purposes and operations to inform potential subjects' decisions about participation in a research registry. In some defined circumstances, the principle of *respect for persons* may be subordinate to other ethical principles and values, with the result that an explicit consent process for participation in the registry may not be necessary. A waiver of informed consent requirements may apply to the registry and be ethically acceptable. (See discussion of waivers of informed consent requirements in this chapter's section "Potential for Individual Patient Identification.") In these situations, alternatives to an explicit consent process for each individual contributing health information to the registry may be adequate (e.g., readily accessible, publicly available information about registry activities).

A general ethical requirement for consent clearly implies that human subjects voluntarily permit the use of their health information in a registry, unless a specific exception to voluntary participation applies to the registry. One such exception is a legally mandated, public health justification for the compilation of health information (e.g., certain infectious disease reporting). Voluntary agreement to the use of health information in a registry necessarily allows a subsequent decision to discontinue participation. Any inability to withdraw information from the registry (e.g., once incorporation into aggregated data has

occurred) should be clearly communicated in the consent process as a condition of initial participation. The consent process should also include instructions about the procedures for withdrawal at any time from participation in the registry unless a waiver of consent applies to the registry. Incentives for registry use of health information (e.g., insurance coverage of payments for health care services) should be carefully evaluated for undue influence on both the individuals whose health information is sought for registry projects, and the health care providers of those services.[286,287]

Conflicts of interest may also result in undue influence on patients and compromise voluntary participation. One potential source of conflict widely identified with clinical research is the use of recruitment incentives paid by funding agencies to health care providers.[288] Some professional societies and research organizations have developed positions on recruitment incentives. Many entities have characterized incentives that are significantly beyond fair market value for the work performed by the health care provider as unethical; others require disclosure to research subjects of any conflicting interest, financial or otherwise.[289] There also have been attempts to enact federal legislation that would require manufacturers of certain drugs, devices, or medical supplies to report, for eventual public display, the amounts of remuneration paid to physicians for research purposes.[290] Some states, including Massachusetts, currently have similar laws in effect.[291] Research organizations, particularly grantees of Federal research funding, may have systematic processes that registry developers can rely on for managing employee conflicts of interest. Nonetheless, in their planning, registry developers should specify and implement recruitment practices that protect patients against inappropriate influences.

Further considerations in applying the principle of *respect for persons* to the research use of health information generate ethical concerns about preserving the privacy and dignity of patients and about protecting the confidentiality of health information. These concerns have intensified as health care services, third-party payment, and health information systems have become more complex. Legal standards for the use and disclosure of health information have replaced professional and cultural norms for handling individually identifiable health information. Nonetheless, depending on the particular health condition or population of interest, safeguards for the confidentiality of registry data beyond applicable legal requirements may be ethically necessary to protect the privacy and dignity of those individuals contributing health information to the registry.

The principle of *beneficence* ethically obligates developers of health information registries for research purposes to minimize potential harms to the individuals or groups[292] whose health information is included in the registry. There are usually no apparent benefits for offsetting harms to individuals or groups whose health information is used in the registry. Exceptions to this arise when the registry is designed to provide benefits to the human subjects, ranging from longitudinal reports on treatment effects or health status to quality-of-care reports. Risks to privacy and dignity are minimized by conscientious protection of the confidentiality of the health information included in the registry[293] through the use of appropriate physical, technical, and administrative safeguards for data in the operations of the registry. These safeguards should also control access to registry data, including access to individual identifiers that may be included in registry data. Minimization of risks also requires a precise determination of what information is necessary for the research purposes of the registry.

In an analysis applying the principle of *beneficence*, research involving human subjects that is unlikely to produce valid scientific information is unethical. This conclusion is based on the lack of social benefit to

offset even minimal risks imposed by the research on participating individuals. Health information registries should incorporate an appropriate design (including, where appropriate, calculation of the patient sample as described in Chapter 3) and data elements, written operating procedures, and documented methodologies, as necessary, to assure the achievement of their scientific purpose.[294]

Certain populations of patients may be vulnerable to social, economic, or psychological harms as a result of a stigmatizing health condition. Developers of registries compiling this health information must make special efforts to protect the identities of the human subjects contributing data to the registry. Pediatric and adolescent populations generate particular ethical concern because of a potential for lifelong discrimination that may effectively exclude them from educational opportunities and other social benefits (e.g., health care insurance).[295]

An ethical analysis employing the principle of *justice* also yields candid recognition of the potential risks to those who contribute health information to a registry, and the probable lack of benefit to those individuals (except in the cases where registries are specifically constructed to provide benefit to those individuals). The imbalance of burden and benefit to individuals, which is an issue of distributive justice, emphasizes the need to minimize the risks from registry use of health information. Reasonably precise and well-developed scientific reasons for inclusion (or exclusion) of defined health information in a registry contribute to making the research participation burden fair.

The above analysis refers to research activities. However, the ethical concerns expressed may also apply to other activities that use the health information of individuals in scientific methodologies solely for non-research purposes. Public health, oversight of the delivery of health care services through government programs, and quality improvement/assurance (I/A) activities all can invoke the same set of ethical concerns as research activities about the protection of patient self-determination, privacy, and dignity; maintaining the confidentiality of individually identifiable health information to avoid potential socioeconomic harms; and imposing a risk of harm on some individuals to the benefit of others not at risk. In the past, different assignments of social value to these activities and different potential for the social benefits and harms they produce created different levels of social acceptance and formal oversight for these activities than for research. Nonetheless, these activities may include a research component in addition to their ostensible and customary objectives, which reinforces the ethical concerns discussed above and produces additional concerns about compliance with the legal requirements for research activities. Registry developers should give careful prospective scrutiny to the proposed purposes for and activities of a registry in consultation with appropriate institutional officials to avoid both ethical and compliance issues that may undermine achievement of the registry's objectives.

Registry developers must also consider confidentiality protections for the identity of the health care providers, at the level of both individual professionals and institutions, and the health care insurance plans from which they obtain registry data. Information about health care providers and insurance plans can also identify certain patient populations and, in rare circumstances, individual patients. Moreover, the objectives of any registry, broadly speaking, are to enhance the value of the health care services received, not to undermine the credibility and thus the effectiveness of health care providers and insurance plans in their communities. Developers of registries created for public health investigations, health system oversight activities, and quality I/A initiatives to monitor compliance with recognized clinical standards must consider and implement confidentiality safeguards for the identity of service professionals and

institutions. At the same time, however, these confidentiality safeguards should be developed in a manner that permits certain disclosures, as designated by the service professionals and institutions, for the reporting of performance data, which is increasingly associated with payment from payers or by regulators.

Transformation of Ethical Concerns into Legal Requirements

Important ethical concerns about the creation, maintenance, and use of patient registries for research purposes involve risks of harm to the human subjects from inappropriate access to registry data and inappropriate use of the compiled health information. These concerns recognize public expectations of confidentiality for health information and the importance of that confidentiality in preserving the privacy and dignity of individual patients.

Over the last decade, two rapid technological developments intensified these ethical concerns. One of these advances was DNA sequencing, replication, recombination, and the concomitant application of this technology to biomedical research activities in human genetics. The other advance was the rapid development of electronic information processing, as applied to the management of health information. Widespread anticipation of potential social benefits produced by biomedical research as a result of these technologies was accompanied by ethical concerns about the potential for dignity, economic, social, or psychological harms to individuals or related third parties.

In addition to specific ethical concerns about the effect of technological advances in biomedical research, general social concerns about the privacy of patient information accompanied the advance of health information systems technology and communications. These social concerns produced legal protections, first in Europe and later in the United States. The discussion below about legal protections for the privacy of health information focuses solely on U.S. law. Health information is also legally protected in European and some other countries by distinctly different and even more complex rules, none of which are discussed in this chapter.[296] If registry developers intend to obtain health information from outside of the United States, they should consult legal counsel early in the registry planning process for the necessary assistance.

The Common Rule. The analysis in the Belmont Report on the ethical conduct of human subjects research eventually resulted in a uniform set of regulations from the Federal agencies that fund such research known as the "Common Rule."[297,298] The legal requirements of the Common Rule apply to research involving human subjects that is conducted or supported by the 17 Federal departments and agencies that adopted it. (Some of these agencies may require additional legal protections for human subjects. The Department of Health and Human Services regulations will be used for all following references to the Common Rule.) Among these requirements is a formal, written agreement from each institution engaged in such research to comply with the Common Rule. For human subjects research conducted or supported by most of the Federal entities that apply the Common Rule, the required agreement is called a Federalwide Assurance (FWA).[299] Research institutions may opt in their FWA to apply Common Rule requirements to all human subjects research activities conducted within their facilities or by their employees and agents, regardless of the source of funding. The application of Common Rule requirements to a particular registry depends on the institutional context of the registry developer, relevant institutional policies, and whether the health information contributed to the registry maintains patient identifiers.

The Office for Human Research Protections (OHRP) administers the regulation of human subjects research conducted or supported by HHS. Guidance published by OHRP discusses research use of identifiable health information. This guidance makes clear that OHRP considers the creation of health information registries for research purposes containing individually identifiable, private information to be human subjects research for the institutions subject to its jurisdiction.[300] In "Research Transparency, Oversight, and Ownership," the applicability of the Common Rule to research registries is discussed in more detail.

Regulations for human subjects protection require prospective review and approval of the research by an institutional review board (IRB) and the informed consent (usually written) of each of the human subjects involved in the research unless an IRB expressly grants a waiver of informed consent requirements.[301] (See Case Example 23.) A research project must satisfy certain regulatory conditions to obtain IRB approval of a waiver of the informed consent requirements. (See "Potential for Individual Patient Identification" for discussion of waivers of informed consent requirements.) A registry plan is the research "protocol" reviewed by the IRB. At a minimum, the protocol should identify (1) the research purpose of a health information registry, (2) detailed arrangements for obtaining informed consent, or detailed justifications for not obtaining informed consent, to collect health information, and (3) appropriate safeguards for protecting the confidentiality of registry data, in addition to any other information required by the IRB on the risks and benefits of the research.[302]

As noted previously, for human subjects research conducted or supported by most Federal departments and agencies that have adopted the Common Rule, an FWA satisfies the requirement for an approved assurance of compliance. Some research organizations extend the application of their FWA to all research, regardless of the funding source. Under these circumstances, any patient information registry created and maintained within the organization may be subject to the Common Rule. In addition, some research organizations have explicit institutional policies and procedures that require IRB review and approval of all human subjects research.

The Privacy Rule. In the United States, the Health Insurance Portability and Accountability Act of 1996 and its implementing regulations[303] (here collectively called the “Privacy Rule”) created legal protections for the privacy of individually identifiable health information created and maintained by so-called "covered entities." Covered entities are health care providers that engage in certain financial and administrative health care transactions electronically, health plans, and health care clearinghouses.[304] For the purposes of this chapter, the relevant entities are covered health care providers and health care insurance plans, which may include individual health care providers (e.g., a physician, pharmacist, or physical therapist). The discussion in this chapter assumes that the data sources for registries are "covered entities" to which the Privacy Rule applies. In the unlikely event a registry developer intends to collect and use data from sources that are *not* covered entities under the Privacy Rule, these sources are subject only to applicable State law and accreditation requirements, if any, for patient information.

Although data sources are assumed to be subject to the Privacy Rule, registry developers and the associated institutions where the registry will reside may not be. Notably, the Privacy Rule does *not* apply to registries that reside outside of a covered entity. Within academic medical centers, for example, registry developers may be associated with units that are outside of the institutional health care component to which the Privacy Rule applies, such as a biostatistics or economics department. But

because many, if not virtually all, data sources for registries are covered entities, registry developers are likely to find themselves deeply enmeshed in the Privacy Rule. This involvement may occur with non-covered entities as well—for instance, as a result of business practices developed in response to the Privacy Rule. In addition, the formal agreements required by the Privacy Rule in certain circumstances in order to access, process, manage, and use certain forms of patient information, impose continuing conditions of use that are legally enforceable by data sources under contract law. Therefore, registry developers should become cognizant of the patient privacy considerations confronting their likely data sources and should consider following certain Privacy Rule procedures, necessary or not, for reasons of solidarity with those data sources.

In general, the Privacy Rule defines the circumstances under which health care providers and insurance plans (covered entities) may use and disclose patient information for a variety of purposes, including research. Existing State laws protecting the confidentiality of health information, that are contrary to the Privacy Rule, are preempted unless the State law is more protective (which it may be).[305] For example, the Privacy Rule requires that certain information be present in patient authorizations to use and disclose individually identifiable information, including an expiration date. The laws of the state of Maryland, however, specifically require that, absent certain exceptions, a patient's authorization may only be valid for a maximum period of one year.[306] As a result, a covered entity located in Maryland must comply with the state's one-year maximum expiration deadline on its patient authorization forms.

The Privacy Rule regulates the use of identifiable patient information within health care providers' and insurance plans, and the disclosure of patient information to others outside of the institution that creates and maintains the information.[307] The initial collection of registry data from covered entities is subject to specific Privacy Rule procedures, depending on the registry's purpose, whether the registry resides within a covered entity or outside of a covered entity, and the extent to which the patient information identifies individuals. The health care providers or insurance plans that create, use, and disclose patient information for clinical use or business purposes are subject to civil and criminal liability for violations of the Privacy Rule.

Registry developers should be sufficiently knowledgeable about the Privacy Rule to facilitate the necessary processes for their data sources. They should expect this assistance to involve interactions with clinicians, the Privacy Officer, the IRB or Privacy Board staff, health information system representatives, legal counsel, compliance officials, and contracting personnel. Registry developers should also become aware of modifications, amendments or new implementing regulations under the Privacy Rule, which can be expected to occur as the use of electronic health information becomes more prevalent.

Subsequent use and sharing of registry data may be affected by the regulatory conditions that apply to initial collection, as well as by new ethical concerns and legal issues. The Privacy Rule created multiple pathways by which registries can compile and use patient information. To use or share compiled registry data for research purposes, a registry developer may need to employ several of these pathways sequentially, and satisfy the regulatory requirements of each pathway. For instance, a registry within a covered entity may arrange to obtain written documentation of an authorization required by the Privacy Rule from each patient contributing identifiable information to a registry for a particular research project, such as the relationship between hypertension and Alzheimer's disease. If the registry then seeks to make a subsequent use of the data for another research purpose, it may do so if it uses another permission in the

Privacy Rule—for example, by obtaining additional patient authorizations or first de-identifying the data to Privacy Rule standards.

The authors recommend that registry developers plan a detailed tracking system, based on the extent to which registry data remain identifiable for individual patients, for the collection, uses, and disclosures of registry data. The tracking system should produce comprehensive documentation of compliance with both Privacy Rule requirements and legally binding contractual obligations to data sources.

The Privacy Rule defines research as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge."[308] Commentary by HHS to the Privacy Rule explicitly includes the development (building and maintenance) of a repository or database for future research purposes within this definition of research.[309] The definition of "research" in the Privacy Rule partially restates the definition of research in the preexisting Common Rule for the protection of human subjects of the HHS and other Federal agencies.[310] Some implications of this partial restatement of the definition of research are discussed later in this chapter.

Guidance published by the National Institutes of Health (NIH) discusses how the Privacy Rule impacts health services research and research databases and repositories. The NIH guidance identifies the options available to investigators under the Privacy Rule for access to the health information held by health care providers and insurance plans.[311] In addition to provisions for the use or disclosure of identifiable patient information for research, the Privacy Rule permits health care providers and insurance plans to use or disclose patient information for certain defined public health activities.[312] The Privacy Rule defines a public health authority as, "an agency or authority of the United States, a State, a territory, a political subdivision of a State or territory, or an Indian tribe, or a person or entity acting under a grant of authority from or contract with such public agency… that is responsible for public health matters as part of its official mandate."[313] The Centers for Disease Control and Prevention (CDC) and HHS have jointly published specific guidance on the Privacy Rule for public health activities.[314] Other Privacy Rule provisions permit the use or disclosure of patient health information as required by other laws.[315]

The privacy protections for patient information created by the Privacy Rule that are generally relevant to registries developed for research purposes include explicit individual patient authorization for the use or disclosure of identifiable information,[316] legally binding agreements for the release of "limited data sets" between health information sources and users,[317] the removal of specified identifiers or statistical certification to achieve de-identification of health information,[318] and an accounting of disclosures to be made available to patients at their request.[319] In addition, if certain criteria required by the Privacy Rule are satisfied, an IRB or Privacy Board can grant a waiver of individual patient authorization for the use or disclosure of health information in research.[320]

FDA regulations. U.S. Food and Drug Administration (FDA) regulatory requirements for research supporting an application for FDA approval of a product also include protections for human subjects, including specific criteria for protection of privacy and maintaining the confidentiality of research data.[321]

Applicability of regulations to research; multiple-purpose registries. At many institutions, the IRB or the office that provides administrative support for the IRB is the final arbitrator of the activities that constitute human subjects research and thus may itself require IRB review. A registry developer is strongly encouraged to consult his or her organization's IRB early in the registry planning process to

avoid delays and revision of documentation for the IRB. Distinctions between research and other activities that apply scientific methodologies are frequently unclear. Such other activities include both public health practice[322] and quality-related investigations.[323] Both the ostensible and secondary purposes of an activity are factors in the determination of whether registry activities constitute research subject to the Common Rule. As interpreted by OHRP, if any secondary purpose of an activity is research, then the activity should be considered research.[324] This OHRP interpretation of research purpose differs from that of the Privacy Rule where quality-related studies performed by health care providers and insurance plans are concerned. Under the Privacy Rule, only if the primary purpose of a quality-related activity is to obtain generalizable knowledge, do the research provisions of the Privacy Rule apply; otherwise, the Privacy Rule defines the activity as a "health care operation."[325]

Registry developers should rely on their Privacy Officer's and IRB's experience and resources in defining research and other activities for their institutions and determining which activities require IRB review as research. In response to accreditation standards, inpatient facilities typically maintain standing departmental (e.g., pediatrics) or service (e.g., pharmacy or nursing) committees to direct, review, and analyze quality-related activities. Some physician groups also establish and maintain quality-related programs, because good clinical practice includes ongoing evaluation of any substantive changes to the standard of care. These institutional quality committees can provide guidance on the activities that usually fall within their purview. Similarly, public health agencies typically maintain systematic review processes for identifying the activities that fit within their legal authority.

As briefly mentioned previously, use of registry data for multiple research purposes may entail obtaining additional permissions from patients or satisfying different regulatory requirements for each research purpose. Standard confidentiality protections for registry data include requirements for physical, technical, and administrative safeguards to be incorporated into plans for a registry. In some instances, an IRB may not consider legally required protections for the research use of patient information sufficient to address relevant ethical concerns, including the protections of the Privacy Rule that may be applicable to registries created and maintained within health care providers' and insurance plans as covered entities. For example, information about certain conditions (such as alcoholism or HIV-positive status) and certain populations (such as children) may present an unusual potential for harm from social stigma and discrimination. Under these circumstances, the IRB can make its approval of a registry plan contingent on additional safeguards that it determines are necessary to minimize the risks to individuals contributing health information to the registry.

Applicable Regulations

This section describes the specific applicability of the Common Rule[326] and the Privacy Rule[327] to the creation and use of health information registries. The discussion in this chapter assumes three general models for health information registries. One model is the creation of a registry containing the contact, demographic, and diagnostic or exposure information of potential research subjects who will be individually notified about projects in which they may be eligible to participate. The notification process permits the registry to shield registry participants from an inordinate number of invitations to participate in research projects, as well as to protect privacy. This model is particularly applicable to patients with unusual conditions, patients who constitute a vulnerable population,[328] or both (e.g., children with a rare condition). A second model is the creation of a registry and all subsequent research use of registry data by the same group of investigators. No disclosures of registry data will occur and all research activities

have the same scientific purpose. This model applies, in general, to quality-related investigations of a clinical procedure or service. A third model is the creation of a registry for an initial, specific purpose by a group of investigators with the express intent to use registry data themselves, as well as to disclose registry data to other investigators for additional related or unrelated scientific purposes. An example of this last model is a registry of health information from patients diagnosed with a condition that has multiple known co-morbidities to which registry data can be applied. This third model is most directly applicable to industry-sponsored registries. The American College of Epidemiology encourages the data sharing contemplated in this last registry model.[329] Data sharing enhances the scientific utility of registry data and diminishes the costs of compilation.

A registry developer should try to evaluate how the regulations apply to each of these models. Registry developers are strongly encouraged to consult with their organization's Privacy Officer and IRB or Privacy Board early in the planning process to clarify applicable regulatory requirements and the probable effect of those requirements on considerations of registry design and development.

Public Health, Health Oversight, FDA-Regulated Products

When Federal, State, or municipal public health agencies create registries in the course of public health practice, specific legislation typically authorizes the creation of the registries and regulates data acquisition, maintenance, security, use, and disclosures of registry data for research. Ethical considerations and concerns about maintaining the confidentiality of patient information used by public health authorities are similar to those for research use, but they are explicitly balanced against potential social benefits during the legislative process. Nonetheless, if the registry supports research activities as well as its public health purposes, Common Rule requirements for IRB review may apply to the creation of the registry.

Cancer registries performing public health surveillance activities mandated by State law are well-known exceptions to Common Rule regulation. Secondary uses of public health registry data for research and the creation of registries funded by public health agencies, such as the CDC and the Agency for Healthcare Research and Quality (AHRQ), as sponsored research activities may be subject to the Common Rule. The Common Rule's definitions of human subjects research[330] may encompass these activities, which are discussed in the next subsections of this chapter. Not all cancer registries support public health practice alone, even though the registries are the result of governmental programs. For example, the Surveillance Epidemiology and End Results (SEER) program, funded by the National Cancer Institute, operates and maintains a population-based cancer reporting system of multiple registries, including public use data sets with public domain software. SEER program data are used for many research purposes in addition to aiding public health practices.[331]

Disclosures of health information by health care providers and insurance plans for certain defined public health activities are expressly recognized as an exception to Privacy Rule requirements for patient authorization.[332] An example of a public health activity is the practice of surveillance, which monitors and disseminates the distributions and trends of designated risk factors, injuries, or diseases in populations.[333] Health care providers or insurance plans are likely to demand documentation of public health authority for legal review before making any disclosures of health information. Registry developers should obtain this documentation from the agency that funds or enters into a contract for the

registry, and present it to the health care provider or insurance plan well in advance of data collection efforts.

The Privacy Rule permits uses and disclosures by health care providers and insurance plans for "health oversight activities" authorized by law.[334] These activities include audits and investigations involving the "health care system" and other entities subject to government regulatory programs for which health information is relevant to determining compliance with program standards.[335] The collection of patient information, such as occurrences of decubitus ulceration, from nursing homes that are operating under a compliance or corporate integrity agreement with a Federal or State health care program, is an example of a health oversight activity.

The Privacy Rule characterizes responsibilities related to the quality, safety, or effectiveness of a product or activity regulated by FDA as public health activities. This public health exception for uses and disclosures of patient information in connection with FDA-regulated products or activities includes adverse event reporting; product tracking; product recalls, repairs, replacement, or look-back; and post-marketing surveillance (e.g., as part of a risk management program that is a condition for approval of an FDA-regulated product).[336]

Research Purpose of Registry

The Common Rule defines "research," and that definition is partially restated in the Privacy Rule. These regulatory definitions affect how the regulatory requirements of each rule are applied to research activities.[337]

In the Common Rule:

Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.[338]

OHRP interprets the Common Rule definition of research to include activities having any research purpose, no matter what the ostensible objective of the activity may be. Compliance with Common Rule requirements depends on the nature of the organization where the registry resides. If an organization receives Federal funding for research, then it is likely that Common Rule requirements apply.

The Privacy Rule's definition of research[339] restates the first sentence of the Common Rule definition. However, the Privacy Rule distinguishes between research and quality improvement/assurance activities conducted by covered entities,[340] which are defined as "health care operations."[341] As a result, if the primary purpose of a quality-related registry, maintained by a covered entity, is to support a research activity (i.e., to create generalizable knowledge), Privacy Rule requirements for research apply to the use or disclosure of the patient information to create the registry and to subsequent research use of registry data. If, however, the primary purpose is other than to create generalizable knowledge, the study is considered a health care operation of the covered entity and is not subject to Privacy Rule requirements for research activities or patient authorization.

As noted earlier, both public health practice and quality I/A activities can be difficult to distinguish from research activities.[342] The determination of whether a particular registry should be considered as or include a research activity depends on a number of different factors, including the nature of the organization where the registry will reside; the employment duties of the individuals performing the activities associated with the registry; the source of funding for the registry; the original, intended purpose of the registry; the sources of registry data; whether subsequent uses or disclosures of registry data are likely; and other circumstances of registry development.

Quality I/A activities entail many of the same ethical concerns about protecting the confidentiality of health information as research activities do. Express consent to quality I/A activities is not the usual practice; instead, the professional and cultural norms of health care providers, both individual and institutional, regulate these activities. Registry developers should consider whether the ethical concerns associated with a proposed quality I/A registry require independent review and the use of special procedures, such as notice to patients. Registry advisory committee members, quality I/A literature,[343] hospital ethics committees, IRB members, and clinical ethicists can make valuable contributions to these decisions.

To avoid surprises and delays, the decision about the nature of the activity that the registry is intended to support should be made prospectively, in consultation with appropriate officials of the funding agency and officials of the organization where the registry will reside. Some research institutions may have policies that either require IRB review for quality I/A activities, especially if publication of the activity is likely, or exclude them from IRB review. Most frequently, IRBs make this determination on a case-by-case basis.

Potential for Individual Patient Identification

The specific regulatory requirements, applicable to the use or disclosure of patient information for the creation of a registry to support research, depend in part on the extent to which patient information received and maintained by the registry can be attributed to a particular person. Various categories of information, each with a variable potential for identifying individuals, are distinguished in the Privacy Rule: individually identifiable health information, "de-identified" information, and a "limited data set" of information.[344] The latter two categories of information may or may not include a code linked to identifiers.

If applicable, Common Rule requirements affect all research involving patient information that is individually identifiable and obtained by the investigator conducting the research. The definition of "human subject" in the Common Rule is, "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information."

This regulatory definition further explains:

Private information includes… information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.[345]

In short, the Common Rule definition of "human subject" makes all research use of identifiable patient information subject to its requirements; if the identity of the patients whose information is used for research purposes is not readily ascertainable to the investigator, the research is not human subjects research to which the Common Rule applies. Moreover, research involving the collection of information from existing records is exempt from the Common Rule if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers (coded link), to the subjects. Registry developers should consult the IRB early in the process of selecting data elements to obtain guidance about whether registry activities constitute human subjects research or may be exempt from Common Rule requirements.

Also among the criteria specified by the Common Rule for IRB approval of research involving human subjects are provisions to protect the privacy of subjects and to maintain the confidentiality of data.[346] In addition, the consent process for research subjects should include explicit information about confidentiality protections for the use of records containing identifiers.[347]

Data collection frequently requires patient identifiers, especially in prospective registries with ongoing data collection, revision, and updates. Secondary or subsequent research use by outside investigators (i.e., those not involved in the original data collection) of patient information containing direct identifiers is complicated, however, because ethical principles for the conduct of human subjects research require that risks, including risks to confidentiality of patient information, be minimized. In addition, the Privacy Rule requires an authorization to specifically describe the purpose of the use or disclosure of patient information. Unless the registry developer sufficiently anticipates the purposes of secondary research, the authorization may not be valid for the use of identifiable registry data for secondary research purposes. The Privacy Rule provides options for the collection and use of health information that is identifiable to a greater or lesser extent; it also contains standards for de-identifying information and creating limited data sets.[348] Nonetheless, use of identifiable health information may be essential to population-based studies and to achieve certain scientific and public health goals.

Direct identifiers generally include a patient's name, initials, contact information, medical record number, and Social Security Number, alone or in combination with other information. As described by the Privacy Rule standard, a limited data set of patient information does not include specified direct identifiers of the patient or the patient's relatives, employer, or household members.[349]

In an electronic environment, masking individual identities is a complex task. Data suppression limits the utility of the information from the registry, and linkage or even triangulation of information can re-identify individuals. A technical assessment of electronic records for their uniqueness within any data set is necessary to minimize the potential for re-identification. In aggregated published data, standard practice assumes that a subgroup size of less than six may also be identifiable, depending on the nature of the data. An evaluation for uniqueness should ensure that the electronic format does not produce a potential for identification greater than this standard practice, even when the information is triangulated within a record or linked with other data files.

If a registry for research, public health, or other purposes will use any of the categories of health information discussed below, a registry developer should consult the IRB, the Privacy Officer, and the institutional policies developed specifically in response to the Privacy Rule early in his or her planning. These consultations should establish the purpose of the registry, the applicability of the Common Rule

requirements to registry activities, and the applicability of the Privacy Rule to the collection and use of registry data. In addition, the registry developer should consult a representative of the Information Technology or Health Information System office of each health care provider or insurance plan that will be a source of data for the registry so as to obtain feasibility estimates of data availability and formats, as well as a representative of the IRB or Privacy Board for each data source.

De-identified patient information. The Privacy Rule describes two methods for de-identifying health information.[350] One method requires the removal of certain data elements. The other method requires a qualified statistician to certify that the potential for identifying an individual from the data elements is negligible. A qualified statistician should have "appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable" in order to make this determination.[351] De-identified information may include a code permitting re-identification of the original record by the data source (covered entity).[352] The code may not be derived from information about an individual and should resist translation. In addition, the decoding key must remain solely with the health care provider or plan that is the source of the patient information.[353]

Research on existing data in which individual patients cannot be identified directly or indirectly through linked identifiers, does not involve human subjects, as defined by the Common Rule, and thus is not subject to the requirements of the Common Rule.[354] Refer to the discussion later in this chapter.

As a prudent business practice, each health care provider or insurance plan that is a source of de-identified information is likely to require an enforceable legal agreement with the registry developer. It should be signed by an appropriate institutional official on behalf of the registry developer. At a minimum, this agreement will likely contain the following terms, some of which may be negotiable: the identification of the content of the data and the medium for the data; a requirement that the data recipient, and perhaps the health care provider or insurance plan providing the data, make no attempt to identify individual patients; the setting of fees for data processing and data use; limitations on disclosure or further use of the data, if any; and an allocation of the risks of legal liability for any improper use of the data.

Limited data sets of health information. De-identified health information may not suffice to carry out the purposes of a registry, especially if the registry will receive followup information through the monitoring of patients over time or information from multiple sources to compile complete information on a health event (e.g., cancer incidence). Dates of service and geographic location may be crucial to the scientific purposes of the registry or to the integrity and use of the data. Health information provided to the registry without direct identifiers may constitute a limited data set as defined by the Privacy Rule.[355] A health care provider or insurance plan may disclose a limited data set of health information by entering into a Data Use Agreement (DUA) with the recipient. The terms of the DUA should satisfy specific Privacy Rule requirements.[356] Institutional officials for both the data source and the registry developer should sign the DUA so a legal contract results. The DUA establishes the uses of the limited data set permitted by the registry developer (i.e., the creation of the registry and subsequent use of registry data for specified research purposes). The DUA may not authorize the registry developer to use or disclose information in a way that would violate the Privacy Rule if done by the data source.[357]

An investigator who works within a health care provider or insurance plan to which the Privacy Rule applies and that is the source of the health information for a registry may use a limited data set to develop

a registry for a research purpose. In these circumstances, the Privacy Rule still requires a DUA that satisfies the requirements of the Privacy Rule between the health care provider or insurance plan and the investigator. This agreement may be in the form of a written confidentiality agreement.[358]

A registry developer may assist a health care provider or insurance plan by creating the limited data set. In some situations, this assistance may be crucial to data access and availability for the registry. In order for the registry developer to create a limited data set on behalf of a data source, the Privacy Rule requires the data source (the covered entity) to enter into a Business Associate Agreement with the registry developer (the business associate) that satisfies certain regulatory criteria.[359] The Business Associate Agreement is a binding legal arrangement that should be signed by appropriate institutional officials on behalf of the data source and registry developer. This agreement contains terms for managing health information that are required by the Privacy Rule and that become a legally binding contract between the data source and data recipient.[360] Most health care providers have developed a standard Business Associate Agreement in response to the Privacy Rule and will likely insist on using it, although it may require some negotiated modifications for the production of registry data.

The registry populated with a limited data set may include a coded link that connects the data back to patient records, provided the link does not replicate part of a direct identifier.[361] The key to the code may allow health information obtained from monitoring patients over time to supplement existing registry data or allow the combination of information from multiple sources.

The DUA for a limited data set of health information requires the data recipient to warrant that no attempt will be made to identify the health information with individual patients or to contact those patients.[362]

If the registry data obtained by investigators constitute a limited data set and do not contain a coded link to identifiers, then the research would not involve human subjects, as defined by HHS regulations at 45 Code of Federal Regulations (CFR) 46.102(f), and the Common Rule requirements would not apply to the registry.[363] An IRB or an institutional official knowledgeable about the Common Rule requirements should make the determination of whether a research registry involves human subjects; frequently, a special form for this purpose is available from the IRB. The IRB (or institutional official) should provide documentation of its decision to the registry developer.

Direct identifiers: authorization and consent. The Privacy Rule permits the use or disclosure of patient information for research with a valid, written authorization from each patient whose information is disclosed.[364] The Privacy Rule specifies the content of this authorization, which gives permission for a specified use or disclosure of the health information.[365] Health care providers and insurance plans frequently insist on use of the specific authorization form they develop to avoid legal review and potential liability from the use of other forms.

One exception to the requirement for an authorization occurs when a health care provider or insurance plan creates a registry to support its "health care operations."[366] Health care operations specifically include quality I/A activities, outcomes evaluation, and the development of clinical guidelines; however, the Privacy Rule definition of health care operations clearly excludes research activities.[367] For example, a hospital registry, created to track its patient outcomes against a recognized clinical care standard as a quality improvement initiative, has a health care operations purpose. The hospital would not have to obtain an authorization for use of the health information from the patients it tracks in this registry.

Research use of health information containing identifiers constitutes human subjects research as defined by the Common Rule.[368] In general, the Common Rule requires documented, legally effective, voluntary, and informed consent of each research subject.[369]

Documentation of the consent process required by the Common Rule may be combined with the authorization required by the Privacy Rule for disclosure and use of health information.[370] A health care provider or insurance plan may not immediately accept the combination of these forms as a valid authorization; it may insist on legal review of the combination form before permitting disclosure of any health information.

Authorizations for the use or disclosure of health information under the Privacy Rule and informed consent to research participation under the Common Rule should be legally effective (i.e., patients must be legally competent to provide these permissions). Adults, defined in most States as 18 years and over, are presumed legally competent in the absence of a judicially approved guardianship. Children under 18 years old are presumed legally incompetent; therefore, a biological, adoptive, or custodial parent or guardian must provide permission on the child's behalf. Registry developers should consult legal counsel about situations in which these presumptions seem inapplicable, such as a registry created to investigate contraceptive drug and device use by adolescents, and to which State law exceptions may exist.

In addition to being voluntary and legally effective, consent should be informed about the research, including what activities are involved, as well as the expected risks and potential benefits from participation. The Common Rule requires the consent process to include specific elements of information.[371] Registry developers should plan to provide non-English-speaking patients with appropriate resources to assure that the communication of these elements during the consent process is comprehensible. All written information for patients should be translated, or alternatively, arrangements should be made for qualified translators to attend the consent process.

IRBs may approve waivers for both authorization (for disclosure of patient information for registry use) and consent (to registry participation), provided the research use of health information satisfies certain regulatory conditions. In addition, the Privacy Rule created Privacy Boards specifically to approve waivers of authorization for the research use of health information in organizations without an IRB.[372] Waivers are discussed in detail below.

An important distinction exists between the Common Rule and Privacy Rule concerning the scope of permission to use health information for research purposes. Under the Common Rule, consent for participation in future, unspecified research may be obtained, provided potential subjects receive clear notice during the consent process that this research is intended to occur. For an authorization to be valid under the Privacy Rule, however, the authorization should describe each purpose of the use or disclosure of health information.[373]

In certain limited circumstances, research subjects can consent to future unspecified research using their identifiable patient information. The Common Rule permits an IRB-approved consent process to be broader than a specific research project[374] and to include information about research that may be done in the future. In its review of such future research, an IRB subsequently can determine that the previously obtained consent (1) satisfies the regulatory requirements for informed consent or (2) does not satisfy the regulatory requirements for informed consent. If it does not satisfy the regulatory requirement for

informed consent, it requires an additional consent process; alternatively, the IRB may grant a waiver of consent, provided the regulatory criteria for waiver are satisfied.

For example, an IRB-approved consent process for the creation of a research registry should include a description of the specific types of research to be conducted using registry data. For any future research that involves identifiable information maintained by the registry, the IRB may determine that the original consent process (for the creation of the research registry) satisfies the applicable regulatory requirements, because the prospect of future research and future research projects were adequately described. The specific details of that future research on registry data may have been unknown when data were collected to create the registry, but the future research may have been sufficiently anticipated and described to satisfy the regulatory requirements for informed consent. For consent to be informed as demanded by the ethical principle of *respect for persons*, however, any description of the nature and purposes of the research should be as specific as possible.

If a registry developer anticipates subsequent research use of identifiable registry data, he or she should request an assessment by the IRB of the description of the research used in the consent process for potential subjects at the time the data are initially collected. Nonetheless, in its review of any subsequent research, an IRB may find it appropriate to require an additional consent process for each research subject or to grant a waiver for obtaining further consent.

The commentary accompanying the publication of the Privacy Rule clearly rejected broadening the description of purpose in authorizations to include future, unspecified research.[375] As a result, the research purpose stated in an original authorization for a registry limits the use of registry data to that purpose.[376] Subsequent use of registry data maintained within a health care provider or insurance plan for a different research purpose requires a new authorization from each individual whose registry data would be involved or an approved waiver of authorization. Alternatively, the use or disclosure of a limited data set or de-identified registry data can occur, provided regulatory criteria are satisfied. Registries maintained by organizations to which the Privacy Rule does *not* apply (e.g., funding agencies for research that are *not* health care providers or insurance plans, professional societies, or non-healthcare components of hybrid entities such as universities) are not legally bound by the limited purpose of the original authorization. However, data sources subject to the Privacy Rule are likely to be unwilling to provide patient information without a written agreement with the registry developer that includes legally enforceable protections against re-disclosure of identifiable patient information. A valid authorization contains a warning to patients that their health information may not be protected by Privacy Rule protections in recipient organizations.[377]

Registry developers can request that patients obtain and share copies of their own records from their health care provider or insurance plan. This strategy can be useful for mobile populations, such as elderly retirees who occupy different residences in winter and summer. A Federal privacy law[378] protects the health records of children which are held by schools from disclosure without explicit parental consent; thus, parents can often obtain copies of these records more easily than investigators. Alternatively, individuals can simply volunteer health information in response to an interview or survey. These collection strategies do not require obtaining a Privacy Rule authorization from each subject; however, IRB review and other requirements of the Common Rule, including careful protections of the confidentiality of registry data, may, nonetheless, apply to a registry project with a research purpose.

Moreover, a registry developer may encounter Privacy Rule requirements for the use or disclosure of patient information by a health care provider or insurance plan for recruitment purposes. For example, a patient authorization or waiver of authorization (discussed below) may be necessary for the disclosure of patient contact information by a health care provider or insurance plan (covered entity) to a registry developer.

Certificates of confidentiality and other privacy protections. Certificates of confidentiality granted by the National Institutes of Health permanently protect identifiable information about research subjects from legally compelled disclosure. For the purposes of certificates of confidentiality, identifiable information is broadly defined to include any item, or combination of items, in research data that could directly or indirectly lead to the identification of a research participant.[379] Federal law authorizes the Secretary of HHS (whose authority is delegated to NIH) to provide this privacy protection for subjects of biomedical, behavioral, clinical, and other research.[380] Federal funding for the research is not a precondition for obtaining a certificate of confidentiality.[381] An investigator whose research project has been granted a certificate of confidentiality may refuse to disclose identifying information collected for that research even though a valid subpoena exists for the information in a civil, criminal, administrative, or legislative proceeding at the Federal, State, or local level. The protection provided by a certificate of confidentiality is intended to prevent the disclosure of personal information that could result in adverse effects on the social, economic, employment, or insurance status of a research subject.[382] Detailed information about certificates of confidentiality is available on the NIH Web site.[383]

The grant of a certificate of confidentiality to a research project, however, is not intended to affect State laws requiring health care and other professionals to report certain conditions to State officials, such as designated communicable diseases, neglect and abuse of children and the elderly, or threatened violent harm. If investigators are mandatory reporters under State law, in general, they continue to have a legal obligation to make these reports.[384] In addition, other legal limitations to the privacy protection provided by certificates of confidentiality exist and may be relevant to particular research projects. Information on the NIH Web site describes some of these other legal limitations.[385]

Registry developers should also be aware that Federal law provides specific confidentiality protections for the identifiable information of patients in drug abuse and alcoholism treatment programs that receive Federal funding.[386] These programs may disclose identifiable information about their patients for research activities only with the documented approval of the program director.[387] The basis for the director's approval is receipt of written assurances about the qualifications of the investigator to conduct the research, the confidentiality safeguards incorporated into the research protocol, and no further disclosure of identifying information by the investigator. Moreover, an independent review of the research project should determine and verify, in writing, that the protocol provides adequate protection of the rights and welfare of the patients and that the benefits of the research outweigh any risks to patients.[388] Prior to submitting proposed consent documentation to an IRB, registry developers should consult legal counsel for important information about the limitations of these confidentiality protections.

As a condition of approval, IRBs frequently require investigators to obtain a certificate of confidentiality for research involving information about substance abuse or other illegal activities (e.g., underage purchase of tobacco products), sexual attitudes and practices, and genetic information. Registry developers should consult legal counsel to determine if and how the limitations of a certificate of

confidentiality may affect privacy protection planning for registry data. In all circumstances, the consent process should communicate clear notice to research subjects about the extent of privacy protections they may expect for their health information when it is incorporated into a registry.

In the absence of a certificate of confidentiality, a valid subpoena or court order for registry data will usually compel disclosure of the data unless State law specifically protects the confidentiality of data. For example, Louisiana's laws specifically protect the collection of information on tobacco use from subpoena.[389] On the other hand, a subpoena or court order may supersede State law confidentiality protections. These legal instruments can be challenged in the court having jurisdiction for the underlying legal proceeding. In some circumstances, research institutions may be willing to pursue such a challenge. The remote, yet definite possibility of this sort of disclosure should be clearly communicated to research subjects as a limitation on confidentiality protections during the consent process and in an authorization for use or disclosure of patient information.

State law may assure the confidentiality of certain quality I/A activities performed by health care providers as peer review activities.[390] When State law protects the confidentiality of peer review activities, generally, it is implementing public policy that encourages internal activities and initiatives by health care providers to improve health care services by reducing the risks of medical errors and systematic failures. Protection by peer review statutes may limit the use of data generated by quality I/A activities for any other purposes.

Waivers and alterations of authorization and consent. As mentioned above, the Privacy Rule authorizes Privacy Boards and IRBs to sometimes waive or alter authorizations by individual patients for the disclosure or use of health information for research purposes (See Case Example 24). In addition, the Common Rule authorizes IRBs to waive or alter the consent process. The Privacy Rule and the Common Rule each specify the criteria under which waivers or alterations of authorization and the consent process are permitted.[391] The potential risks to patients participating in the registry resulting from these waivers of permission differ. A waiver of authorization potentially imposes the risk of a loss of confidentiality and consequent invasion of privacy. A waiver of consent potentially imposes risks of harm from the loss of self-determination, dignity, and privacy expected under the ethical principles of *respect for persons* and *beneficence*. Acknowledging these potential risks, regulatory criteria for waiver and alterations require an IRB or Privacy Board to determine that risks are minimal. This determination is a necessary condition for approval of an investigator's request for a waiver or alteration of these permissions.

The following discussion refers only to waivers; registry developers should note that Privacy Boards and IRBs may approve alterations to authorizations or the consent process, provided a requested alteration satisfies *all* the same criteria required for a waiver by the Privacy Rule or Common Rule. Alterations are generally preferable to waivers in an ethical analysis based on the principle of *respect for persons*, because they acknowledge the importance of self-determination. In requesting alterations to an authorization or to the consent process, registry developers should be prepared to justify each proposed change or elimination of required elements. Plausible justifications include a registry to which a specific element does not apply or a registry in which one element contradicts other required information in the authorization or consent documentation. The justifications for alterations should relate as specifically and directly as possible to the regulatory criteria for IRB or Privacy Board approval of waivers and alterations.

The Privacy Rule authorizes an IRB or Privacy Board to approve a waiver of authorization if the following criteria are met: (1) the use or disclosure involves no more than minimal risk to the privacy of individuals; (2) the research cannot be practicably conducted without the waiver; and (3) the research cannot be practicably conducted without access to, and use of, health information. The determination of minimal risk to privacy includes several elements: an adequate plan to protect identifiers from improper use or disclosure; an adequate plan to destroy identifiers, unless a health or research justification exists to retain them; and adequate written assurances that the health information will not be reused or disclosed to others, except as required by law, as necessary for oversight of the research, or as permitted by the Privacy Rule for other research.[392] The Privacy Board or IRB should provide detailed documentation of its decision for presentation to the health care provider or insurance plan (covered entity) which is the source of the health information for registry data.[393] The documentation should clearly communicate that each of the criteria for a waiver required by the Privacy Rule has been satisfied.[394] The Privacy Board or IRB documentation should also provide a description of the health information it determined necessary to the conduct of the research and the procedure it used to approve the waiver.[395] A health care provider or insurance plan may insist on legal review of this documentation before permitting the disclosure of any health information.

The criteria for a waiver of consent in the Common Rule are similar to those for a waiver of authorization under the Privacy Rule. An IRB should determine that: (1) the research involves no more than minimal risk to subjects; (2) the waiver will not adversely affect the rights and welfare of subjects; (3) the research cannot practicably be carried out without a waiver; and (4) whenever appropriate, subjects will be provided with additional information after participation.[396] The criterion for additional information can be satisfied at least in part by public disclosure of the purposes, procedures, and operations of a registry, as discussed later in "Registry Transparency."

Some IRBs produce guidance about what constitute "not practicable" justifications and the circumstances in which these justifications apply. For population-based research projects, registry developers may also present the scientific justification of avoiding selection bias. A waiver permits the registry to include the health information of all patients who are eligible. An IRB may also agree to consider requests for a limited waiver of consent that applies only to those individuals who decline use of their health information in a registry project. This limited waiver of consent most often permits the collection of de-identified and specified information, sufficient to characterize this particular population.

An important difference between the Common Rule and FDA regulations for the protection of human subjects involves consent to research participation. The FDA regulations require consent, except for emergency treatment or research, and do not permit the waiver or alteration of informed consent.[397] If registry data are intended to support the labeling of an FDA-regulated product, a registry developer should plan to obtain the documented, legally effective, voluntary, and informed consent of each individual whose health information is included in the registry.

The Privacy Rule creates a legal right for patients, by request, to receive an accounting of certain disclosures of their health information that are made by health care providers and insurance plans.[398] The accounting must include disclosures that occur with a waiver of authorization approved by a Privacy Board or IRB. The Privacy Rule specifies the information that an accounting should contain[399] and requires it to cover a 6-year period or any requested shorter period of time.[400] If multiple disclosures are

made to the same recipient for a single purpose, including a research purpose, a summary of these disclosures may be made. In addition, because most waivers of authorization cover records of many individuals, and thus an individualized accounting in such circumstances may be burdensome, the Privacy Rule provides that if the covered entity has disclosed the records of 50 or more individuals for a particular research purpose, the covered entity may provide to the requestor a more general accounting, which lists the research protocols for which the requestor's information may have been disclosed, among other items.[401]

The Common Rule permits an IRB to waive documentation of the consent process under two different sets of regulatory criteria. The first set of conditions for approval of this limited waiver require that the only record linking an individual subject to the research is the consent document; the principal risk to subjects is the potential harm from a breach of confidentiality; *and* each subject individually determines whether his or her consent should be documented.[402] Alternatively, an IRB can waive documentation of consent if the research involves no more than minimal risk of harm to subjects and no procedures for which written consent is normally obtained outside of a research context.[403] For either set of regulatory criteria, the IRB may require the investigator to provide subjects with written information about the research activities in which they participate.[404] The written information may be as simple as a statement of research purposes and activities, or it may be more elaborate, such as a Web site for regularly updated information describing progress on the research project.

Patient Safety Organizations. The final rule (the "Rule") implementing the Patient Safety and Quality Improvement Act of 2005 (PSQIA) became effective on January 19, 2009[405]. The PSQIA was enacted in response to a 1999 report by the Institute of Medicine, which identified medical errors as a leading cause of hospital deaths in the United States, with many such errors being preventable.[406] The PSQIA allows healthcare providers to voluntarily report patient safety data, known as patient safety work product (PSWP), to independent patient safety organizations (PSOs). In general, patient safety work product falls into three general categories: (1) information collected or developed by provider for reporting to a PSO that is actually reported; (2) information developed by the PSO itself as part of patient safety activities; and (3) information that identifies or constitutes the deliberations or analysis of, or identifies the fact of reporting to, a patient safety evaluation system.[407] The PSQIA broadly defines PSWP to include any data, reports, records, memoranda, analyses, and statements that can improve patient safety, healthcare quality, or healthcare outcomes, provided that all such data must be developed for the purpose of reporting it to a PSO. Certain categories of information are expressly excluded from being PSWP. This includes, "a patient's medical record, billing and discharge information, or any other original patient or provider information … [and] information that is collected, maintained, or developed separately, or exists separately, from a patient safety evaluation system."[408]

Once PSWP is collected by a PSO it is aggregated and analyzed by the PSO to assist a provider in determining, among other things, certain quality benchmarks and underlying causes of patient risks. Under the PSQIA, PSWP is considered privileged and confidential. Once PSWP is transmitted from the provider to the PSO, it may not be disclosed unless certain requirements are met. Penalties may be imposed for any breaches.[409]

PSOs may disclose PSWP—meaning, release, transfer, provide access to, or otherwise divulge PSWP to another person—as long as it is an authorized disclosure under the PQIA and Rule by meeting one or

more exceptions. These exceptions include disclosures authorized by the identified healthcare providers and disclosures of non-identifiable PSWP and disclosures to the FDA, among others.[410] With respect to disclosure of PSWP for purposes of research, the regulations provide a very narrow exception. The Rule allows for disclosure of identifiable PSWP to entities carrying out, "research, evaluations or demonstration projects that are funded, certified or otherwise sanctioned by rule or other means by the Secretary [of Health and Human Services].' [411] (Keep in mind that, in addition to the PSQIA, all such disclosures must comply with HIPAA.) Notably, the disclosure of PSWP for general research activities is not permitted under the PSQIA or the Rule.

An organization desiring to become a PSO must complete and submit a certification form to the Agency for Healthcare Research and Quality to become "listed" as a PSO.[412] A registry may choose to become listed as a PSO, however, the registry should consider whether the obligations imposed on it in its capacities as a PSO would limit or otherwise restrict the registry in performing its original objectives and whether it can fully meet the requirements of the PSQIA. In evaluating whether or not to be listed as a PSO, the registry developer should carefully review the registry's organizational structure and data collection processes to help ensure that there is a clear distinction between the collection of registry-related data and PSWP. For example, certain registries may publish certain information and results related to the data collected in the registry. As described above, if that registry is a PSO, then it must ensure that any data published does not constitute unauthorized disclosure for purposes of the PSQIA. It is imperative that an applicable exception to disclose PSWP exists. As opposed to a registry itself becoming a PSO, it may elect to form a separate division or legal organization that it controls. These types of PSOs are referred to as "Component PSOs." This structure may help segregate registry data and PSWP, thus reducing the possibility of an impermissible disclosure of PSWP.

Recent Developments Affecting the Privacy Rule

IOM Report. On February 4, 2009, the Institute of Medicine (IOM) published a report that examined how research was being conducted within the framework of the Privacy Rule. Within the IOM Report were findings of the IOM Committee on Health Research and the Privacy of Health Information (the IOM Committee)—the group that had assessed whether the Privacy Rule had an impact on the conduct of health research and that had proposed recommendations to ensure that important health research may be conducted while maintaining or strengthening privacy protections for research subjects' health information.[413] The IOM Report specifically acknowledged that the Privacy Rule was difficult to reconcile with other regulations governing the conduct of research, including the Common Rule and the FDA Regulations, and it noted a number of inconsistencies among applicable regulations related to the de-identification of data and the use of informed consent for future research studies, among others.

Citing more uniform regulations in other countries, the IOM Report affirmed that, "a new direction is needed, with a more uniform approach to patient protections, including privacy, in health research."[414] As its primary recommendation, the IOM Committee held that research should be entirely exempt from the Privacy Rule. In making such a recommendation, the IOM Committee encouraged Congress to allow HHS and other federal agencies to develop separate guidance for the conduct of health research. Until such an overhaul could be accomplished, the IOM Committee called upon HHS to revise the Privacy Rule and associated guidance. While neither of the above recommendations have been enacted to date, registry operators should be aware that modifications to, or elimination of the Privacy Rule as it relates to research activities, may be a possibility in the near future.

GINA. The Genetic Information Nondiscrimination Act of 2008 (GINA) was signed into law on May 21, 2008. In general, GINA prohibits discrimination in health coverage (Title I of GINA) and employment (Title II of GINA) based on genetic information. GINA defines genetic information as information about an individual's genetic tests, the genetic tests of an individual's family members, and the manifestation of a disease or disorder in an individual's family (e.g., family history). Title I of GINA took effect for most health plans on May 22, 2009 and Title II became effective for employers on November 21, 2009. GINA also specifies that the definition of genetic information includes genetic information of a fetus carried by a pregnant woman and an embryo legally held by an individual or family member utilizing an assisted reproductive technology. Pursuant to GINA, health insurers and employers are prohibited from using genetic information of individuals or their family members in determining insurance eligibility and coverage, in underwriting and premium setting, or in making employment-related decisions.

In addition to the non-discrimination requirements, GINA also amended the Privacy Rule to clarify that genetic information is included within the Privacy Rule definition of protected health information. As a result, health plans and employers that are covered entities are required to treat any genetic information they collect as protected health information.

The HITECH Act. The American Recovery and Reinvestment Act of 2009 (ARRA) was signed into law on February 17, 2009. Funds resulting from passage of the ARRA are supporting new registries developed to study comparative effectiveness. It should be noted that there are no regulatory or ethical exceptions for such comparative effectiveness registries. Title XIII of the ARRA, the Health Information Technology for Economic and Clinical Health Act (HITECH Act) significantly modifies the rights and obligations of healthcare providers as covered entities and those who perform certain services on behalf of covered entities, namely their so-called business associates, as defined in the HIPAA Privacy Rule.

Perhaps most significantly, the HITECH Act expands the scope of many key privacy and security obligations contained in the Privacy Rule to business associates. Specifically, business associates will be required to comply with obligations related to administrative, physical, and technical safeguards, plus documentation. While many Business Associate Agreements previously contained general safeguarding requirements (e.g., requiring the business associate to maintain appropriate technical safeguards), these agreements often had not imposed specific security requirements (e.g., requiring the business associate to implement procedures to terminate an electronic session after a predetermined time of inactivity). These expanded obligations will also subject business associates to civil and criminal penalties once reserved only for covered entities under the Privacy Rule. The obligations imposed on business associates are scheduled to take effect on February 17, 2010.

The HITECH Act also creates a new requirement for covered entities and business associates to report data security breaches. If unsecured protected health information is accessed, acquired or disclosed as a result of a data security breach, a covered entity must notify each individual whose information was improperly accessed, acquired or disclosed. Depending on the number of affected individuals, such notifications may be made via first-class mail, email, posting on the entity's website or providing notice to media outlets.

If any unsecured protected health information stored or maintained by a business associate is breached or compromised, the business associate must provide notification to the applicable covered entity, without unreasonable delay, and in no case later than 60 days after the breach becomes known, or reasonably

should have become known, to the business associate. Any notification by a business associate must include the identification of any individual(s) whose information was accessed, acquired or disclosed during the breach. Under the Privacy Rule, business associate agreements would contain similar breach notification requirements; however, the HITECH Act imposes a statutory obligation on business associates. The data breach notification requirements are scheduled to take effect within thirty days after HHS issues the final rules to implement the breach notification regulations.

Summary of Regulatory Requirements

The use and disclosure of health information by health care providers and insurance plans for research purposes, including registries, *are assumed* by the authors of this chapter to be subject to regulation under the Privacy Rule and *may be* subject to the Common Rule.

In general, the Privacy Rule permits the use or disclosure of patient information for a registry, subject to specific conditions, in the following circumstances: (1) registries serving public health activities, including registries developed in connection with FDA-regulated products; (2) registries developed for the health care operations of health care providers and insurance plans (covered entities), such as quality I/A; (3) registries created by health oversight authorities for health system oversight activities authorized by law; (4) registries using de-identified health information; (5) registries using a "limited data set" of patient information that lacks specified direct identifiers; (6) registries using information obtained with patient authorizations; or (7) registries using information obtained with a waiver of authorization.

The Common Rule will apply to the creation and use of registry data if (1) the organization where the registry resides is subject to Common Rule requirements and has an FWA that encompasses the registry project; *and* (2) the creation of the registry and subsequent research use of the registry data constitute human subject research as defined by the Common Rule and are not exempt from Common Rule requirements; *and* (3) registry activities include a research purpose, which may be in addition to the main purpose of the registry. Registry developers are strongly encouraged to consult the IRB, not only about the applicability of the Common Rule, but also about the selection of data elements, the content of the consent process or the regulatory criteria for waiver, and any anticipated future research involving identifiable registry data.

State laws regulate public health activities and also may apply in various ways to the research use of health information. NIH can issue certificates of confidentiality to particular research projects for the protection of identifiable personal information from most legally compelled disclosures. Federal law provides specific privacy protections to the health information of patients in substance abuse programs that receive Federal funding. The institutional policies of health care providers and insurance plans may also affect the use and disclosure of the health information from their patient and insured populations.

Legal requirements applying to use or disclosures of health information for research are evolving and can significantly influence the planning decisions of registry developers and investigators. Early and frequent consultation with institutional privacy officers, Privacy Board, or IRB staff and members, information system representatives of health care providers and insurance plans, plus technology transfer representatives and legal counsel, as necessary is prudent.

Registry Transparency, Oversight, and Data Ownership

Registry Transparency

Efforts to make registry operations transparent (i.e., making information about registry operations public and readily accessible to anyone who is interested) are desirable. Such efforts may be crucial to realizing the potential benefits of research using health information. Registry transparency can also educate about scientific processes. Transparency contributes to public and professional confidence in the scientific integrity and validity of registry processes, and therefore in the conclusions produced by registry activities. Public information about registry operations may also increase the scientific utility of registry data by promoting inquiries from scientists with interests to which registry data may apply.

Registry developers can achieve transparency by making the registry's scientific objectives, governance, eligibility criteria, sampling and recruitment strategies, general operating protocol, and sources of data available to anyone who is interested. Proprietary interests by funding agencies, contractual conditions, and licensing terms for the use of patient or claims information may limit, to some extent, the information about the registry that is available to the public. It is important to stress that, while transparency and access to information are values to be encouraged, investments in-patient registries that produce proprietary information are not intended to be discouraged or criticized. Neither the funding source nor the generation of proprietary information from a registry determines whether a registry achieves the good practices described in this handbook. Funding agencies, health care providers, and insurance plans, however, also have an important stake in maintaining public confidence in health information management. The extent of registry transparency should be prospectively negotiated with these entities.

Creating a Web site of information about registry objectives and operations is one method of achieving transparency; ideally, registry information should be available in various media. An IRB may require registry transparency as a condition of approval to satisfy one of the regulatory criteria for granting a waiver of consent. The regulatory requirement is to provide "additional pertinent information after participation."[415] Currently, an international transplant registry maintains a Web site that provides a useful model of registry transparency.[416]

Registry Oversight

Registry governance must reflect the nature and extent of registry operations. As described in Chapter 2, possible governing structures can vary widely, from the registry developer as a sole decision maker to committee(s) comprising representatives of all stakeholders in the registry, including investigators, the funding agency, patients, clinicians, biostatisticians, information technology specialists, and government agencies.

Registry developers should also consider appointing an independent advisory board to provide oversight of registry operations. An advisory board can assist registry operations in two important areas: (1) providing guidance for the technical aspects of the registry operations, and (2) establishing the scientific independence of the registry. The latter function can be valuable when dealing with controversies, especially those about patient safety and treatment, or actions by a regulatory agency. Advisory board members collectively should have relevant technical expertise but include appropriate representatives of other registry stakeholders, including patients. Advisory board oversight should be limited to making

recommendations to the ultimate decision maker, whether that is an executive committee or the registry developer.

Registry developers may also appoint other types of oversight committees to resolve specific recurring problems, such as verifying diagnoses of patient conditions or adjudicating data inconsistencies.

Data Ownership

Health information ownership in general. Multiple entities are positioned to assert ownership claims to health information in various forms. Certain States have enacted laws that assign ownership to health records.[417] The Privacy Rule was not intended to affect existing laws governing the ownership of health records.[418] At the current time, such claims of ownership are plausible, but none is known to be legally tested or recognized, with the exception of copyright. The entities potentially claiming ownership include health care providers and insurance plans, funding agencies for registry projects, research institutions, and government agencies. Notably, health care providers are required by state law to maintain documentation of the services they provide. This documentation is the medical-legal record compiled on each patient who receives health care services from an individual or institutional provider. Individuals, including patients (in addition to a potential liberty interest in maintaining control of its use), registry developers, and investigators, may also assert ownership claims to health information. The basis for these claims is control of the tangible expression of and access to the health information.

There is no legal basis for assertions of ownership for facts or ideas; in fact, established public policy supports the free exchange of ideas and wide dissemination of facts as fundamental to innovation and social progress.[419] As health information moves from its creation as a tangible expression to various forms in the control of successive entities, rights of ownership may be transferred (assigned), shared, or maintained, with use of the information licensed (i.e., a limited transfer of rights for use on specific terms and conditions). Currently, in each of these transactions, the rights of ownership will be negotiated on a case-by-case basis and formalized in written private agreements. The funding agency for a registry may also assert claims to ownership as a matter of contract law in their sponsorship agreements with research organizations.

Many health care providers are currently installing systems for electronic health records at great expense. Many are also contemplating an assertion of ownership in their health records, which may include ownership of copyright. The claim to ownership by health care providers may be an overture to commercialization of their health care information in aggregate form.[420] Public knowledge of and response to such assertions of ownership are uncertain at this time. A licensing program for the use of health information may permit health care providers to recoup some of their investment in electronic health records and the infrastructure, including full-time technicians, required to maintain them. In the near future, research use of health information for a registry may require licensing, in addition to the terms and conditions in data use agreements and, if necessary, in business associate agreements required by Privacy Rule regulations. Subsequent research use of the registry data will likely depend on the terms of the original license for use.

Among the changes to the regulation of health care information established by ARRA, is a prohibition on its sale, subject to certain exceptions, including one for research use. This exception permits covered entities to recover reasonable payment for processing of health information for research use.[421]

Publication rights are an important component of intellectual property rights in data for academic institutions. Formal institutional policies may address publication rights resulting from faculty educational and research activities. Moreover, the social utility and benefit of any registry is evaluated on the basis of its publicly known findings and any conclusions based on them. The authors strongly encourage registry developers to maximize public communication of registry findings through the customary channels of scientific conferences and peer-reviewed journals. The goals of public communication for scientific findings and conclusions apply equally to registries operated outside of academic institutions (i.e., directly by industry or professional societies). For further discussion of developing data access and publication policies for a registry, see Chapter 2.

The concept of ownership does not fit health information comfortably, because it largely fails to acknowledge individual patient privacy interests in health information. An inescapable personal nexus exists between individuals and information about their health. A similar failure that occurred recently, with regard to patient interests in residual tissue from clinical procedures, resulted in widely publicized litigation.[422] Alternatively, the legal concept of custody may be useful. Custodians have legal rights and responsibilities; for instance, those that a guardian has for a ward or parents have for their children. Custody also has a protective function, which supports public expectations of confidentiality for health information that preserves the privacy and dignity of individual patients. Custody and its associated legal rights and responsibilities are also transferable from one custodian to another. The concept of custody can support health care provider investments in information systems and the licensed use of health information for multiple, socially beneficial purposes without denying patient interests in their health information.

The sharing of registry data subsequent to their collection currently presents special ethical challenges and legal issues.[423] The arrangements that will determine the essential conditions for shared use include applicable Federal or State law and regulatory requirements under which the health information was originally obtained. These legal and regulatory requirements, as well as processing and licensing fees, claims of property rights, and concerns about legal liability are likely to result in formal written agreements for each use of registry data. To educate patients and to establish the scientific independence of the registry, registry developers should make transparent the criteria under which uses of data occur.

In short, no widely accepted social or legal standards currently govern property rights in health information, with the possible exception of copyright, which is discussed below. At this time, agreements between health information sources and other users privately manage access and control. The Privacy Rule regulates the use and disclosure of health information by covered entities (certain health care providers and insurance plans), plus certain third parties working on behalf of covered entities, but does not affect current laws regarding property rights in health information, when they exist.

Copyright protection for health information registries. In theory, a health information registry is likely to satisfy the statutory definition of a compilation[424] and reflect independent creativity by its developer.[425] Thus, copyright law may provide certain protections for a health information registry existing in any medium, including electronic digital media. The "facts" compiled in a health information registry, however, do not correlate closely to other compilations protected by copyright, such as telephone books or even genetic databases.[426] Instead, registry data constitute legally protected, confidential information about individual patients to which independent and varied legal protections apply. Copyright

protections may marginally enhance, but do not diminish, other legal restrictions on access to and use of health information and registry data. For more information on copyright law, see Appendix B.

Conclusions

Ethical considerations are involved in many of the essential aspects of planning and operating a registry. These considerations can affect the scientific, logistical, and regulatory components of registry development, as well as claims of property rights in health information. The guiding ethical principles for these considerations are *respect for persons*, *beneficence*, and *justice*.

At the most fundamental level, investigations that involve human subjects and that are not capable of achieving their scientific purpose are unethical. The risk-benefit ratio of such studies is unacceptable in an analysis based on the principle of *beneficence*, which obligates investigators to avoid harming subjects, as well as maximizing the benefits and minimizing the harms of research projects. Ethical scientific design must be robust, based on an important question, and incorporate sufficient statistical power, precise eligibility criteria, appropriately selected data elements, and adequately documented operating procedures and methodologies.

In addition, an ethical obligation to minimize harms involves planning adequate protections for the confidentiality of the health information disclosed to a registry. Such planning should include devising physical, technical, and administrative safeguards for access to and use of registry data. Reducing the potential harms from the use of health information in a registry is particularly important, because generally, no directly offsetting benefit from participation in a registry accrues to individuals whose health information is used in the registry. In an analysis applying the principle of *justice*, research activities that produce a significant imbalance of potential risks and benefits to participating individuals are unethical.

Protection of the confidentiality of the health information used to populate a registry reflects the ethical principle of *respect for persons*. Health information intimately engages the privacy and dignity of patients. Registry developers should acknowledge public expectations of protection for patient privacy and dignity with clear and consistent communications to patients about protections against inappropriate access to and use of registry data.

The regulatory requirements of the Privacy Rule and Common Rule have deep connections to past ethical concerns about research involving human subjects, to general social anxiety about privacy associated with rapid advances in health information systems technology and communications, and to current biomedical developments in human genetics. Compliance with these regulatory requirements not only is a cost of doing business for a registry project, but also demonstrates recognition of the ethical considerations accompanying use of health information for scientific purposes. Compliance efforts by registry developers also acknowledge the important public relations and liability concerns of health care providers and insurance plans, public health agencies, health oversight agencies, and research organizations. Regulatory compliance contributes to, and generally supports, the credibility of scientific research activities and research organizations, as well as that of particular projects. Public confidence is crucial to the continuing support of health care institutions, to which society entrusts the sick, and to academic institutions, to which society entrusts its children and its hopes for the future.

Other Federal and State privacy laws may affect registry development, especially registries created for public health purposes. These laws express an explicit, legislatively determined balance of individual patient interests in health information against the potential social benefits from various uses of health information, including research. Consultation with legal counsel is strongly recommended to determine the possible effect of these laws on a particular registry project.

Ethical considerations also affect the operational aspects of registries, including governance, transparency, and data ownership. Registry governance, discussed in Chapter 2, should reflect both appropriate expertise and representation of stakeholders, including patients. Advisory committee recommendations can provide useful guidance in dealing with controversial issues. Transparency involves making information about registry governance and operations publicly available. Registry transparency improves both public and professional credibility for the scientific endeavors of a registry, the confidential use of health information for scientific purposes, and the results produced from analyses of registry data. In short, registry transparency promotes public trust.

Claims of "ownership" for health information and registries are plausible, but have not yet been legally tested. In addition, public response to such claims is uncertain. Ostensibly, such claims do not seem to acknowledge patient interests in health information. Nonetheless, in theory, copyright protections for compilations may be applied to the patient information held by health care providers and insurance plans, as well as to registries. In general, claims of property rights in health information are likely to be negotiated privately as additions to the regulatory terms and conditions in formal agreements between registry developers, funding agencies, and health care providers or insurance plans. As a practical matter, "ownership" implies operational control of registry data and publication rights.

In summary, careful attention to the ethical considerations related to the design and operation of a registry, as well as the applicable legal requirements, will contribute to the success of registry projects and ensure the realization of their social and scientific benefits.

Summary of Privacy Rule and Common Rule Requirements

In Table 11, which summarizes Privacy Rule and Common Rule requirements, it is generally assumed that the Privacy Rule applies to the data source— i.e., that the data source is a "covered entity." The exception is Category 8, registry developers that use data not subject to the Privacy Rule.

Table 11: Summary of Privacy Rule and Common Rule Requirements

	Extent an individual may be identified from health information	Extent an individual may be identified from health information	Extent an individual may be identified from health information	
Registry developer or purpose of registry	**Health information is de-identified[a]**	**Health information excludes direct identifiers**	**Health information includes direct identifiers**	**Waiver of authorization, documentation of consent, or consent process**

[a] Information lacks the data elements specified in the Privacy Rule standard for de-identification.

[b] The Common Rule likely applies if: (1) Federal funding is involved with the registry project, (2) the organization within which the registry will reside has agreed in its Federal-wide Assurance (FWA) to apply the Common Rule to all research activities conducted in its facilities or by its employees, or (3) institutional policy applies the Common Rule.

Note: FDA = U.S. Food and Drug Administration. IRB = Institutional Review Board.

Note: The information in the table is merely a simplified summary that is subject to change by other applicable law and may be amplified by institutional policies. In addition, each research project is unique, and this table does not address all of the nuances of the regulatory requirements. Reference to this table is not a substitute for consultation with appropriate institutional officials about the regulatory requirements that may apply to a particular registry project.

Registry developer or purpose of registry	Extent an individual may be identified from health information Health information is de-identified[a]	Extent an individual may be identified from health information Health information excludes direct identifiers	Extent an individual may be identified from health information Health information includes direct identifiers	Waiver of authorization, documentation of consent, or consent process
1A. Federal or State public health agency: Registry for *public health practice within agency's legal authority* **not** *involving research*	No requirements.	The Privacy Rule permits use or disclosure to a public health authority for public health activities. The Common Rule is not applicable.	The Privacy Rule permits use or disclosure to a public health authority for public health activities. The Common Rule is not applicable.	Waivers are not applicable.

Registry developer or purpose of registry	Extent an individual may be identified from health information Health information is de-identified[a]	Extent an individual may be identified from health information Health information excludes direct identifiers	Extent an individual may be identified from health information Health information includes direct identifiers	Waiver of authorization, documentation of consent, or consent process
1B. Federal or State public health agency: Registry as agency *research project*	No requirements.	The Privacy Rule permits the use or disclosure of limited data set, provided the data source and registry developer enter into a data use agreement. If the Common Rule applies,[b] it permits an IRB grant of exemption unless a re-identification code is used.	The Privacy Rule permits use or disclosure with patient authorization or IRB or Privacy Board waiver of authorization. If the Common Rule applies,[b] IRB review and documented consent are required, unless an IRB grants a waiver of documentation or waiver for the consent process.	Privacy Board or IRB approval of a waiver of authorization depends on satisfaction of specific regulatory criteria. If the Common Rule applies,[b] IRB approval of a waiver of consent documentation or process depends on satisfaction of specific regulatory criteria.

Registry developer or purpose of registry	Extent an individual may be identified from health information Health information is de-identified[a]	Extent an individual may be identified from health information Health information excludes direct identifiers	Extent an individual may be identified from health information Health information includes direct identifiers	Waiver of authorization, documentation of consent, or consent process
2. Registry producing evidence in support of labeling for an *FDA-regulated product*.	No requirements.	The Privacy Rule permits use or disclosure to a person responsible for an FDA-regulated product.	The Privacy Rule permits use or disclosure to a person responsible for an FDA-regulated product. FDA regulations, and Common Rule, if applicable,[b] require IRB review, a documented consent process, and protection of confidentiality of research data.	Waivers are not applicable.
3. Health oversight agency registry to perform *a health oversight activity* **not** *involving research*	No requirements.	The Privacy Rule permits use or disclosure for health oversight activities authorized by law. The Common Rule is not applicable.	The Privacy Rule permits use or disclosure for health oversight activities authorized by law. Institutional policy may apply the Common Rule or require IRB review.	Waiver of authorization is not applicable. If institutional policy applies the Common Rule, IRB approval of a waiver of consent documentation or process depends on satisfaction of specific regulatory criteria.

Registry developer or purpose of registry	Extent an individual may be identified from health information Health information is de-identified[a]	Extent an individual may be identified from health information Health information excludes direct identifiers	Extent an individual may be identified from health information Health information includes direct identifiers	Waiver of authorization, documentation of consent, or consent process
4. Registry *required by law*; Common Rule may apply[b] if registry *involves research*	No requirements.	The Privacy Rule permits use or disclosure required by other law. If the Common Rule applies,[b] it permits an IRB grant of exemption, unless a re-identification code is used.	The Privacy Rule permits use or disclosure required by other law. Institutional policy may apply the Common Rule or require IRB review whether or not a research purpose is involved.	Waiver of authorization is not applicable. If the Common Rule applies,[b] IRB approval of a waiver of consent documentation or process depends on satisfaction of specific regulatory criteria.
5. *Quality improvement or assurance registry* **not** *involving research*	No requirements.	The Privacy Rule permits the use or disclosure of a limited data set, provided the data source and registry developer enter into a data use agreement. The Common Rule is not applicable.	The Privacy Rule permits use or disclosure for the "health care operations" of the data source and, in certain circumstances, of another covered entity. The Common Rule is not applicable.	Waivers are not applicable.

Registry developer or purpose of registry	Extent an individual may be identified from health information Health information is de-identified[a]	Extent an individual may be identified from health information Health information excludes direct identifiers	Extent an individual may be identified from health information Health information includes direct identifiers	Waiver of authorization, documentation of consent, or consent process
6. Research registry residing in organization to which Common Rule applies[b]	No requirements.	The Privacy Rule permits the use or disclosure of a limited data set for research, provided the data source and registry developer enter into a data use agreement. The Common Rule permits an IRB grant of exemption from review unless a re-identification code is used.	The Privacy Rule permits use or disclosure for research with individual patient authorization or an IRB or Privacy Board waiver of authorization. The Common Rule requires IRB review and documented consent unless the IRB grants a waiver of documentation of consent or a waiver for the consent process.	IRB or Privacy Board approval depends on satisfaction of specific regulatory criteria.

Registry developer or purpose of registry	Extent an individual may be identified from health information Health information is de-identified[a]	Extent an individual may be identified from health information Health information excludes direct identifiers	Extent an individual may be identified from health information Health information includes direct identifiers	Waiver of authorization, documentation of consent, or consent process
7. *Research registry* developed by organization that is not a health care provider or insurance plan and is not subject to the Common Rule, using health information obtained from a health care provider or insurance plan	No requirements.	The Privacy Rule permits the disclosure of a limited data set, provided the data source and registry developer enter into a data use agreement.	The Privacy Rule permits use or disclosure for research with individual patient authorization or waiver of authorization.	Privacy Board approval of a waiver of authorization depends on satisfaction of specific regulatory criteria.

Registry developer or purpose of registry	Extent an individual may be identified from health information Health information is de-identified[a]	Extent an individual may be identified from health information Health information excludes direct identifiers	Extent an individual may be identified from health information Health information includes direct identifiers	Waiver of authorization, documentation of consent, or consent process
8. Research registry developed by organization that is not a health care provider or insurance plan and is not subject to the Common Rule, using health information collected from entities not subject to the Privacy Rule.	No requirements.	No requirements.	No requirements.	Waivers are not applicable.

Case Example 23: Considering the institutional review board process during registry design

Description:	The National Oncologic PET Registry (NOPR) collects data to assess the impact of positron emission tomography with F-18 fluorodeoxyglucose (PET) on cancer patient management. The registry was designed to meet the Centers for Medicare & Medicaid Services (CMS) data submission requirements for expanded coverage for new indications and additional cancers.
Sponsor:	Academy of Molecular Imaging (AMI), managed by American College of Radiology (ACR) through the American College of Radiology Imaging Network (ACRIN)
Year Started:	2006
Year Ended:	Ongoing
No. of Sites	Began accepting registrations in late 2005
No. of Patients:	Began accepting patients in 2006

Challenge

The NOPR is one of the first examples of CMS's new coverage with evidence development (CED) approach. For the expanded coverage of PET for cancer, the agency required the collection of prospective clinical and demographic data. From the beginning, the organizations developing the registry understood the need to define the requirements for institutional review board (IRB) approval and informed consent. They were uncertain, however, about how Department of Health and Human Services (HHS) regulations for the protection of human research subjects, including IRB requirements, would apply to the planned registry. Implementing NOPR required ACR and AMI, in conjunction with CMS and HHS's Office for Human Research Protections (OHRP), to resolve these issues.

Based on their initial assessment of the registry, as well as discussions with CMS, the sponsors believed that the registry was not subject to IRB approval because it was "conducted by or subject to the approval of Department or Agency heads" for the purpose of evaluating a "public benefits or services program." The ACR IRB likewise judged upon review of the proposal that the registry qualified for the "public benefits" exemption. Several IRBs at institutions planning to participate in the registry reached the same conclusion. Accordingly, the registry's original design did not include a provision for obtaining IRB approval or patient consent. However, 1 week before the registry was to begin operation, registry investigators and CMS staff received an email from OHRP rejecting that interpretation on the grounds that the purpose of the registry was not only to evaluate Medicare coverage policy but also to generate clinical data that would potentially affect patient management. OHRP's decision raised the prospect that each of the hundreds of participating hospitals and freestanding PET facilities would be required to obtain approval from its own IRB (or a commercial IRB)—a process that would have been administratively cumbersome, expensive, and very time consuming. The registry investigators suspended the launch and, in consultation with several IRB Chairs, CMS, and other HHS staff, sought to develop an alternative approach.

Proposed Solution

The issue was ultimately resolved only when registry investigators and IRB Chairs from Duke University, Washington University, and ACR spoke directly with OHRP. The parties reached consensus that ACR, the institution operating the registry, was the only entity engaged in research, and that the registry therefore needed to be approved only by a single IRB designated under ACR's Federalwide Assurance

(FWA). This plan reflects guidance under development at OHRP, and likely could not have been devised without the help of that agency. The ACR IRB has since approved the use of data collected by the registry for research purposes based on this model.

Results

Under this approach, individual PET facilities and referring physicians do not have to obtain IRB approval in order to submit data to the registry, thus avoiding the waste and redundancy of requiring parallel action by hundreds of individual IRBs. Both patients and referring physicians are considered research subjects, however, and must therefore provide informed consent before their data can be used for research. With the guidance of OHRP, registry investigators also developed a rationale for waiver of written consent. Either before or upon arrival at a PET facility, each patient receives a standard registry information document, describing the registry and requesting that the patient provide oral consent for the use of his or her identified data for research purposes. Consent from the referring physician, who also receives a standard registry information sheet, is recorded on one of the two data collection forms the physician must complete. If either the patient or the referring physician withholds consent, the identified data are still collected by the PET facility, sent electronically to the registry, and then submitted to CMS for the purpose of determining payment; however, the data will not be used for research. In such cases, CMS nevertheless pays for the PET scan.

Key Point

Even when the primary purpose of a medical data registry is to evaluate Medicare payment policy, its implementation necessarily involves a host of issues related to protecting the subjects whose data will be used. It is essential to address these issues early, so that appropriate systems and procedures can be incorporated into the design of the registry. Additionally, if the institution operating the registry is the only entity engaged in research, then the registry needs to be approved only by a single IRB designated under that institution's FWA.

Case Example 24: Issues with obtaining informed consent

Description:	The Registry of the Canadian Stroke Network (RCSN) is a prospective, national registry of stroke patients in Canada. The registry, currently in Phase IV, is a non-consent-based registry that collects detailed clinical data on the acute stroke event, from the onset of symptoms, emergency medical service transport, and emergency department care to hospital discharge status. The purposes of the registry are to monitor stroke care delivery, to evaluate the Ontario Stroke System, and to provide a rich clinical database for research.
Sponsor:	Canadian Stroke Network, Networks of Centres of Excellence, and Ministry of Health and Long Term Care of Ontario
Year Started:	2001
Year Ended:	Ongoing
No. of Sites	154
No. of Patients:	Over 35,000

Challenge

The registry began in 2001 with Phase I, which gathered data from 21 hospitals in Canada. All patients admitted to the hospital or seen in the emergency department with symptoms of acute stroke within 14

days of onset or transient ischemic attack (TIA), as well as those with acute in-hospital stroke, were included in this phase. Research nurse coordinators identified eligible patients through daily reviews of emergency and admission patient lists and approached these patients for consent. Informed patient consent was required for full data collection, linkages to administrative data, and 6-month followup interviews.

Despite the need for informed consent for full data collection, consent was obtained for only 39 percent of eligible patients. Subsequent analyses showed that patients who consented to participate were not representative of the overall stroke population, as they were less likely to have severe or fatal stroke, and also less likely to have minor stroke or TIA.

Phase II of the registry began in 2002, with 21 hospitals and 4 Ontario Telestroke sites. In this phase, all patients admitted to the hospital or seen in the emergency department with symptoms of acute stroke within 14 days of onset or TIA were included. Patients with in-hospital stroke were no longer recruited. In order to standardize workload across the country, a random sample of eligible patients was selected to be approached for consent for full data collection. Consent was obtained on 50 percent of eligible patients.

After obtaining consent of only 39 percent and 50 percent of patients in Phases I and II, the team realized that obtaining written patient consent for participation in the registry on a representative sample of stroke patients was impractical and costly. Patient enrollment threatened the viability and generalizability of the stroke registry. The registry team published these findings in the New England Journal of Medicine in April 2004.

Proposed Solution

The registry team approached the Ontario Information and Privacy Commissioner to discuss a non-consent-based registry for Phase III. Because of these discussions, the registry was "prescribed" by the Privacy Commissioner under the Personal Health Information Protection Act, 2004, which allowed the registry to collect data legally on stroke patients without written consent.

Results

Phase III of the registry included all patients presenting to emergency departments of the 11 Stroke Centres in Ontario and 1 Stroke Centre in Nova Scotia with a diagnosis of acute stroke or TIA within 14 days of onset. Nurse coordinators identified eligible patients through daily reviews of emergency and admission patient lists. Patients were identified prospectively, with retrospective chart review without consent. No followup interviews were done. Because informed consent was not required, the data collected provided a representative sample of stroke patients seen at tertiary care centres in Canada, making the data more viable for use in research and in developing initiatives to improve quality of care. The registry has now expanded to include a population-based, province-wide audit of stroke care delivery on a 20 percent sample of patients from every acute care institution in Ontario.

Key Point

The impact of obtaining informed consent should be considered in developing a registry. Requiring that registries obtain the consent of patients with acute medical conditions such as stroke may result in limited selective participation, as it is not possible to obtain consent on all patients. For example, patients who die in the emergency department and patients who have brief hospital visits may be missed. Mechanisms such as obtaining a waiver of informed consent or using the approach outlined in this case may be alternatives.

For More Information

Tu JV, Willison DJ, Silver FL et al. The impracticability of obtaining informed consent in the Registry of the Canadian Stroke Network. *N Engl J Med* 2004 Apr; 350:1414-21.

Section II: Operating Registries

Chapter 9: Recruiting and Retaining Participants in the Registry

Recruitment and retention of participants are essential elements in the design and operation of a registry. Registries are often intended to be representative of a certain population of patients and reflective of the practices of certain providers and geographies. The problems commonly associated with clinical studies, such as difficulties with patient enrollment, losses to followup, and certain sites contributing the majority of patients, can also have profound consequences on validity of registry data. When registry patients are not representative of the target population, the value of the results is diminished. For example, in regards to policy determinations, the enrolled sites or providers must be representative of the types of sites and providers to which the policy determination would apply in order for the results of the registry to be generalizable. Differences in how effectively sites enroll or follow patients can skew results and overly reflect the sites with the most data. This oversampling within a particular site or location must also be considered in sample size calculations. If the sample size of a key unit of analysis (patient, provider, or institution) is not sufficient to detect a clinically important difference, the validity of the entire registry is weakened. (See Chapters 3 and 13.)

Well-planned strategies for enrollment and retention are critical to avoiding these biases that may threaten registry validity. Because registries typically operate with limited resources and with voluntary rather than mandatory participation, it is particularly important to balance the burdens and rewards of participation in the registry. The term "voluntary" in this context is intended to mean that participation in the registry by either providers or patients is not mandated (e.g., by the U.S. Food and Drug Administration), nor is participation required as a necessary condition for a patient to gain access to a health care product or for a provider to be eligible for payment for a health care service. Registries that are not voluntary have different drivers for participation. In general, the burden of participation should be kept as low as possible while the relative rewards, particularly nonmonetary rewards, should be maximized. As described in Chapters 2 and 5, minimizing burden typically starts with focusing on the key goals of the registry.

Building participation incentives into a registry should also be included in the planning phase. A broad range of incentives, spanning a spectrum from participation in a community of researchers, to access to useful data or quality improvement benefits, to continuing medical education to public recognition or certification to payments or access to patients, have been used in registries. The ability to offer certain incentives (e.g. linking payment for a service to participation in a registry or access to patients) may only be available to certain registry developers (e.g. payers, licensing entities). Many registries incorporate multiple types of incentives, even when they pay for participation. Monetary incentives (e.g., from payers or sponsors) are very helpful in recruiting sites. However, because the payments should not exceed fair market value for work performed, registries cannot solely rely on these incentives. A number of non-

mandated registries have achieved success in recruitment and retention by providing a combination of ethical incentives that are tailored to and aligned with the specific groups of sites, providers, and patients that are asked to participate. (See Case Examples 25, 26, 27, and 28.)

Recruitment

Depending on the purpose of a registry, recruitment may occur at any of three levels: facility (e.g., hospital, practice, and pharmacy), provider, or patient. While frequently these levels are a means to accrue patients for sample size purposes, such as for a safety registry, they may also constitute potential units of analysis (and as such may further affect sample size, as discussed in Chapter 3). As an example, a registry focused on systems of care that is examining both hospital system processes and patient outcomes might need to consider characteristics of the individual patients, the providers, and/or the places where they practice (i.e., clusters). If the question is about the practices of orthopedic surgeons in the United States, the registry will be strengthened by describing the number and characteristics (e.g., age, gender, and geographic distribution) of U.S. orthopedic surgeons, perhaps by citing membership data from the American Academy of Orthopedic Surgeons.

This will allow documentation of the similarities and differences in the characteristics of the surgeons participating in the registry compared with the target population. (See Chapter 3.)

Hospital Recruitment

A hospital or health system may choose to participate in a patient registry for many reasons, including the research interest of a particular investigator or champion, the ability for the hospital to achieve other goals through the registry (such as requirements for reimbursement, certification, or recognition), or the general interest of the particular institution in the disease area (e.g., specialty hospitals). Increasingly, external mandates to document compliance with practice standards provide an incentive for hospitals to participate in registries that collect and report mandatory hospital performance or quality-of-care data. For example, a number of registries allow hospitals to document their performance to meet the Joint Commission requirements for hospital accreditation.[427] Hospitals in the United States must submit these data to maintain accreditation. Therefore, hospital administrators may be willing to supply the staff time to collect these data without the need for any additional financial incentives from the registry sponsor, provided that registry participation allows the hospital to meet external quality-of-care mandates. In other cases, participation in a quality monitoring or health system surveillance registry may be required by payers or governments for reimbursement or differential payments or patient referrals under various programs, ranging from the Centers for Medicare & Medicaid Services public reporting initiative, to centers of excellence programs, to pay-for- performance programs. One particular example, CMS' Coverage under Evidence Development (CED) programs[428], which may require participation in a registry for the center or provider to qualify for payment for a procedure, can have a dramatic impact on registry participation. These requirements have existed for Implantable Cardioverter Defibrillators (ICD) for preventing sudden cardiac death in heart failure, bariatric surgery, positron emission tomography (PET) scan use in cancer, and others, and have rapidly resulted in high participation rates for registries meeting those requirements.

The presence of quality assurance departments in U.S. hospitals provides an infrastructure for participation in many hospital-based registries and therefore, a natural target for recruiting. However, hospital size, service line, and competing activities may limit institutional interest. The American

Hospital Association database provides a valuable resource for identifying hospitals by key characteristics, including hospital ownership, number of beds, and the presence of an intensive care unit.

Table 12 summarizes the key factors for successful hospital recruitment and lists specific methods that might be used for recruiting hospitals. While programs need not incorporate all of these characteristics or use all of these methods, successful programs typically incorporate several.

Physician Recruitment

There are many reasons why a physician practice may or may not choose to participate in a voluntary registry. As with hospitals, these reasons can include the research interests of the physician and the ability of the practice to achieve other goals through the registry (such as reimbursement or recognition). When deciding to participate, physicians often focus on several concerns:

- *Relevance*: Does the registry have meaning for the practice and patients?
- *Trust*: Are the registry leaders credible? Are the goals clearly stated?
- *Risks*: Will confidentiality be maintained? Are patient records secure?
- *Effort*: Will the amount of effort expended be fairly compensated?
- *Disruption*: Will participation disrupt workflow of the staff?
- *Value*: What benefits will be derived from my participation? Will it improve the care I provide? Will it enhance the evidence-base for future practice?

Physicians who manage only a few patients per year with the disease that is the subject of the registry are less likely to be interested in enrolling their patients than physicians who see many such patients, unless the disease is rare or extremely rare, in which case the registry may be of great interest.

Because most registries are voluntary and physicians in non-academic practice settings may have less infrastructure and staff available to enroll their patients, recruitment of representative physicians is a major challenge for registries that aim to compare physician practices across a full spectrum of practice settings. In general, community-based physicians are less well equipped to collect data for research studies because they work in busy practices that are geared to routine clinical care rather than research. To increase recruitment of non-academic physicians, it can be helpful to clearly explain the purpose and objectives of the registry, how registry data will be used, and, specifically, that individual results will not be shared (except at the direction of the physician) or published and that registry outcomes data will be released only in large aggregates that protect the identities of individual hospitals, physicians, and patients. In addition, any incentives should be clearly articulated.

Table 13 describes the key factors for successful physician recruitment and lists several methods that might be used for recruiting physicians.

Vetting Potential Hospital and Physician Participants

Once potential hospital or physician participants have been identified, it is important to vet them to ensure that the registry is gathering the appropriate mix of data. Issues to consider when vetting potential participants include:

- Representativeness.
- Hospital characteristics (e.g., bed size, geographic location).
- Physician characteristics (e.g., specialty training).
- Practice setting (health maintenance organization [HMO], private practice).
- Ability to recruit patients.
- Volume of target cases
- Internal resources.
- Availability of a study coordinator
- Availability of internet connectivity for studies with electronic data capture.
- Prior performance, including reliability and accuracy of data entry

Table 12. Hospital Recruitment

Keys to hospital recruitment	• The condition being studied satisfies one of the hospital's quality assurance mandates. • Sufficient funds, data, or other benefits will be realized to justify the effort required to participate. • The confidentiality of the hospital's performance data is ensured, except to the extent that the hospital elects to report it. • Clinically relevant, credible, timely, actionable self-assessment data—ideally data that are risk adjusted and benchmarked—are provided back to the hospital to help it identify opportunities for enhancing patient care outcomes. • High-profile hospitals (regional or national) are participating in the registry. • Burden is minimized. • Participation assists the hospital in meeting coverage and reimbursement mandates, gaining recognition as a center of excellence, or meeting requirements for pay-for-performance initiatives.
Methods of hospital recruitment	• Identify eligible hospitals from the American Hospital Association database. • Utilize stakeholder representatives to identify potentially interested hospitals. • Enroll hospitals through physicians who work there and are interested in the registry. • Use invitation letters or calls to directors of quality assurance or chiefs of the clinical department which is responsible for the condition targeted by the registry. • Ask physician members of an advisory board (if applicable) to network with their colleagues in other hospitals.

	• Reach out to physician contacts or hospital administrators through relevant professional societies or hospital associations. • Leverage mandates by external stakeholders, including third-party payers, health plans, or government agencies.

Table 13. Physician Recruitment

Keys to physician recruitment	• The condition being studied is part of the physician's specialty. • The registry is a valuable scientific endeavor. • The registry is led by respected physician opinion leaders. • The registry is endorsed by leading medical, government, or patient advocacy organization(s). • The effort needed to recruit patients and collect and submit data is perceived as reasonable. • Useful practice pattern and/or outcome data are provided. • The registry meets other physician data needs, such as maintenance of certification requirements, credentialing requirements, or quality-based, differential, reimbursement payment programs (pay-for-performance).
Methods of physician recruitment	• Purchase mailing lists from physician specialty organizations. • Ask opinion leaders in the field to suggest interested colleagues. • Partner with local and national medical societies or large physician hospital organizations. • Use stakeholder representatives to identify interested physicians. • Recruit and raise awareness at conferences. • Advertise using e-mail and Web. • Leverage practice-based research networks.

Patient Recruitment

Patients may be recruited based on: the judgment of the physician who provides their care; the diagnosis of a disease; receipt of a procedure, operation, device, or pharmaceutical; membership in a health insurance plan; or patients may also be recruited based on being a member of a group of individuals who have a particular exposure. Recruitment of patients by the physician who is providing their care is one of the most successful strategies. The direct involvement in and support of the registry by their personal physicians is an important factor for patients. Since registries should not modify the usual care that physicians provide to their patients, there should be little or no conflict between the role as a physician and that as a participant in the registry (See Chapter 8.) In addition, patients may see participation in the registry as an opportunity to increase their communication with their doctor. Another incentive for many patients is the feeling that they are contributing to the knowledge base of sometimes poorly understood and undertreated conditions.

Recruitment of patients presents different challenges, depending on the nature of the condition being studied. In general, patient recruitment plans should address the following questions:

- Does the plan understand the needs and interests of potential participants?

- Does the plan address patient recruitment issues and procedural challenges, including informed consent and explanation of risks?
- What are the patient retention goals? What is a reasonable followup period? What is a reasonable followup rate? When does retention compromise validity?
- What, if any, patient incentives are offered, including different types of incentives and the ethical, legal, or study validity issues to be considered with patient incentives?
- What are the costs of patient recruitment and retention?

Table 14 summarizes the key factors for patient recruitment and lists several specific methods that might be used for recruiting patients, grouped by the basic categories of patients at the time of recruitment.

Table 14. Patient Recruitment

Keys to patient recruitment	• Recruit through a physician who is caring for the patient. • Communicate to the patient that registry participation may help to improve care for all future patients with the target condition. • Write all patient materials (brochures, consent forms) in a manner that is easily understandable by the lay public. • Keep the survey forms short and simple. • Provide incentives—non-monetary (such as functions relevant to the patient's care (reports) or community (newsletters, portals)) and in some cases, monetary (if approved by the Institutional Review Board). • Actively plan how to be inclusive of minorities or other populations of interest.

Methods of patient recruitment	• Non-institutionalized residents of the general U.S. population:
	  o Recruit via letter survey, telephone, email.
	  o Recruit during well-patient visits to outpatient clinics.
	  o Recruit via patient advocacy and support groups, health information websites, etc.
	• Outpatients attending the clinic of a physician who is participating in the registry:
	  o Recruit through the patient's physician.
	  o Recruit via brochures placed in physician's office.
	• Hospital inpatients who are hospitalized for treatment of a condition that is the subject of the registry:
	  o Recruit through the patient's physician.
	  o Recruit through hospitalists or consultant specialists.
	  o Recruit through a hospital research coordinator.
	• Residents of nursing homes and similar long-term care facilities:
	  o Establish a relationship with the nursing home and staff.

Partnerships May Facilitate Recruitment

Many agencies/organizations can assist in the recruitment of physicians and patients. These partners may have access to patients or their families and physicians who treat the condition, and they may lend credibility to the effort. These agencies/organizations include:

- Government agencies
- Physician professional associations or State medical associations
- Certifying boards (e.g., American Board of Neurological Surgeons)
- Patient advocacy groups (e.g., Muscular Dystrophy Association)
- Nonprofit foundations (e.g., Robert Wood Johnson Foundation)
- Industry (e.g., pharmaceutical companies)
- HMOs and other third-party insurance providers

Procedural Considerations Related to Recruitment

When developing a recruitment plan for a registry, consideration should be given to the procedural concerns that may be factored into potential participants' decisions. These concerns include the roles and responsibilities of each party, the need and process for obtaining institutional review board (IRB) approval, and the management of patient and provider confidentiality.

The contract between registry sites and the sponsor or coordinating center should clearly state the roles and responsibilities of the participants, the registry-coordinating center, and the sponsor. If monetary remuneration is being offered, the data entry requirements that need to be fulfilled before payments are made should be stated. It is often helpful to explain to sites the concept of fair market value. There is no specific formula (such as whether to separate start-up payments from per-patient payments), but total remuneration must reflect work effort for the specific registry. Some individual factors, ranging from location to specialty, may have a bearing on fair market value. It is also important to spell out which entity will have ownership of the data and how the data will be used.

The contract should clearly explain the registry policy regarding any necessary approvals. If review by an IRB is required, generic templates can be offered to participants to assist them in obtaining ethical and IRB approval. Because the costs of obtaining IRB approval are often substantial, it is essential that the contract with the participants clearly indicates which party is responsible for bearing this cost. If the registry developer believes that IRB or Privacy Board review or approval is not required or may be waived, then a clear rationale should be provided to the prospective participants. As discussed in Chapter 8, the research purpose of the registry, the status of the developer, whether the Common Rule applies to the particular site, and the extent to which the data are individually identifiable, largely determine applicable regulatory requirements. For example, for registries limited to certain purposes, such as quality improvement, institutions may not require IRB approval.[429]

Patient privacy and participant confidentiality should be addressed in the registry materials. Methods of ensuring patient privacy need to be clearly elucidated in all registry-related documentation. Case Report

Forms and patient logs must be designed to minimize patient identification (such as by transmitting limited data sets rather than more identifiable information, if such information is not required to meet a registry objective).

The intended management of the confidentiality of participating providers should be explained in the contract. Additional mechanisms for protecting provider confidentiality, including Certificates of Confidentiality and Patient Safety Organizations are discussed in Chapter 8. If third party or pubic reporting is an intended component of the registry, the specific data to be shared, the level of the disclosure (e.g. hospital and/or physician level) and the permitted receiving entities need to be articulated and the control mechanisms explained.

Retention

Providers

Once hospitals and physicians are recruited to participate in a registry, retaining them becomes a key to success. All of the factors identified as important for recruitment are important for retention as well. A critical factor in retention is delivery on promises made during recruitment (e.g., that the burden of participation is low). By carefully pilot testing all aspects of the registry prior to full recruitment, there is less likelihood that problems will arise that threaten the reputation of the registry. Registries with an advisory board or steering committee can use this resource to help with retention. A visible and independent advisory board adds transparency and credibility, sets appropriate expectations among its peers on what to expect from a registry (e.g., compared with a clinical trial), ensures that the burden of the registry is minimized (or at least never outweighs its value to participants), and maintains the relevancy and currency of the registry for the investigators. Ideally, advisory board members serve as ambassadors for the program. The level of credibility, engagement, practicality, and enthusiasm of the advisory board can significantly affect provider recruitment and retention. For example, an advisory board whose clinical members are not, themselves, participating in the registry will have greater difficulty addressing the concerns of participating practices that invariably arise over the course of the registry.

Throughout the duration of the registry, communication from the data-coordinating center and the advisors, as well as community building, are important for strong retention. Early and continued engagement of the site champions or principal investigators is very important. Some registries utilize periodic face-to-face meetings of principal investigators from participating sites. When this approach is not economically feasible, well-planned online meetings can serve the same purpose. Visibility of the registry at relevant national meetings can help maintain clinician awareness and sense of community, and regular demonstration of its value through presentations and publications reinforce the credibility of the registry to its participants. As the data set grows, so too does the value of the registry for all participants, and regular updates on the registry growth can be important. Finally, enhancing site value through non-financial rewards can be particularly useful in retention, and the registry should continually seek to bring value to the participants in creative and useful ways. Participation retention tools include:

- Web sites
- Newsletters
- Telephone help lines

- Instruction manuals
- Training meetings
- Site audit/retraining visits
- Customer satisfaction/opinion surveys
- Regular data reports to stakeholders
- Presentations at conferences
- Regular reports to registry participants on registry growth and publications

Patients

Retaining patients as active participants in registries with longitudinal followup is an ongoing challenge. Many factors need to be considered in developing a retention plan, including how long the patient is likely to return to the enrolling site. Patients enrolled in a primary care practice for a chronic illness can likely be followed in that practice for some time, although there should be a plan for how the registry will (or will not) address patients who transfer to unenrolled practices. Patients enrolled in a hospital at discharge, or through a specialist that does not follow the patient long-term, require different solutions. These may range from enlisting the site to reach out to patients beyond their standard interactions[430], following patients directly through a central patient management center[431], or linking to other data sources (e.g., National Death Index, claims data, etc.) to obtain key long-term outcomes data on patients who are lost to followup. Retention plans, including contingencies, should be considered during registry planning as they may require additional permissions (e.g., for direct contact) or data elements (e.g., for linkage). Maintaining ethical incentives for patient participation (ranging from newsletters to payments) are important for some registries (e.g., those that collect patient-reported outcomes data). Beyond planning for how to retain patients in a registry, it is important to track actual versus expected followup rates over time and to respond if rates are not meeting expectations. The resources available for patient retention efforts should also be clear. Followup rates can often be improved with more efforts, such as more attempts to contact the patient, but these efforts add costs and, at some level, will yield diminishing returns.

Pitfalls in Recruitment and Retention

Pitfalls abound in recruitment and retention. The most important of these pitfalls is the risk of selection bias. Targeting hospital- or academic-based physicians to the exclusion of community-based physicians is tempting because the former are often more accessible and are frequently more open to involvement in, and more experienced in, research projects. Similarly, targeting high volume practices or centers will improve efficiency of patient enrollment, but may not yield an adequately representative sample of care practices. If an advisory board or committee is used to help design the registry and aid in recruitment, there may be a tendency for advisors to recruit known colleagues or target disease experts, when a wider range of participants may be necessary to provide the appropriate data to meet the research goals. Including representatives from the range of anticipated site types on the advisory board can be helpful.

Even with an appropriate mix of physician participants in a registry, biases in patient recruitment may still occur. For example, older and more seriously ill patients may be excluded because of challenges in enrollment and followup, or poorer outcomes. From the outset, physicians involved in recruitment efforts need to be aware of the potential for bias, and they must understand the importance of adhering to well-delineated inclusion and exclusion criteria. They must also adhere to the registry's enrollment strategy, which is typically designed to reduce this bias (e.g., consecutive or randomized enrollment). In addition, overly demanding data collection requirements can affect retention. The schedule should be designed to obtain relevant data in a timely fashion without overtaxing the resources of patients and providers. It is also important to consider approaches that will distinguish patients who are lost to followup from those who have missing data for other reasons (such as a patient who missed a visit but is still in the registry).

Another major pitfall is confusing terminology. This can be a major problem when the registry is international. When designing training materials, instruction manuals, and questionnaires, it is critical that the language and terminology are clear and concise. Materials that are translated into other languages must undergo strict quality assurance measures to ensure that terms are translated properly (e.g., back translation).

International Considerations

While many general principles are similar for participant enrollment and retention in other parts of the world, there are many different customs or regulations regarding contract language, requirements for Ethics Committee or other submissions, informed consent and allowable approaches to patient retention. Registries that extend to other countries should consult national and local regulations in those countries.

Case Example 25: Building value as a means to recruit hospitals

Description:	Get With The Guidelines® is the flagship program for in-hospital quality improvement of the American Heart Association (AHA) and American Stroke Association (ASA). The program uses the experience of the AHA and ASA to ensure the care that hospitals provide for coronary artery disease, heart failure, and stroke is aligned with the latest evidence-based guidelines.
Sponsor:	American Heart Association and American Stroke Association
Year Started:	2000
Year Ended:	Ongoing
No. of Sites	3,046
No. of Patients:	2,087,667

Challenge

Recruiting hospitals for registries or quality improvement (QI) programs can be arduous. Human and financial capital is constrained. Accreditation and reimbursement programs, such as those of The Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations, or JCAHO) and Centers for Medicare & Medicaid Services (CMS), contend for the same valuable human and financial capital. As a result, in the absence of specific benefits, many hospitals defer the data collection and report utilization required for successful QI execution.

Like most registries and QI programs, the sponsor's program faced barriers to data entry. Unlike other registries, Get With The Guidelines offered no reimbursements for data entry and entered a market characterized by significant competition. The registry team wanted to motivate resources-trapped hospitals to consistently and proactively enter data and analyze improvement.

Proposed Solution

The registry team began by listening to the hosptials through in-depth interviews designed to understand the motivations and deterrents underlying behavior. Interviews were conducted with hospital decisionmakers at all levels (nurses, QI professionals, administrators/chief executive officers, and physicians).

Based on the research findings, the team developed strategies that differentiated and built value for the program. Some of the more noteworthy strategies included the following:

- Systems were designed to allow data transmission from and to Joint Commission and CMS vendors, enabling hospitals to reduce the burden of duplicate data entry while still participating in other programs.
- A new tag line, Turning Guidelines into Lifelines℠, linked the brand's value proposition to the brand name and logo. Key messages for each target audience were included in marketing communications.
- A newly designed national recognition program motivated participation and advancement and received the attention of hospital decisionmakers.
- Return-on-investment studies for the program demonstrated the value of participation.

Product innovations/enhancements created additional incentives to participate. Immediate, point-of-care flags highlighted variances from guidelines. Benchmarking filters/reports empowered decisionmakers to

benchmark performance with national averages and similar institutions. Customizable notes explaining diseases, tests, and medications can be sent to both the referring physician and the patient.

Results

By providing a mix of innovative, nonfinancial incentives, the program increased both enrollment and advancement by about one-third in 12 months. Currently, 3,046 hospitals participate in the program. The database includes 2,087,667 patient records and is considered by many to be the most robust database for coronary artery disease, heart failure, and stroke. In 2004, the program received the Innovation in Prevention Award from the Department of Health and Human Services.

Key Point

Nonfinancial incentives that meet the needs of decisionmakers can assist in site recruitment. When creating such incentives, consider both tangible and non-tangible benefits.

For More Information

http://www.americanheart.org/getwiththeguidelines

Case Example 26: Using registry tools to recruit sites

Description:	The objective of the OPTIMIZEHF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry was to improve quality of care and promote evidence-based therapies in heart failure. The registry provided a comprehensive process-of-care improvement program and gathered data that allowed hospitals to track their improvement over time.
Sponsor:	GlaxoSmithKline
Year Started:	2003
Year Ended:	2005
No. of Sites	270 hospitals
No. of Patients:	Over 50,000

Challenge

The registry was designed to help hospitals improve care for patients hospitalized with heart failure. The objective was to accelerate the adoption of evidence-based guidelines and increase the use of the guideline-recommended therapies, thereby improving both short-term and long-term clinical outcomes for heart failure patients.

Proposed Solution

To increase compliance with guidelines, the registry team promoted the implementation of a process-of-care improvement component and the use of comprehensive patient education materials. They combined these materials into a hospital toolkit, which included evidence-based practice algorithms, critical pathways, standardized orders, discharge checklists, pocket cards, and chart stickers. The toolkit also included algorithms and dosing guides for the guideline-recommended therapies and a comprehensive set of patient education materials. The team engaged the steering committee in designing the toolkit to ensure that the materials reflected both the guideline-recommended interventions and the practical aspects of hospital processes.

In addition to the toolkit, the registry offered point-of- care tools, such as referral notes and patient letters, that could be customized for each patient based on data entered into the registry. The registry also included real-time performance reports that hospitals could use to assess their improvement on a set of standardized measures based on the guidelines.

Results

The hospital toolkit was a key component of the marketing campaign for the registry. Hospitals could view the toolkit at recruitment meetings, but they did not receive their own copy until they joined the program. The toolkit gained credibility among hospitals because its creators included some of the most prominent members of the heart failure community. Hospitals also actively used the reports to track their improvement over time and identify areas for additional work. Overall, the registry recruited 270 hospitals and met its patient accrual goal 6 months ahead of schedule.

Key Point

Nonfinancial incentives, such as patient education materials, toolkits, and reports, can encourage sites to join a registry. Incentives that also add value for the site by improving their processes or providing materials that they use frequently can aid retention.

For More Information

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Gheorghiade M, She L, Abraham WT, et al. Systolic Blood Pressure at Admission, Clinical Characteristics, and Outcomes in Patients Hospitalized With Acute Heart Failure. Journal of American Medical Associates 2006;296:2217-26.

Fonarow GC, Abraham WT, Albert NM, et al. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. JAMA 2007;297:61-70.

Case Example 27: Using proactive awareness activities to recruit patients for a pregnancy exposure registry

Description:	The Ribavirin Pregnancy Registry is a component of the Ribavirin Risk Management Program. It was designed to evaluate the association between ribavirin and birth defects occurring in the offspring of female patients exposed to ribavirin during pregnancy or the 6 months prior to conception, as well as female partners of male patients exposed to ribavirin during the same time period. The registry collects prospective, observational data on pregnancies and outcomes following pregnancy exposure to ribavirin.
Sponsor:	Hoffmann-La Roche Inc.; Sandoz Pharmaceuticals Inc.; Schering-Plough Corp.; Teva Pharmaceuticals USA, Inc.; Three Rivers Pharmaceuticals, LLC; Zydus Pharmaceuticals (USA) Inc.
Year Started:	2003
Year Ended:	Ongoing
No. of Sites	N/A (population-based)
No. of Patients:	Approximately 200

Challenge

Ribavirin is used in combination with interferon alfa or pegylated interferon alfa for the treatment of hepatitis C. Chronic hepatitis C presents a serious health concern for approximately three million Americans, as the infection, if left untreated, can lead to end-stage liver disease, primary liver cancer, and death. When used as part of a combination therapy, ribavirin can significantly increase both viral clearance and liver biopsy improvement for hepatitis C patients. However, ribavirin showed teratogenic properties in all animal models tested, making pregnancy exposure a concern. There are minimal data on ribavirin exposure in human pregnancies. Thus, the U.S. Food and Drug Administration (FDA) designated ribavirin as a Pregnancy Category X product based on the animal data, and ribavirin carries product label warnings against becoming pregnant.

Despite the product warnings, pregnancies continue to occur. Health care professionals have insufficient data on the teratogenic properties of ribavirin in humans to counsel pregnant women exposed to ribavirin either during pregnancy or in the 6 months prior to conception. The registry was established to gather prospective data on ribavirin exposure in pregnancy and pregnancy outcomes to better understand the actual risk.

The registry collects data on direct exposures through the pregnant female and indirect exposures through her male sexual partner. Health care providers, pregnant patients, or pregnant patients' male sexual partners may submit data to the registry. The registry collects minimal, targeted data at each trimester and at the outcome of the pregnancy through the obstetric health care providers. For live births, the registry collects data at 6 months and 12 months after the birth by contacting the pediatric health care provider.

To gather data on these patients, the registry needed to develop proactive awareness activities to make patients and providers aware of the program and encourage enrollment without promoting ribavirin use during pregnancy.

Proposed Solution

The registry team developed a multipronged approach to recruiting patients. First, the team developed a comprehensive Web site with information for patients and providers. The Web site contains fact sheets, data forms, information on how to participate, and contact information. The site also contains a complete slide set that health care providers can use for teaching activities. While the site contains detailed information on the scientific reasons for the registry, the tone and content of the Web site are patient friendly, making it a good resource for both potential patients and providers.

Next, the team began targeting professional service groups whose members might treat patients with ribavirin exposure during pregnancy. The groups included hepatologists, gastroenterologists, obstetricians, and pediatricians. By contacting the groups' leadership and sending individualized mailings to members, the team hoped to raise awareness across a broad spectrum of providers. The team communicated with nursing groups, including publishing an article in a nursing journal targeted to gastroenterology nurses, with the goal of utilizing the nurse's role as a patient educator. As a result of these efforts, the American Gastroenterological Association placed a link for the registry Web site on its Web site, and the American Association for the Study of Liver Diseases posted an expert opinion piece written by the former registry advisory board chair on its Web site.

The registry team also raised awareness among professional groups by attending conferences. In 2005, the team presented a poster about the registry, including some information on demographics and program objectives, at the Centers for Disease Control and Prevention (CDC) National Viral Hepatitis Prevention Conference.

To raise awareness among patients, the team talked to hepatitis C patient advocacy groups. The registry gained exposure with patients when one patient group wrote an article about the registry for its newsletter and included the registry phone number on its fact sheet. This effort led to many patient-initiated enrollments, despite the lack of patient incentives. In working with patients, the registry has found that emphasizing the goal, which is to gather information to help future patients make better decisions, resonates with patients. Most patients submit data to the registry over the phone, and the rapport that the interviewers have developed with patients has helped to reduce the number of patients who are lost to followup.

In addition to targeting providers and patients directly, the team enlisted the help of public health agencies, since the registry has a strong public health purpose. Registry Web links are posted on the websites of the FDA Office of Women's Health, Veterans Affairs, and the Centers for Disease Control and Prevention (CDC). A description of the Registry is posted on ClinicalTrials.gov.

The team also reviewed the registry process to identify any potential barriers to enrollment. Under the initial rules for giving informed consent, the registry call center contacted patients and asked them if they were interested in participating. If patients agreed to participate over the phone, the call center sent a package of information through the mail, including an informed consent document, which the patients needed to sign and return before they could enroll. While many patients agreed to participate over the phone, a much smaller number actually returned the informed consent document. The team identified the process of obtaining written informed consent as a key barrier to enrollment.

After discussions with FDA, the registry team and FDA approached the study Institutional Review Board (IRB) about receiving a waiver of written informed consent because of the public health importance of the registry. The IRB agreed that oral consent over the phone would be sufficient for this study. Now, the call center can complete the enrollment process in a single step, as they can obtain oral consent over the phone and then proceed with the interview. This change improved and streamlined the enrollment

process and significantly increased the number of participants in the registry.

Throughout all of these recruitment activities, the registry team has emphasized that the purpose of the registry is to answer important safety questions for the benefit of future patients and providers. By focusing on the public health purpose of the registry, the team has been able to encourage participation from both patients and providers. The team has also found that a key element of their recruitment strategy is their detailed awareness plan, which calls for completing awareness activities monthly. Because the leadership and membership of professional groups change and new patients begin taking ribavirin, the team has found that continual awareness activities are important for keeping patients and providers aware of the registry.

Results

Through proactive awareness activities, the registry team has generated interest in the project and enrolled approximately 200 exposed pregnancies with outcome information to date. The streamlined oral consent process has proven successful in this registry, and other pregnancy registries have begun adopting it as a way to increase enrollments.

Key Point

Recruitment activities may include working with professional groups, contacting patient groups, targeting public health agencies, publications, and using a Web site to share information. Once recruitment and enrollment have begun, the registry team may need to re-evaluate the process to identify any potential barriers to enrollment, if enrollment is not proceeding as planned. If a registry has an ongoing enrollment process, a plan to continually raise awareness about the registry is an important part of the recruitment plan.

For More Information

Roberts S. Assessing Ribavirin Exposure During Pregnancy: The Ribavirin Pregnancy Registry. Gastroenterology Nursing. 2008 November/December 31 (6); 413-417.

Case Example 28: Using reimbursement as an incentive for participation

Description:	The ICD Registry™ collects detailed information on implantable cardioverter defibrillator (ICD) implantations and tracks the relationship between physician training and in-hospital patient outcomes. The registry meets the Centers for Medicare & Medicaid Services (CMS) Coverage with Evidence Development policy for data collection on ICD implantations.
Sponsor:	Currently none. Medtronic, Boston Scientific, and St. Jude provided the initial funding.
Year Started:	2006
Year Ended:	Ongoing
No. of Sites	1,460 hospitals
No. of Patients:	Over 400,000 records

Challenge

Identifying and incorporating appropriate incentives to develop and maintain provider participation in patient registries is an ongoing challenge. As this example shows, when registry participation is linked to

reimbursement, participation rates can be very high.

In March 2004, a manufacturer requested that CMS reconsider its prior coverage decision on ICDs, using the new evidence from the Sudden Cardiac Death in Heart Failure Trial (SCDHeFT). CMS agreed to this request and reviewed evidence from SCD-HeFT, as well as outcomes from other trials. CMS concluded that "the available evidence does not provide a high degree of guidance to providers to target these devices to patients who will clearly derive benefit." In other words, the evidence did not clearly support the appropriateness of the procedure for Medicare patients, who, with a median age of 70-75 years, are significantly older than the patients in the SCD-HeFT trial, where the median age was 60 years.

In addition, CMS raised questions about the relationship between the expanding physician specialties implanting ICDs, and patient outcomes, stating, "As with any invasive procedure, physicians who insert ICDs must be appropriately trained and fully competent to perform the implantation." While CMS had clear concerns, the evidence from the randomized controlled trials presented strong evidence that ICDs are effective for primary prevention of sudden cardiac death. CMS needed to make a coverage determination that would be in the best interest of its beneficiaries, but the gaps in the evidence made this difficult.

In September 2004, CMS proposed that a national registry be developed as a condition for coverage for Medicare beneficiaries receiving ICDs for primary prevention. The Heart Rhythm Society convened a new National ICD Registry Working Group, which consisted of physician associations, health insurance providers, government officials, medical device manufacturers, and members-at-large with expertise in registry development, to determine how best to develop and implement the registry. Upon defining the core characteristics of a national clinical registry, which included organizational structure, evidence based science, data quality and accuracy, and research, CMS announced in October 2005 that the National Cardiovascular Data Repository (NCDR) ICD Registry would become the sole-source data repository as of April 2006.

Now that a registry had been developed, CMS needed to ensure that over 1,400 hospitals nationwide entered information on all Medicare beneficiaries receiving ICDs.

Proposed Solution

To incentivize sites to participate, CMS linked procedure reimbursement to participation in the registry. Hospitals are required to submit data to the ICD Registry regarding an ICD implantation procedure on a Medicare beneficiary prior to receiving reimbursement from Medicare for the procedure.

Results

From the official launch date of the newly mandated ICD registry in April 2009, nearly 100 percent of sites enrolled into the registry within four months. Over 400,000 procedures have been entered into the registry to date.

Key Point

Reimbursement for participation is a major driver in getting hospitals to participate in national registries. CMS' Coverage with Evidence Development decision for ICDs provided a platform to observe this phenomenon at a national level.

For More Information

http://www.ncdr.com/webncdr/ICD/Default.aspx

Chapter 10: Data Collection and Quality Assurance

This chapter focuses on data collection procedures and quality assurance principles for patient registries. The integrated system for collecting, cleaning, storing, monitoring, reviewing, and reporting on registry data determines the utility of the data for meeting the goals of the registry. Quality assurance, on the other hand, aims to assure that the data were, in fact, collected in accordance with these procedures and that the data stored in the registry database meet the requisite standards of quality, which are generally defined based on the intended purposes. In this chapter, the term "registry coordinating activities" is used to refer to the centralized procedures performed for a registry and the term "registry coordinating center" refers to the entity or entities that performs these procedures and oversees the registry activities at the site and patient levels.

Because the range of registry purposes can be broad, a similar range of data collection procedures may be acceptable, but only certain methodologies may be suitable for particular purposes. Furthermore, certain end users of the data may require that data collection or validation be performed in accordance with their own guidelines or standards. For example, a registry that collects data electronically and intends for those data to be used by the U.S. Food and Drug Administration (FDA) should meet the systems validation requirements of that end user of the data, such as Title 21 of the Code of Federal Regulations Part 11 (21 CFR Part 11). Such requirements may have a substantial effect on the registry procedures. Similarly, registries may be subject to specific processes depending on the type of data collected, the types of authorization obtained, and the applicable governmental regulations.

Requirements for data collection and quality assurance should be defined during the registry inception and creation phases. Certain requirements may have significant cost implications, and these should be assessed on a cost-to-benefit basis in the context of the intended purposes of the registry. This chapter describes a broad range of centralized and distributed data collection and quality assurance activities that are currently in use or expected to become more commonly used in patient registries.

Data Collection

Database Requirements and Case Report Forms

Chapter 1 defined key characteristics of patient registries for evaluating patient outcomes to include collecting data elements with specific and consistent data definitions in a uniform manner for every patient. As in randomized controlled trials, the case report form (CRF) is the paradigm for this structure. A CRF is a formatted listing of data elements that can be presented in paper or electronic formats. Those data elements and data entry options in a CRF are represented in the database schema of the registry by patient-level variables. Defining the registry CRFs and corresponding database schema are the first steps in data collection for a registry. Chapter 5 describes the selection of data elements for a registry.

Two related documents should also be considered part of the database specification: the data dictionary (including data definitions and parameters) and the data validation rules, also known as queries or edit checks. The data dictionary and definitions describe both the data elements and how those data elements are interpreted. The data dictionary contains a detailed description of each variable used by the registry, including the source of the variable, coding information, if used, and normal ranges, if relevant. For example, the term "current smoker" should be defined as to whether "smoker" refers to tobacco or other

substances and whether "current" refers to active or within a recent time period. Several cardiovascular registries, such as the Get With The Guidelines® Coronary Artery Disease program,[432] define "current smoker" as someone who smoked tobacco within the last year.

Data validation rules refer to the logical checks on data entered into the database against predefined rules for either value ranges (e.g., systolic blood pressure less than 300 mmHg) or logical consistency with respect to other data fields for the same patient; these are described more fully under "Cleaning Data," below. While neither registry database structures nor database requirements are standardized, the Clinical Data Interchange Standards Consortium[433] is actively working on representative models for data interchange and portability using standardized concepts and formats. Chapter 5 further discusses these models, which are applicable to registries as well as clinical trials.

Procedures, Personnel, and Data Sources

Data collection procedures need to be carefully considered in planning the operations of a registry. Successful registries depend on a sustainable workflow model that can be integrated into the day-to-day clinical practice of active physicians, nurses, pharmacists, and patients with minimal disruption. (See Chapter 9.) Programs can benefit tremendously from preliminary input from health care workers or study coordinators who are likely to be participants.

Pilot testing. One method of gathering input from likely participants before the full launch of a registry is pilot testing. Whereas feasibility testing, which is discussed in Chapter 2, focuses on whether a registry should be implemented, pilot testing focuses on how it should be implemented. Piloting can range from testing a subset of the procedures, CRFs, or data capture systems, to a full launch of the registry in a limited subset of sites and patients.

The key to effective pilot testing is to conduct it at a point where the results of the pilot can still be used to modify the registry implementation. Through pilot testing, one can assess comprehension, acceptance, feasibility, and other factors that influence how readily the patient registry processes will fit into patient lifestyles and the normal practices of the health care provider. For example, some data sources may or may not be available for all patients. Chapter 5 discusses pilot testing in more detail.

Documentation of procedures. The data collection procedures for each registry should be clearly defined and described in a detailed manual. The term "manual" here refers to the reference information in any appropriate form, including hard copy, electronic, or via interactive Web or software-based systems. Although the detail of this manual may vary from registry to registry depending on the intended purpose, the required information generally includes protocols, policies, and procedures, the data collection instrument, and a listing of all the data elements and their full definitions. If the registry has optional fields (i.e., fields that do not have to be completed on every patient), these should be clearly specified. In addition to patient inclusion and exclusion criteria, the screening process should be specified, as should any documentation to be retained at the site level and any plans for monitoring or auditing of screening practices. If sampling is to be performed, the method or systems used should be explained, and tools should be provided to simplify this process for the sites. The manual should clearly explain how patient identification numbers are created or assigned and how duplicate records should be prevented. Any required training for data collectors should also be described.

If paper CRFs are utilized, the manual should describe specifically how the paper CRFs are used and which parts of the forms (e.g., two-part or three-part no-carbon-required forms) should be retained, copied, submitted, or archived. If electronic CRFs are utilized, clear user manuals and instructions should be available. These procedures are an important resource for all personnel involved in the registry (and for external auditors who might be asked to assure the quality of the registry).

The importance of standardizing procedures to ensure that the registry uses uniform and systematic methods for collecting data cannot be overstated. At the same time, some level of customization of data entry methods may be required or permitted to enable the participation of particular sites or subgroups of patients within some practices. As discussed in Chapter 9, if the registry provides payments to sites for participation, then the specific requirements for site payments should be clearly documented, and this information should be provided with the registry documents.

Personnel. All personnel involved in data collection should be identified, and their job descriptions and respective roles in data collection and processing should be described. Examples of such "roles" include patient, physician, data entry personnel, site coordinator, help desk, data manager, and monitor. The necessary documentation or qualification required for any role should be specified in the registry documentation. As an example, some registries require personnel documentation such as a curriculum vitae, protocol signoff, attestation of intent to follow registry procedures, or confirmation of completion of specified training.

Data sources. The sources of data for a registry may include new information collected from the patient, new or existing information reported by or derived from the clinician and the medical record, and ancillary stores of patient information, such as laboratories. Since registries for evaluating patient outcomes should employ uniform and systematic methods of data collection, all data-related procedures—including the permitted sources of data; the data elements and their definitions; and the validity, reliability, or other quality requirements for the data collected from each source—should be predetermined and defined for all collectors of data. As described under "Quality Assurance," data quality is dependent on the entire chain of data collection and processing. Therefore, the validity and quality of the registry data, as a whole, ultimately derive from the least rigorous link, not the most.

In Chapter 6, data sources are classified as primary or secondary, based on the relationship of the data to the registry purpose and protocol. Primary data sources incorporate data collected for direct purposes of the registry (i.e., primarily for the registry). Secondary data sources are comprised of data originally collected for purposes other than the registry (e.g., standard medical care, insurance claims processing). The section below incorporates and expands on these definitions.

Patient-reported data. Patient-reported data are data specifically collected from the patient for the purposes of the registry rather than interpreted through a clinician or an indirect data source (e.g., laboratory value, pharmacy records). Such data may range from basic demographic information, to validated scales of patient-reported outcomes. From an operational perspective, a wide range of issues should be considered in obtaining data directly from patients. These range from presentation (e.g., font size, language, reading level), to technologies (e.g., paper-and-pencil questionnaires, computer inputs, telephone or voice inputs, or hand-held patient diaries). Mistakes at this level can inadvertently bias patient selection, invalidate certain outcomes, or significantly affect cost. Limiting the access for patient-reporting to particular languages or technologies may limit participation. Patients with specific diagnoses

may have difficulties with specific technologies (e.g., small font size for visually impaired, paper and pencil for those with rheumatoid arthritis). Other choices, such as providing a patient-reported outcomes instrument in a format or method of delivery that differs from how it was validated (e.g., questionnaire rather than interview), may invalidate the results.

Clinician-reported data. Clinician-reported or -derived data can also be divided into primary and secondary. As an example, specific clinician rating scales (e.g., National Institutes of Health Stroke Scale)[434] may be required for the registry but not routinely captured in clinical encounters. Some variables might be collected directly by the clinician for the registry or obtained from the medical record. Data elements that must be collected directly by the clinician (e.g., because of a particular definition or need to assess a specific comorbidity that may or may not be routinely present in the medical record) should be specified. These designations are important because they determine who can collect the data for a particular registry or what changes must be made in the procedures that the clinician follows in recording a medical record for a patient in a registry. Furthermore, the types of error that arise in registries (discussed under "Quality Assurance") will differ by the degree of primary and secondary sources, as well as other factors. As an example, registries that utilize medical chart abstracters, as discussed below, may be subject to more interpretive errors.[435]

Data abstraction. Data abstraction is the process by which a data collector, other than the clinician interacting with the patient, extracts clinician-reported data. While physical exam findings, such as height and weight, or laboratory findings, such as white blood cell counts, are straightforward, abstraction usually involves varying degrees of judgment and interpretation.

Clarity of description and standardization of definitions are paramount to the assurance of data quality and to the prevention of interpretive errors when using data abstraction. Knowledgeable registry personnel should be designated as resources for the data collectors in the field, and processes should be put in place to allow the data collectors in the field continuous access to these designated registry personnel for questions on specific definitions and clinical situations. Registries that span long periods, such as those intended for surveillance, might be well served by a structure that allows for the review of definitions on a periodic basis to ensure the timeliness and completeness of data elements and definitions and to add new data elements and definitions. A new product or procedure introduced after the start of a registry is a common reason for such an update.

Abstracting data from unformatted hard copy (e.g., a hospital chart) is often an arduous and tedious process, especially if free text is involved, and it usually requires a human reader. The reader, whose qualifications may range from a trained "medical record analyst" or other health professional to an untrained research assistant, may be required to decipher illegible handwriting, translate obscure abbreviations and acronyms, and understand the clinical content to sufficiently extract the desired information. Registry personnel should develop formal chart abstraction guidelines, documentation, and coding forms for the analysts and reviewers to use. Generally, the guidelines include instructions to search for particular types of data that will go into the registry (e.g., specific diagnoses or lab results). Often the analyst will be asked to code the data, using either standardized codes from a codebook (e.g., the ICD-9 code [International Classification of Diseases, 9th Revision]) corresponding to a text diagnosis in a chart, or codes that may be unique to the registry, (e.g., a severity scale of 1 to 5). All abstraction and coding instructions must be carefully documented and incorporated into a data dictionary for the registry.

Because of the "noise" in unstructured, hard-copy documents (e.g., spurious marks or illegible writing) and the lack of precision in natural language, the clinical data abstracted by different abstracters from the same documents may differ. This is a potential source of error in a registry.

To reduce the potential for this source of error, registries should ensure proper training on the registry protocol and procedures, condition(s), data sources, data collection systems, and, most importantly, data definitions and their interpretation. While training should be provided for all registry personnel, it is particularly important for nonclinician data abstracters. Training time depends on the nature of the source (charts or CRFs), complexity of the data, and number of data items. A variety of training methods, from live meetings to online meetings to interactive multi-media recordings, have all been used with success.[436] Training often includes test abstractions using sample charts. For some purposes, it is best practice to train abstracters using standardized test charts. Such standardized tests can be further used both to obtain data on the inter-rater reliability of the case report forms, definitions, and coding instructions and to determine whether individual abstracters can perform up to a defined minimum standard for the registry. Registries that rely on medical chart abstraction should consider reporting on the performance characteristics associated with abstraction, such as inter-rater reliability.[437] Some key considerations in standardizing medical chart abstractions are:

- Standardized materials (e.g., definitions, instructions).
- Standardized training.
- Testing with standardized charts.
- Reporting of inter-rater reliability.

Electronic Medical Record. An Electronic Medical Record (EMR) is an electronic record of health-related information on an individual that can be created, gathered, managed, and consulted by authorized clinicians and staff within one health care organization. More complete than an EMR, an Electronic Health Record (EHR) is an electronic record of health-related information on an individual that conforms to nationally recognized, interoperability standards and that can be created, managed, and consulted by authorized clinicians and staff, across more than one health care organization.[438] For the purposes of this discussion, we will refer to the more limited capabilities of the EMR.

The EMR (and EHR) will play an increasingly important role as a source of clinical data for registries. The medical community is currently in a transition period in which the primary repository of a patient's medical record is changing from the traditional hard-copy chart to the EMR. The main function of the EMR is to aggregate all clinical electronic data about a patient into one database, in the same way that a hard-copy medical chart aggregates paper records from various personnel and departments responsible for the care of the patient. Depending on the extent of implementation, the EMR may include patient demographics, diagnoses, procedures, progress notes, orders, flow sheets, medications, and allergies. The primary sources of data for the EMR are the health care providers. Data may be entered into the EMR through keyboards or touch-screens in medical offices or at the bedside. In addition, the EMR system is usually interfaced to ancillary systems (see below), such as laboratory, pharmacy, radiology, and pathology. Ancillary systems, which usually have their own databases, export relevant patient data to the EMR system, which imports the data into its database.

Since EMR include the majority of clinical data available about a patient, they can be a major source of patient information for a registry. What an EMR usually does not include is registry-specific (primary source) data that are collected separately from hard-copy or electronic forms. In the next several years, suitable EMR system interfaces may be able to present data needed by registries in accordance with registry-specified requirements, either within the EMR (which then populates the registry), or in an electronic data capture system (which then populates the EMR). EMR already serve as secondary data sources in some registries, and this practice will continue to grow as EMR become more widely used. In these situations, data may be extracted from the EMR, transformed into registry format, and loaded into the registry, where they will reside in the registry database together with registry-specific data imported from other sources. In a sense, this is similar to medical chart abstraction except that it is performed electronically. There are two key differences. First, the data are "abstracted" once for all records. In this context, abstraction refers to the mapping and other decisionmaking that needs to be made to bring the EMR data into the registry database. It does not eliminate the potential for interpretive errors, as described later in this chapter, but it centralizes that process, making the rules clear and easily reviewed. Second, the data are uploaded electronically, eliminating duplicative data entry, potential errors associated with data re-entry, and the related cost with this redundant effort.

When the EMR is used as a data source for a registry, a significant problem occurs when the information needed by the registry is stored in the EMR as free text, rather than codified or structured data. Examples of structured data include ICD9 diagnoses and laboratory results. In contrast, physician progress notes, consultations, radiology reports, etc. are usually dictated and transcribed as narrative free text. While data abstraction of free text derived from an EMR can be done by a medical record analyst, with the increasing use of EMRs, automated methods of data abstraction from free text have been developed. Natural language processing (NLP) is the term given to this technology. It allows computers to process and extract information from human language. The goal of NLP is to parse free text into meaningful components based on a set of rules and a vocabulary that enable the software to recognize key words, understand grammatical constructions and resolve word ambiguities. Those components can be extracted and delivered to the registry along with structured data extracted from the EMR, and both stored as structured data in the registry database.

An increasing number of NLP software packages are available (e.g., caTIES from the National Cancer Institute[439], i2b2 – Informatics for Integrating Biology at the Bedside[440], and a number of commercial products). However, NLP is still in an early phase of development and cannot yet be used for all-purpose chart abstraction. In general, NLP software operates in specific clinical domains (e.g., radiology, pathology, etc.), whose vocabularies have been included in the NLP software's database. Nevertheless, NLP has been used successfully to extract diagnoses and drug names from free text in various clinical settings.

With the passage and implementation of the American Recovery and Reinvestment Act of 2009 (ARRA) health information technology provisions, it is anticipated that EMR/EHR use will grow significantly. Currently, only a minority of U.S. patients have their data stored in systems that are capable of retrieval at the level of a data element. Furthermore, only a small number of these systems currently store data in structured formats with standardized data definitions for those data elements that are common across different vendors. While a significant amount of attention is currently focused on both interchange formats between clinical and research systems (e.g., from Health Level Seven [HL-7][441] to Clinical Data

Interchange Standards Consortium[442] models) and the problems of data syntax and semantics (See Chapter 5.), the adoption of common database structures and open interoperability standards will be critical for future interchange between EHRs and registries. This topic is discussed in depth in Chapter 11.

Other data sources. Some of the clinical data used to populate registries may be derived from repositories other than EMRs. Examples of other data sources include billing systems, laboratory databases, and other registries. Chapter 6 discusses the potential uses of other data sources in more detail.

Data Entry Systems

Once the primary and any secondary data sources for a registry have been identified, the registry team can determine how data will be entered into the registry database. Many techniques and technologies exist for entering or moving data into the registry database, including paper CRFs, direct data entry, facsimile or scanning systems, interactive voice response systems (IVRS), and electronic CRFs. There are also different models for how quickly those data reach a central repository for cleaning, reviewing, monitoring, or reporting. Each approach has advantages and limitations, and each registry must balance flexibility (the number of options available) with data availability (when the central repository is populated), data validity (whether all methods are equally able to produce clean data), and cost. Appropriate decisions depend on many factors, including the number of data elements, number of sites, location (local preferences that vary by country, language differences, and availability of different technologies), registry duration, followup frequency, and available resources.

Paper CRFs. With paper CRFs, the clinician enters clinical data on the paper form at the time of the clinical encounter or other data collectors abstract the data from medical records after the clinical encounter. CRFs may include a wide variety of clinical data on each patient, gathered from different sources (e.g., medical chart, laboratory, pharmacy) and from multiple patient encounters. Before the data on formatted paper forms are entered into a computer, the forms should be reviewed for completeness, accuracy, and validity. Paper CRFs can be entered into the database by either direct data entry or computerized data entry via scanning systems.

With direct data entry, a computer keyboard is used to enter data into a database. Key entry has a variable error rate depending on personnel, so an assessment of error rate is usually desirable, particularly when a high volume of data entry is performed. Double data entry is a method of increasing the accuracy of manually entered data by quantifying error rates as discrepancies between two different data entry personnel, and improving data accuracy by having up to two individuals enter the data and a third person review and manage discrepancies. With upfront data validation checks on direct data entry, the likelihood of data entry errors significantly decreases. Therefore, the choice of single versus double data entry should be driven by the requirements of the registry for a particular error rate, and the ability of each method to achieve that rate in key measures in the particular circumstance. Double data entry, while a standard of practice for registrational trials, may add significant cost. Its use should be guided by the need to reduce an error rate in key measures and the likelihood of accomplishing that by double data entry as opposed to other approaches. In some situations, assessing the data entry error rates by re-entering a sample of the data is sufficient for reporting purposes.

With hard-copy structured forms, entering data using a scanner and special software to extract the data from the scanned image is possible. If data are recorded on a form as marks in checkboxes, the scanning

software enables the user to map the location of each checkbox to the value of a variable represented by the text item associated with the checkbox, and to determine whether the box is marked. The presence of a mark in a box is converted by the software to its corresponding value, which can then be transmitted to a database for storage. If the form contains hand-printed or typed text or numbers, optical character recognition (OCR) software is often effective in extracting the printed data from the scanned image. However, the print font must be of high quality to avoid translation errors, and spurious marks on the page can cause errors. Error checking is based on automated parameters specified by the operator of the system for exception handling. The comments on assessing error rates in the section above are applicable for scanning systems as well.

Electronic CRFs (eCRFs). An eCRF is defined as an auditable electronic form designed to record information required by the clinical trial protocol to be reported to the sponsor on each trial subject.[443] An eCRF allows clinician-reported data to be entered directly into the electronic system by the data collector (the clinician or other data collector). Site personnel in many registries still commonly complete an intermediate hard-copy worksheet representing the CRF, and subsequently enter the data into the eCRF. While this approach increases work effort and error rates, it is not yet practical for all electronic data entry to be performed at the bedside, during the clinical encounter, or in the midst of a busy clinical day.

An eCRF may originate on local systems (including those on an individual computer, a local area network server, or a handheld device) or directly from a central database server via an Internet-based connection or a private network. For registries that exist beyond a single site, the data from the local system must subsequently communicate with a central data system. An eCRF may be presented visually (e.g., computer screen) or aurally (e.g., telephonic data entry, such as interactive voice response systems). Specific circumstances will favor different presentations. For example, in one clozapine patient registry that is otherwise similar to Case Example 21, both pharmacists and physicians can obtain and enter data via a telephone-based interactive voice response system as well as a Web-based system.[444] The option is successful in this scenario because telephone access is ubiquitous in pharmacies, and the eCRF is very brief.

A common method of electronic data entry is to use Web-based data entry forms. Such forms may be used by patients, providers, and interviewers to enter data into a local repository. The forms reside on servers, which may be located at the site of the registry or co-located anywhere on the Internet. To access a data entry form, a user on a remote computer with an Internet connection opens a browser window and enters the address of the Web server. Typically, a login screen is displayed and the user enters a user identification and password, provided by personnel responsible for the Web site or repository. Once the server authenticates the user, the data entry form is displayed, and the user can begin entering data. As described in "Cleaning Data," many electronic systems can perform data validation checks or edits at the time of data entry. When data entry is complete, the user submits the form, which is sent over the Internet to the Web server.

Hand-held devices, such as personal digital assistants (PDAs) and cell phones, may also be used with Web-based or other forms to submit data to a server. Mobility has recently become an important attribute for clinical data collection. Software has been developed that enables wireless PDAs and cell phones to collect data and transmit them over the Internet to database servers in fixed locations. As wireless

technology continues to evolve and data transmission rates increase, these will become more essential data entry devices for patients and clinicians.

Advantages and Disadvantages of Data Collection Technologies

When the medical record or ancillary data are in electronic format, they may be abstracted to the CRF by a data collector or, in some cases, uploaded electronically to the registry database. The ease of extracting data from electronic systems for use in a registry depends on the design of the interfaces of ancillary and registry systems, and the ability of the EMR or ancillary system software to make accessible the requested data. However, as system vendors increasingly adopt open standards for interoperability, transferring data from one system to another will likely become easier. Many organizations are actively working toward improved standards including Health Level Seven (HL7)[445], the National eHealth Collaborative[446] the National Institute of Standards and Technology (NIST)[447] and others. Chapter 11 describes standards and certifications specific to electronic health record systems.

Electronic interfaces are necessary to move data from one computer to another. If clinical data are entered into a local repository from an eCRF form or entered into an EMR the data must be extracted from the source data set in the local repository, transformed into the format required by the registry, and loaded into the registry database for permanent storage. This is called an "extract, transform, and load" (ETL) process. Unless the local repository is designed to be consistent with the registry database in terms of the names of variables and their values, data mapping and transformation can be a complex task. In some cases, manual transfer of the data may be more efficient and less time consuming than the effort to develop an electronic interface. Emerging open standards can enable data to be transferred from an EHR directly into the registry. This topic is discussed in more detail in Chapter 11.

If an interface between a local electronic system and registry system is developed, it is still necessary to communicate to the ancillary system the criteria for retrieval and transmission of a patient record. Typically, the ancillary data are maintained in a relational database, and the system needs to run an SQL (Structured Query Language) query against the database to retrieve the specified information. An SQL query may specify individual patients by an identifier (e.g., a medical record number) or by values or ranges of specific variables (e.g., all patients with hemoglobin A1C over 8 mg/dl). The results of the query are usually stored as a file (e.g., XML, CSV, CDISC ODM) that can be transformed and transferred to the registry system across the interface. A variety of interface protocols may be used to transfer the data.

Because data definitions and formats are not yet nationally standardized, transfer of data from an EMR or ancillary system to a registry database is prone to error. Careful evaluation of the transfer specifications for interpretive or mapping errors is a critical step that should be verified by the registry-coordinating center. Furthermore, a series of test transfers and validation procedures should be performed and documented. Finally, error checking must be part of the transfer process because new formats or other errors not in the test databases may be introduced during actual practice, and these need to be identified and isolated from the registry itself. Even though each piece of data may be accurately transferred, the data may have different representations on the different systems (e.g., value discrepancies such as the meaning of "0" vs. "1," fixed vs. floating point numbers, date format, integer length, and missing values). In summary, any system used to extract EMR records into registry databases should be validated and

should include an interval sampling of transfers to ensure that uploading of this information is consistent over time.

The ancillary system must also notify the registry when an error correction occurs in a record already transferred to the registry. Registry software must be able to receive that notification, flag the erroneous value as invalid, and insert the new, corrected value into its database. Finally, it is important to recognize that the use of an electronic-to-electronic interchange requires not only testing but also validation of the integrity and quality of the data transferred. Few ancillary systems or electronic medical records systems are currently validated to a defined standard. For registries that intend to report data to the FDA or to other sponsors or data recipients with similar requirements, including electronic signatures, audit trails, and rigorous system validation, the ways in which the registry interacts with these other systems must be carefully considered.

Cleaning Data

Data cleaning refers to the correction or amelioration of data problems, including missing values, incorrect or out-of-range values, or responses that are logically inconsistent with other responses in the database. While all registries strive for "clean data," in reality, this is a relative term. How and to what level the data will be cleaned should be addressed upfront in a data management manual that identifies the data elements that are intended to be cleaned, describes the data validation rules or logical checks for out-of-range values, and explains how missing values and values that are logically inconsistent will be handled.

Data management manual. Data managers should develop formal data review guidelines for the reviewers and data entry personnel to use. The guidelines should include information on how to handle: missing data; invalid entries (e.g., multiple selections in a single-choice field, alphabetic data in a numeric field); erroneous entries (e.g., patients of the wrong gender answering gender-based questions); and inconsistent data (e.g., an answer to one question contradicting the answer to another one). The guidelines should also include procedures to attempt to remediate these data problems. For example, with a data error on an interview form, it may be necessary to query the interviewer or the patient, or to refer to other data sources that may be able to resolve the problem. Documentation of any data review activity and remediation efforts, including dates, times, and results of the query, should be maintained.

Automated data cleaning. Ideally, automated data checks are preprogrammed into the database for presentation at the time of data entry. These data checks are particularly useful for cleaning data at the site level while the patient or medical record is readily accessible. Even relatively simple edit checks, such as range values for laboratories, can have a significant effect on improving the quality of data. Many systems allow for the implementation of more complex data edit checks, and these checks can substantially reduce the amount of subsequent manual data cleaning. A variation of this method is to use data cleaning rules to deactivate certain data fields so that erroneous entries cannot even be made. A combination of these approaches can also be used. For paper-based entry methods, automated data checks are not available at the time the paper CRF is being completed, but can be incorporated when the data are later entered into the database.

Manual data cleaning. Data managers perform manual data checks or queries to review data for unexpected discrepancies. This is the standard approach to cleaning data that are not entered into the database at the site (e.g., for paper CRFs entered via data entry or scanning). By carefully reviewing the

data using both data extracts analyzed by algorithms and hand review, data managers identify discrepancies and generate "queries" to send to the sites to resolve. Even eCRF-based data entry with data validation rules may not be fully adequate to ensure data cleaning for certain purposes. Anticipating all potential data discrepancies at the time that the data management manual and edit checks are developed is very difficult. Therefore, even with the use of automated data validation parameters, some manual cleaning is often still performed.

Query reports. The registry-coordinating center should generate, on a periodic basis, query reports that relate to the quality of the data received, based on the data management manual and, for some purposes, additional concurrent review by a data manager. The content of these reports will differ depending on what type of data cleaning is required for the registry purpose and how much automated data cleaning has already been performed. Query reports may include missing data, "out-of-range" data, or data that appear to be inconsistent (e.g., positive pregnancy test for a male patient). They may also identify abnormal trends in data, such as sudden increases or decreases in laboratory tests compared to patient historical averages or clinically established normal ranges. Qualified registry personnel should be responsible for reviewing the abnormal trends with designated site personnel. The most effective approach is for sites to provide one contact representative for purposes of queries or concerns by registry personnel. Depending on the availability of the records and resources at the site to review and respond to queries, resolving all queries can sometimes be a challenge. Creating systematic approaches to maximizing site responsiveness is recommended.

Data tracking. For most registry purposes, tracking of data received (paper CRFs), data entered, data cleaned, and other parameters are important components of active registry management. By comparing indicators, such as expected to observed rates of patient enrollment, CRF completion, and query rates, the registry-coordinating center can identify problems and potentially take corrective action–either at individual sites or across the registry as a whole.

Coding data. As further described in Chapter 5, the use of standardized coding dictionaries is an increasingly important tool in the ability to aggregate registry data with other databases. As the health information community adopts standards, registries should routinely apply them, unless there are specific reasons not to use such standard codes. While such codes should be implemented in the data dictionaries during registry planning, including all codes in the interface is not always possible. Some free text may be entered as a result. When free text data are entered into a registry, recoding these data using standardized dictionaries (e.g., MedDRA, WHODRUG, SNOMED®) may be worthwhile. There is cost associated with recoding, and in general, it should be limited to data elements that will be used in analysis or that need to be combined or reconciled with other datasets, such as when a common safety database is maintained across multiple registries and studies.

Storing and securing data. When data on a form are entered into a computer for inclusion in a registry, the form itself, as well as a log of the data entered, should be maintained for the regulatory archival period. Data errors may be discovered long after the data have been stored in the registry. The error may have been made by the patient or interviewer on the original form or during the data entry process. Examination of the original form and the data entry log should reveal the source of the error. If the error is on the form, correcting it may require re-interviewing the patient. If the error occurred during data entry, the corrected data should be entered and the registry updated. By then, the erroneous registry data

may have been used to generate reports or create cohorts for population studies. Therefore, instead of simply replacing erroneous data with corrected data, the registry system should have the ability to flag data as erroneous without deleting them, and to insert the corrected data for subsequent use.

Once data are entered into the registry, the registry must be backed up on a regular basis. There are two basic types of backup, and both types should be considered for use as best practice by the registry-coordinating center. The first type is real-time disk backup, which is done by the disk storage hardware used by the registry server. The second is a regular (e.g., daily) backup of the registry to removable media (e.g., tape, CD-ROM, DVD). In the first case, as data are stored on disk in the registry server, they are automatically replicated to two or more physical hard drives. In the simplest example, called "mirroring," registry data are stored on a primary disk and an exact replica is stored on the mirrored disk. If either disk fails, data continue to be stored on the mirrored disk until the failed disk is replaced. This failure can be completely transparent to the user, who may continue entering and retrieving data from the registry database during the failure. More complex disk backup configurations exist, in which arrays of disks are used to provide protection from single disk failures.

The second type of periodic backup is needed for disaster recovery. Ideally, a daily backup copy of the registry database stored on removable media should be maintained off site. In case of failure of the registry server or disaster that closes the data center, the backup copy can be brought to a functioning server and the registry database restored, with the only potential loss of data being for the interval between the regularly scheduled backups. The lost data can usually be reloaded from local data repositories or re-entered from hard copy. Other advanced high availability database solutions and disaster recovery techniques may support a “standby” database that can be located at an alternate remote data center. In case of a failure at the primary data center, the standby database can be utilized, minimizing downtime and preventing data loss.

Managing Change

Like all other registry processes, the extent of change management will depend on the types of data being collected, the source(s) of the data, and the overall timeframe of the registry. There are two major drivers behind the need for change during the conduct of a registry: internal-driven change to refine or improve the registry or the quality of data collected and external-driven change that comes as a result of changes in the environment in which the registry is being conducted.

Internal-driven change is generally focused on changes to data elements or data validation parameters that arise from site feedback, queries, and query trends that may point to a question, definition, or CRF field that was poorly designed or missing. If this is the case, the registry can use the information coming back from sites or data managers to add, delete, or modify the database requirements, CRFs, definitions, or data management manual as required. At times, more substantive changes such as the addition of new forms or changes to the registry workflow may be desirable to examine new conditions or outcomes. External-driven change generally arises in multiyear registries, as new information about the disease and/or product under study becomes available, or as new therapies or products are introduced into clinical practice. Change and turnover in registry personnel is another type of change, and one that can be highly disruptive if procedures are not standardized and documented.

A more extensive form of change may occur when a registry either significantly changes its case report forms or changes the underlying database. Long-standing registries address this issue from time to time

as information regarding the condition or procedure evolves and data collection forms and definitions require updating. One approach to managing the change is to lock the prior database and begin anew. However, more often, there is a desire to make prior datasets available for review by the sites or inclusion in reports. This requires data migration.

Data migration involves moving data from one data source to another with a modified or different structure. The process involves extracting data from the previous data source and loading that data into the current version of the registry. If this process is performed manually, which can be done for small amounts of data, then the considerations will be similar to those listed for manual data entry or for data abstraction, if there are more substantial differences between the two systems. For larger amounts of data, migration is normally performed electronically.

A detailed mapping document should be created for the data migration, describing how each data element and value in the source system maps to an associated data element and value in the destination system. General assumptions, such as how to treat inconsistent data, need to be documented at the outset of the data migration project and maintained as new assumptions are introduced based on any issues that are discovered during the migration process. The data being moved to the destination system should be checked to make sure that it complies with the receiving system's data dictionary and data validation parameters. Once migrated, the accuracy of the migration should be confirmed through a quality control process.

Proper management of change is crucial to the maintenance of the registry. A consistent approach to change management, including decisionmaking, documentation, data mapping, and validation, is an important aspect of maintaining the quality of the registry and the validity of the data. While the specific change management processes might depend on the type and nature of the registry, change management in registries that are designed to evaluate patient outcomes requires, at the very least, the following structures and processes:

Detailed manual of procedures: As described earlier, a detailed manual that is updated on a regular basis—containing all the registry policies, procedures, and protocols, as well as a complete data dictionary listing all the data elements and their definitions—is vital for the functioning of a registry. The manual is also a crucial component for managing and documenting change management in a registry.

Governing body: As described in Chapter 2, registries require oversight and advisory bodies for a number of purposes. One of the most important is to manage change on a regular basis. Keeping the registry manual and data definitions up to date is one of the primary responsibilities of this governing body. Large prospective registries, such as the National Surgical Quality Improvement Program, have found it necessary to delegate the updating of data elements and definitions to a special Definitions Committee.

Infrastructure for ongoing training: As mentioned above, change in personnel is a common issue for registries. Specific processes and an infrastructure for training should be available at all times to account for any unanticipated changes and turnover of registry personnel or providers who regularly enter data into the registry (See Case Example 29).

Method to communicate change: Since registries frequently undergo change, there should be a standard approach and timeline for communicating to sites when changes will take place.

In addition to instituting these structures, registries should also plan for change from a budget perspective (Chapter 2) and from an analysis perspective (Chapter 13).

Using Data for Care Delivery, Coordination and Quality Improvement

As registries increasingly collect data in electronic format closer to the time that care is delivered, there are significant opportunities to utilize registry functionalities to improve care delivery at the patient and population levels. These functionalities (Table 15) include generating outputs that promote care delivery and coordination at the individual patient level (e.g., decision support, patient reports, reminders, notifications, lists for proactive care, educational content, etc.), and providing tools which assist with population management, quality improvement and quality reporting (e.g., risk adjustment, population views, benchmarks, quality report transmissions). A number of registries are designed primarily for this purpose (see Case Example 30). Several large, national registries[448,449,450,451] have shown large changes in performance during the course of hospital or practice participation in the registry. For example, in one head to head study that used hospital data from Hospital Compare, an online database created by the Centers for Medicare & Medicaid Services (CMS), patients enrolled in the American Heart Association's Get with the Guidelines® Coronary Artery Disease (CAD) registry, which includes evidence based reminders and real-time performance measurement reports (223), fared significantly better in measures of guidelines compliance than 3407 non-Get With The Guidelines-CAD hospitals.[452]

Table 15: Registry Functionalities

Inputs: Obtaining data	• **Identify/enroll representative patients** (e.g. sampling) • **Collect data from multiple sources and settings** (providers, patients, labs, pharmacies) at key points • **Use uniform data elements and definitions** (risk factors, treatments and outcomes) • **Check and correct data** (validity, coding, etc.) • **Link data from different sources at patient level** (manage patient identifiers) • **Maintain security and privacy** (e.g. access control, audit trail)
Outputs: Care Delivery and Coordination	• **Provide real-time feedback with decision support** (evidence/guidelines) • **Generate patient level reports and reminders** (longitudinal reports, care gaps, summary lists/plans, health status) • **Send relevant notifications to providers and patients** (care gaps, prevention support, self management) • **Share information** with patients and other providers • **List patients/subgroups** for proactive care • **Link** to relevant patient education
Outputs: Population Measurement and QI	• **Provide population level reports** o Real-time/rapid cycle

- Risk adjusted
- Include standardized measures
- Include benchmarks
- Enable different reports for different levels of users

- **Enable ad-hoc reports** for exploration
- **Provide utilities to manage** populations or subgroups
- **Generate dashboards** that facilitate action
- **Facilitate 3rd party quality reporting** (transmission)

Special Case: Performance-Linked Access System (PLAS)

A performance-linked access system (PLAS), also known as a restricted access or limited distribution system, is another application of a registry to serve more than an observational goal. Unlike a disease and exposure registry, a PLAS is part of a detailed risk minimization action plan that sponsors develop as a commitment to enhance the risk-benefit balance of a product when approved for the market. The purpose of a PLAS is to mitigate a certain known drug-associated risk by ensuring that product access is linked to a specific performance measure. Examples include systems that monitor laboratory values, such as white blood cell counts during clozapine administration to prevent severe leukopenia or routine pregnancy testing during thalidomide administration to prevent in utero exposure to this known teratogenic compound. Additional information on PLAS can be found in Guidance for Industry: Development and Use of Risk Minimization Action Plans.[453] (See Case Example 31.)

Quality Assurance

Critical factors in determining the utility of a registry for decisionmaking are understanding the quality of the procedures used to obtain the data and the quality of the data stored in the database. As patient registries that meet sufficient quality criteria (see Chapters 1 and 14) are increasingly being seen as important means to generate evidence regarding effectiveness, safety, and quality of care, the quality of data within the registry must be understood to a sufficient level in order to evaluate its suitability for use in decisionmaking. Registry planners should consider how to assure quality to a sufficient level for the intended purposes (as described below) and should also consider how to develop appropriate quality assurance plans for their registries. Those conducting the registry should assess and report on those quality assurance activities. Methods of quality assurance will vary depending on the intended purpose of the registry. A registry intended to serve as key evidence for decisionmaking[454] (e.g., coverage determinations, product safety evaluations, or performance-based payment) will require higher levels of quality assurance than a registry describing the natural history of a disease. Quality assurance activities generally fall under three main categories: (1) quality assurance of data, (2) quality assurance of registry procedures, and (3) quality assurance of computerized systems. Since many registries are large, the level of quality assurance that can be obtained may be limited by budgetary constraints. To balance the need for sufficient quality assurance with reasonable resource expenditure for a particular purpose, a risk-based approach to quality assurance is highly recommended. A risk-based approach focuses on the most important sources of error or procedural lapses from the perspective of the registry's purpose. Such sources of error should be defined during inception and design phases. As described below, registries with different purposes may be at risk for different sources of error and focus on different practices and levels of assessment. Standardization of methods for particular purposes (e.g. for national performance

measurement) will likely become more common in the future if results between registries are to be combined or compared.

Assurance of Data Quality

Structures, processes, policies, and procedures need to be put in place to ascertain the quality of the data in the registry and to ensure against several types of errors, including:

- *Errors in interpretation or coding:* An example of this type of error would be two abstracters looking for the same data element in a patient's medical record but extracting different data from the same chart. Variations in coding of specific conditions or procedures also fall under the category of interpretive errors. Avoidance or detection of interpretive error includes adequate training on definitions, testing against standard charts, testing and reporting on inter-rater reliability, and re-abstraction.

- *Errors in data entry, transfer, or transformation accuracy:* These occur when data are entered into the registry inaccurately—for example, a laboratory value of 2.0 is entered as 20. Avoidance or detection of accuracy errors can be achieved through upfront data quality checks (such as ranges and data validation checks), reentering samples of data to assess for accuracy, and rigorous attention to data cleaning.

- *Errors of intention:* Examples of intentional distortion of data (often referred to as "gaming") are inflated reporting of preoperative patient risk in registries that compare risk-adjusted outcomes of surgery or selecting only cases with good outcomes to report ("cherry-picking"). Avoidance or detection of intentional error can be challenging. Some approaches include checking for consistency of data between sites, assessing screening log information against other sources (e.g., billing data), or performing onsite audits (including monitoring source records) either at random or "for cause."

Steps for assuring data quality include:

- *Training:* Educate data collectors/abstracters in a structured manner.

- *Data completeness:* When possible, provide sites with immediate feedback on issues such as missing or out-of-range values and logical inconsistencies.

- *Data consistency:* Compare across sites and over time.

- *Onsite audits for a sample of sites*: Review screening logs and procedures and/or samples of data.

- *For-audits cause*: Use both predetermined and data informed methods to identify potential sites at higher suspicion for accuracy or intentional errors, such as discrepancies between enrollment and screening logs; narrow data ranges; overly high or low enrollment, etc.

To further minimize or identify these errors and to ensure the overall quality of the data, the following should be considered.

A designated individual accountable for data quality at each site. Sites submitting data to a registry should have at least one person who is accountable for the quality of these data, irrespective of whether the person is collecting the data as well. The site coordinator should be fully knowledgeable of all protocols, policies, procedures, and definitions in a registry. The site coordinator should ensure that all site personnel involved in the registry are knowledgeable and that all data transmitted to registry coordinating centers are valid and accurate.

Assessment of training and maintenance of competency of personnel. Thorough training and documentation of maintenance of competency, for both site and registry personnel, are imperative to the quality of the registry. A detailed and comprehensive operations manual, as described earlier, is crucial for the proper training of all personnel involved in the registry. Routine cognitive testing (surveys) of health care provider knowledge of patient registry requirements and appropriate product use should be performed to monitor maintenance of the knowledge base and compliance with patient registry requirements. Retraining programs should be initiated when survey results provide evidence of lack of knowledge maintenance. All registry-training programs should provide means by which the knowledge of the data collectors about their registries and their competence in data collection can be assessed on a regular basis, particularly when changes in procedures or definitions are implemented.

Data quality audits. As described above, the level to which registry data will be cleaned is influenced by the objectives of the registry, the type of data being collected (e.g., clinical data vs. economic data), the sources of the data (e.g., primary vs. secondary), and the timeframe of the registry (e.g., 3-month followup vs. 10-year followup). These registry characteristics often affect the types and number of data queries that are generated, both electronically and manually. In addition to identifying missing values, incorrect or out-of-range values, or responses that are logically inconsistent with other responses in the database, specifically trained registry personnel can review the data queries to identify possible error trends and to determine whether additional site training is required. For example, such personnel may identify a specific patient outcome question or eCRF field that is generating a larger than average proportion of queries, either from one site or across all registry sites. Using this information, the registry personnel can conduct targeted followup with the sites to retrain them on the correct interpretation of the eCRF field in question, with the goal of reducing the future query rate on that particular question or field. These types of "training tips" can also be addressed in a registry newsletter as a way to maintain frequent, but unobtrusive, communication with the registry sites.

Should the registry purpose require a more stringent verification of the data being entered into the database by registry participants, registry planners may decide to conduct audits of the registry sites. Like queries discussed above, the audit plan for a specific registry will be influenced by the purpose of the registry, the type of data being collected, the source of the data, and the overall timeframe of the registry. In addition, registry developers must find the appropriate balance between the extensiveness of an audit and the impact on overall registry costs. Based on the objectives of the registry, a registry developer can define specific data fields (e.g., key effectiveness variables or adverse event data) on which the audit can be focused.

The term “audit” may describe examination or verification, may take place on site (sometimes called monitoring) or off site, and may be extensive or very limited. The audit can be conducted on a random sample of participating sites (e.g., 5-20 percent of registry sites); "for cause" (meaning only when there is

an indication of a problem, such as one site being an outlier compared with most others); on a random sample of patients; or using sampling techniques based on geography, practice setting (academic center vs. community hospital), patient enrollment rate, or query rate ("risk based" audit strategy). The approach to auditing the quality of the data should reflect the most significant sources of error with respect to the purpose of the registry. For example, registries used for performance measurement may have a higher risk of exclusion of higher risk patients ('cherry-picking') and the focus of an audit might be on external sources of data to verify screening log information (e.g., billing data) in addition to data accuracy (see Case Example 32). Finally, the timeframe of the registry may help determine the audit plan. A registry with a short followup period (e.g., 3 months) may require only one round of audits at the end of the study, prior to database lock and data analysis. For example, in the OPTIMIZE-HF registry (see Case Example 26), a data quality audit was performed, based on predetermined criteria, on a 5% random sample of the first 10,000 patient records verified against source documents.[455] For registries with multiyear followup, registry personnel may conduct site audits every 1 or 2 years for the duration of the registry. In addition to the site characteristics mentioned above, sites that have undergone significant staffing changes during a multiyear registry should be considered prime audit targets to help confirm adequate training of new personnel and to quickly address possible inter-rater variability. To minimize any impact on the observational nature of the registry, the audit plan should be documented in the registry manual.

Registries that are designed for the evaluation of patient outcomes and the generation of scientific information, and that utilize medical chart abstracters, should assess inter-rater reliability in data collection with sufficient scientific rigor for their intended purpose(s). For example, in one registry that uses abstractions extensively, a detailed system of assessing inter-rater reliability has been devised and published; in addition to requiring that abstracters achieve a certain level of proficiency, a proportion of charts are scheduled for re-abstraction on the basis of predefined criteria. Statistical measures of reliability from such re-abstractions are maintained and reported (e.g., kappa statistic).[456]

Subsequent to audits (onsite or remote), communication of findings with site personnel should be conducted in a face-to-face manner along with followup written communication of findings and opportunities for improvement. As appropriate to meet registry objectives, the sponsor may request corrective actions from the site. Site compliance may also be enhanced with routine communication of data generated from the patient registry system to the site for reconciliation.

Registry Procedures and Systems

External audits of registry procedures. If registry developers determine that external audits are necessary to assure the level of quality for the specific purpose(s) of the registry, they should be conducted in accordance with pre-established criteria. Pre-established criteria could include monitoring of sites with high patient enrollment , prior audit history with findings that require attention, or monitoring could be based on level of site experience, rate of serious adverse event reporting, or identified problems. The registry-coordinating center may perform monitoring of a sample of sites, which could be focused on one or several areas. This approach could range from review of procedures and interviewing site personnel, to checking screening logs, to monitoring individual case records.

The importance of having a complete and detailed registry manual that describes policies, structures, and procedures cannot be overemphasized in the context of quality assurance of registry procedures. Such a

manual serves both as a basis for conducting the audits and as a means of documenting changes emanating from these audits. As was stated in relation to data quality audits, feedback of the findings of registry procedure audits should be communicated to all stakeholders and documented in the registry manual.

Assurance of system integrity and security. All aspects of data management processes should fall under a rigorous life-cycle approach to system development and quality management. Each process is clearly defined and documented. The concepts described below are consistent across many software industry standards and health care industry standards (e.g., 21 CFR Part 11, legal security standards), although some specifics may vary. The processes and procedures described should be regularly audited by an internal quality assurance function at the registry-coordinating center. When third parties other than the registry-coordinating center perform activities that interact with the registry systems and data, they are typically assessed for risk and are subject to regular audits by the registry-coordinating center.

System development and validation. All software systems used for patient registries should follow the standard principles of software development, including following one of the standard software development life cycle (SDLC) models that are well described in the software industry.

In parallel, quality assurance of system development utilizes approved specifications to create a validation plan for each project. Test cases are created by trained personnel and systematically executed, with results recorded and reviewed. Depending on regulatory requirements, a final validation report is often written and approved. Unresolved product and process issues are maintained and tracked in an issue tracking or CAPA (Corrective Action / Preventive Action) system.

Processes for development and validation should be similarly documented and periodically audited. The information from these audits is captured, summarized, and reviewed with the applicable group, with the aim of ongoing process improvement and quality improvement.

Security

All registries maintain health information, and, therefore, security is an important issue. The HIPAA (Health Insurance Portability and Accountability Act of 1996) Security Rule lists the standards for security for electronic protected health information to be implemented by health plans, health care clearinghouses, and certain health care providers.[457] Although these standards are specific to electronic protected health information, the principles themselves are more broadly applicable. Security is achieved not simply by technology but by clear processes and procedures. Overall responsibility for security is typically assigned. Security procedures are well documented and posted. The documentation is also used to train staff. Note, some registries may also maintain personal information, such as information needed to contact patients to gather or remind them to submit patient-reported outcome information. The federal government as well as most states and territories of the U.S. have enacted legislation regarding the safekeeping of personal information and requirements for reporting notification of certain security breaches involving personal information. Specific requirements vary state by state.

System security plan. A system security plan consists of documented policies and standard operating procedures defining the rules of systems, including administrative procedures, physical safeguards, technical security services, technical security mechanisms, electronic signatures, and audit trails, as

applicable. The rules delineate roles and responsibilities. Included in the rules are the policies specifying individual accountability for actions, access rights based on the principle of least privilege, and the need for separation of duties. These principles and the accompanying security practices provide the foundation for the confidentiality and integrity of registry data. The rules also detail the consequences associated with noncompliance.

Security assessment. Clinical data maintained in a registry can be assessed for the appropriate level of security. Standard criteria exist for such assessments and are based on the type of data being collected. Part of the validation process is a security assessment of the systems and operating procedures. One of the goals of such an assessment is effective risk management, based on determining possible threats to the system or data and identifying potential vulnerabilities.

Education and training. All staff members of the registry-coordinating center should be provided with periodic training on aspects of the overall systems, security requirements, and any special requirements of specific patient registries. Individuals should receive training relating to their specific job responsibilities and document that appropriate training has been received.

Access rights. Access to systems and data should be based on the principles of least privilege and separation of duties. No individual should be assigned access privileges that exceed job requirements, and no individual should be in a role that includes access rights that would allow circumvention of controls or the repudiation of actions within the system. In all cases, access should be limited to authorized individuals.

Access controls. Access controls provide the basis for authentication and logical access to critical systems and data. Since the authenticity, integrity, and auditability of data stored in electronic systems depend on accurate individual authentication, management of electronic signatures is an important topic.

Logical access to systems and computerized data should be controlled in a way that only permits authorized individuals to gain access to the system. This is normally done through a unique access code such as a unique user ID and password combination that is assigned to the individual whose identity has been verified and whose job responsibilities require such access. The system should require the user to change the password periodically, and should detect possible unauthorized access attempts, such as multiple failed logins, and automatically deauthorize the user account.

The identification code can also be an encrypted digital certificate stored on a password-protected device or a biometric identifier that is designed so that it can only be used by the designated individual.

Rules should be established for situations in which access credentials are compromised. New password information should be sent to the individual by a secure method.

Intrusion detection and firewalls should be employed on sites accessible to the Internet, with appropriate controls and rules in place to limit access to authorized users. Desktop systems should be equipped with antivirus software, and servers should run the most recent security patches. System security should be reviewed throughout the course of the registry to ensure that management, operational, personnel, and technical controls are functioning properly.

Data Enclaves. With the growth of and demands for increasing amounts of clinical data by multiple parties and researchers, new approaches to access are evolving. Data enclaves are secure, remote access systems that allow researchers to share respondents' information in a controlled and confidential manner[458]. The data enclave utilizes statistical, technical, and operational controls at different levels chosen for the specific viewer. This can be useful for both enhancing protection of the data and for enabling certain organizations to access data in compliance with their own organization or agency requirements. Data enclaves can be used to also allow other researchers to access a registry's data in a controlled manner. With the growth of registries and their utility for a number of stakeholders, data enclaves will become increasingly important.

Electronic signatures. Electronic signatures provide one of the foundations of individual accountability, helping to ensure an accurate change history when used in conjunction with secure, computer-generated, time-stamped audit trails.

Most systems utilize an electronic signature. For registries that report data to FDA, such signatures must meet criteria specified in 21 CFR Part 11 for general signature composition, use, and control (11.100, 11.200, and 11.300). However, even registries that do not have such requirements should view these as reasonable standards. Before an individual is assigned an electronic signature, it is important to verify the person's identity and train the individual in the significance of the electronic signature. In cases where a signature consists of a user ID and a password, both management and technical means should be used to ensure uniqueness and compliance with password construction rules. Password length, character composition, uniqueness, and validity life cycle should be based on industry best practices and guidelines published by the NIST.

Passwords that are used in electronic signatures should abide by the same security and aging constraints as those listed for system access controls.

Validation. Systems that store electronic records (or depend on electronic or handwritten signatures of those records) that are required to be acceptable to FDA must be validated according to the requirements set forth in the 21 CFR Part 11 Final Rule,[459] dated March 20, 1997. The rule describes the requirements and controls for electronic systems that are used to fulfill records requirements set forth in agency regulations (often called "predicate rules") and for any electronic records submitted to the agency. FDA publishes nonbinding guidance documents from time to time that outline its current thinking regarding the scope and application of the regulation. The current guidance document is *Guidance for Industry, Part 11, Electronic Records; Electronic Signatures – Scope and Application*,[460] dated August 2003. Other documents that are useful for determining validation requirements of electronic systems are *Guidance for Industry, Computerized Systems Used in Clinical Investigations*,[461] dated May 2007, and *General Principles of Software Validation; Final Guidance for Industry and FDA Staff*,[462] dated January 11, 2002.

Resource Considerations

Costs for registries can be highly variable, depending on the overall goals. Costs are also associated with the total number of sites, the total number of patients, and the geographical reach of the registry program. Each of the elements described in this chapter has an associated cost. Table 16 provides a list of some of the activities of the registry-coordinating center as an example. Not all registries will require or can afford all of the functions, options, or quality assurance techniques described in this chapter. Registry

planners must evaluate benefit vs. available resources to determine the most appropriate approach to achieve their goals.

Table 16: Data Activities Performed During Registry Coordination

**Note: CRF = case report form.*

Data management	• Defines all in-process data quality control steps, procedures, and metrics • Defines the types of edit checks that are run against the data • Defines required file-format specifications for electronic files, as well as schedules and processes for transfers of data • Defines quality acceptance criteria for electronic data, as well as procedures for handling exceptions • Develops guidelines for data entry • Identifies areas of manual review where electronic checks are not effective • Develops and maintains process for reviewing, coding, and reporting adverse event data • Develops and maintains archiving process • Develops and documents the process for change management • Develops and maintains process for query tracking and creates standard reports to efficiently identify outstanding queries, query types per site, etc. • Relates queries to processes and activities (e.g., CRF design) requiring process improvements • Follows up on query responses and errors identified in data cleaning by performing accurate database updates • Defines registry-specific dictionaries and code lists • Performs database audits as applicable • Conducts user testing of systems and applications per written specifications • Establishes quality criteria and quality error rate acceptance limits • Evaluates data points that should be audited and identifies potential sources of data errors for audits • Identifies root cause of errors in order to recommend change in process/technology to assure the error does not occur again (continuous improvement) • Ensures that sampling audit techniques are valid and support decisions made about data • Outlines all other data flow, including external data sources
Documentation	• Documents the process, procedures, standards, and checklist(s) and provides training • Documents and maintains process and standards for identifying signals and trends in data • Documents database quality control actions performed
Reporting	• Generates standard reports of missing data from the patient database • Creates tools to track and inventory CRFs, and reports anticipated vs. actual CRF receipts

Case Example 29: Data collection challenges in rare disease registries

Description:	Fabry disease is a rare lysosomal storage disorder caused by deficiency of the enzyme α-galactosidase A. The Fabry Outcome Survey (FOS) was established in 2001 to increase understanding of the natural history of Fabry disease and assess patients' response to enzyme replacement therapy with agalsidase alfa (Replagal®). Development and analysis of FOS data are driven by the participating physicians. An Executive Committee and International Board oversee the types of data collected and any changes required. In addition, a number of working groups (e.g., pediatric, renal, cardiac) are responsible for analyzing and improving data collection for their specialties.
Sponsor:	Shire HGT
Year Started:	2001
Year Ended:	Ongoing
No. of Sites	132 centers in 21 countries
No. of Patients:	1,616 patients

Challenge

Rare disease registries such as the Fabry Outcome Survey (FOS) face unique challenges in data collection and quality assurance. Because there are very few patients with the disease of interest, most participating physicians have only one to two patients in the registry. The registry is not part of their daily – or even weekly – practice, and many of the physicians have difficulty remembering what to collect for the registry and how to capture the data when they do see an eligible patient. The FOS registry is also a global project, and the standard of care for patients with a rare disease often differs among physicians and between countries. As a result, a lab value or other data element that is routinely captured at one site may not be readily available at another site, leading to missing data. Finally, FOS is a long-term registry, with no defined end date. As physicians learn more about the disease and new treatments become available, the registry must adapt and update its data collection tools. This creates a need for continual training with participating physicians.

Despite these challenges, it is essential that the registry collect high-quality data to fulfill its goal of increasing knowledge about Fabry disease. A recent major objective of the registry staff has been to improve collection and quality of the data so as to provide a more robust data set for analysis.

Proposed Solution

Beginning in 2006, three measures were implemented to improve the collection and quality of data: development of a core data set to ensure evaluation of variables relevant to disease progression and the effect of treatment; increased concentration on centers that have enrolled 20 or more patients in FOS; and use of clinical projects associates to monitor data capture and quality.

The clinical projects associates are employees of the registry sponsor who generally have experience with clinical trial monitoring. For FOS, a clinical projects associate is typically assigned to a specific geographical area to serve as the contact person for the centers, examine that center's data for inconsistencies, and help with training center staff. The registry staff developed guidelines for the clinical projects associates to use when examining the data for inconsistencies, with particular focus on core variables. The clinical projects associates visit the sites in person to examine the data and provide targeted training based on any inconsistencies that they may find. The data examination is not

monitoring, as in a clinical trial (there is no source validation), but instead, a review for logical consistencies and missing data.

Results

A random sample (25%) of all enrolled patients was taken before and after the introduction of the above measures to assess their effectiveness. This sample consisted of 197 out of 815 patients enrolled in 2005 and 404 out of 1616 patients enrolled in 2008.

Increases in data capture were found for 9 of the 10 core variables, the only exception being patient weight which remained unchanged at 90% for both time points. Data capture increased from 66% to 83% for signs and symptoms, from 89% to 91% for serum creatinine, from 48% to 55% for left ventricular mass, and from 84% to 87% for NYHA (New York Heart Association) score. The proportion of females enrolled increased from 48% to 54%, which is more representative of the true Fabry population.

During 2008, results from three important patient subgroups were also analyzed: patients who had received agalsidase alfa treatment for at least five years; females who had received agalsidase alfa for at least three years; and children who had received agalsidase alfa for at least two years. Data capture from the core variables increased in all three subgroups during 2008; for example, data capture increased by 20% for proteinuria and by 19% for left ventricular mass in the 153 females who were available for evaluation.

Key Point

Periodic review of a random sample of data can provide important information on the quality of data in a registry. Due to the unique challenges facing rare disease registries, additional efforts may be necessary to improve data collection and data quality. These efforts may include site visits, ongoing training programs, and regular audits of the data for completeness. Because these efforts may require significant resources, it is important to conduct assessments of the effectiveness of the efforts and to alter the strategies as needed.

For More Information

Mehta A, Beck M, Elliott P et al. Evidence of benefit of 5 years of enzyme replacement therapy with agalsidase alfa in patients with Fabry disease - a report from the Fabry Outcome Survey (FOS). Lancet 2009; in press.

Mehta A, Clarke JTR, Giugliani R et al. Natural course of Fabry disease: changing pattern of causes of death in FOS - Fabry Outcome Survey. J Med Genet 2009;46:548-52.

Feriozzi S, Schwarting A, Sunder-Plassmann G et al. Agalsidase alfa slows the decline in renal function in patients with Fabry disease. Am J Nephrol 2009;29:353-61.

Deegan PB, Baehner AF, Barba Romero M-Á et al. Natural history of Fabry disease in females in the Fabry Outcome Survey. J Med Genet 2006;43:347-52.

Case Example 30: Managing care and quality improvement for chronic diseases

Description:	The Tri State Child Health Services, web-based asthma registry is part of an asthma improvement collaborative aimed at increasing the use of evidence-based medicine and strengthening the improvement capacity of primary care practices.
Sponsor:	Physician-Hospital Organization (PHO) affiliated with Cincinnati Children's Hospital Medical Center
Year Started:	2003
Year Ended:	Ongoing
No. of Sites	39 community-based pediatric practices
No. of Patients:	12,000 children with asthma

Challenge

Asthma, a highly prevalent chronic disease managed in the primary care setting, has proven to be amenable to quality improvement initiatives. This asthma improvement collaborative was initiated in 2003 with goals of improving evidence-based care, reducing adverse outcomes, such as asthma-related emergency room visits and missed school days, and strengthening the quality of knowledge and capacity within primary care practices. As the asthma initiative spans 39 primary care practices and encompasses approximately 35 percent of the region's pediatric asthma population, the PHO needed a strategy to accommodate the large network of pediatric practices while improving the link between inpatient and outpatient care.

Proposed Solution

To address the project's focus on improving process and outcome measures, the asthma collaborative decided to initiate a web-based asthma registry. Based on National Heart, Lung, and Blood Institute's guidelines, key measures surrounding effective control and management of asthma are captured in a self-reported clinical assessment form. The questions include missed school and work days, parent's confidence in managing asthma, health resource utilization (e.g., emergency department visit) and rating of disease control. In addition, the clinical assessment form facilitates interactive dialogue between the physician and family during office visits.

The web-based registry allows real-time reporting at the patient level, practice level, and network level. Reporting is transparent, with comparative reports between practices, the identification of best practices, and the development of strategies for performance measures. In addition, different reporting functionalities exist that allow longitudinal results and the identification of high-risk patients. The web-based registry also has the potential to create real-time utilization reports that provide emergency room visit dates and reasons to the pediatric practices. All reports are available to participating practices and physicians at any time.

Results

The registry has provided data for the asthma collaborative to use in identifying best practices and tracking quality improvement. The pediatric practices have documented improvement against standard performance measures since the registry launch.

Key Point

Registries can be useful tools for quality improvement initiatives in chronic disease areas. By collecting

standard data and feeding back that data in reports, registries can track adherence to guidelines and evidence-based practices and provide information to support ongoing quality improvement.

For More Information

Keith E. Mandel M.D; Uma R. Kotagal, MSc, MBBS. Pay for Performance Alone Cannot Drive Quality, *Archives of Pediatrics and Adolescent Medicine*, Vol. 161, July 2007.

Case Example 31: Developing a performance-linked access system

Description:	The Teva Clozapine Patient Registry is one of several national patient registries for patients taking clozapine. The registry is designed as a performance-linked access system (PLAS) mandated by the U.S. Food and Drug Administration to comply with a Risk Evaluation Mitigation Strategy (REMS). The goal is to prevent clozapine rechallenge in patients at risk for developing clozapine-induced agranulocytosis, by monitoring lab data for signs of leukopenia or granulocytopenia.
Sponsor:	Teva Pharmaceuticals USA
Year Started:	1997
Year Ended:	Ongoing
No. of Sites	48,000 active physicians and pharmacies
No. of Patients:	49,000 active patients

Challenge

Clozapine is indicated for patients with severe schizophrenia who fail standard therapy, and for reducing the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder. However, it has potentially serious side effects that require careful medical supervision. The primary goal of the registry is to prevent clozapine from being prescribed and dispensed to patients with a known history of clozapine-induced agranulocytosis and to detect leukopenic events (decrease in white blood cell counts).

Because of the potential serious side effects, the U.S. Food and Drug Administration (FDA) requires manufacturers of clozapine to maintain a patient monitoring system. Designed as a performance-linked access system, the registry needs to assure the eligibility of patients, pharmacies, and physicians; monitor white blood cell (WBC) and absolute neutrophil (ANC) reports for low counts; assure compliance with lab report submission timelines; and respond to inquiries and reports of adverse events.

Proposed Solution

The registry was developed in the following ways to meet the above goals. Patients must be enrolled in the registry prior to receiving clozapine, and they must be assigned to a dispensing pharmacy and treating physician. After the patient has initiated therapy, a current and acceptable WBC count and ANC value are required prior to dispensing clozapine. Once a patient is enrolled and eligibility is confirmed, a 1-, 2-, or 4-week supply of clozapine can be dispensed, depending on patient experience and the physician's prescription.

Health care professionals are required to submit lab reports to the registry based on the patients' monitoring frequency. Patients are monitored weekly for the first 6 months. If there are no low counts, the patient can be monitored every 2 weeks for an additional 6 months. Afterward, the patient may

qualify for monitoring every 4 weeks (depending on the physician's prescription). The registry provides reminders if lab data are not submitted according to the schedule. If a low count is identified, registry staff will inform the health care providers to make sure that they are aware of the event and appropriate action is taken.

Results

By linking access to clozapine to a strict schedule of lab data submissions, the sponsor can ensure that only eligible patients are taking the drug. To the same effect, the sponsor is able to detect low counts, prevent inappropriate rechallenge (or re-exposure) in at-risk patients, and monitor the patient population for any adverse events. This system provides the sponsor with data on the frequency and severity of adverse events while ensuring that only the proper patient population receives the drug.

Key Point

A PLAS can ensure that only appropriate patients receive a treatment. These systems can also help sponsors to monitor the patient population to learn more about adverse events and the frequency of these events.

For More Information

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Honigfeld, G., The Clozapine National Registry System: Forty Years of Risk Management. J Clin Psychiatry Monograph, 1996. 14(2): p. 29-32.

FDA. Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting. 2003 [Available from: http://www.fda.gov/ohrms/dockets/ac/03/minutes/3959M1.htm.

Case Example 32: Using audits to monitor data quality

Description:	The Vascular Study Group of Northern New England (VSGNNE) is a voluntary, cooperative group of clinicians, hospital administrators, and research personnel, organized to improve the care of patients with vascular disease. The purpose of the registry is to collect and exchange information to support continuous improvements in the quality, safety, effectiveness, and cost of caring for patients with vascular disease.
Sponsor:	Funded by participating institutions (initial funding provided by Centers for Medicaid & Medicare Services)
Year Started:	2002
Year Ended:	Ongoing
No. of Sites	11 hospitals in Massachusetts, Maine, New Hampshire, and Vermont
No. of Patients:	Over 11,000 patients

Challenge

The Vascular Study Group of Northern New England (VSGNNE) established a registry in 2002 as part of an effort to improve quality of care for patients undergoing carotid endarterectomy, carotid stenting, lower extremity arterial bypass, and open and endovascular repair of abdominal aortic aneurysms. The

registry collects over 80 patient, process, and outcome variables for each procedure at the time of hospitalization, and one-year results are collected during a followup visit at the surgeon's office. All patients receiving one of the procedures of interest at a participating hospital are eligible for enrollment in the registry.

In considering the areas of greatest risk in evaluating the quality of this registry, the registry developers determined that incomplete enrollment of eligible patients was one major potential area for bias. It was determined that an audit of included versus eligible patients could reasonably address whether this was a significant issue. However, the group needed to overcome two logistical challenges: 1) the audit had to review thousands of eligible patients at participating hospitals in a timely, cost-effective manner; and 2) the audit could not overburden the hospitals, as they participate in the study voluntarily.

Proposed Solution

The registry team developed a plan to conduct the audit using electronic claims data files from the hospitals. Each hospital was asked to send claims data files for the appropriate time periods and procedures of interest to the registry. The registry team at Dartmouth-Hitchcock Medical Center then matched the claims data to the registry enrollment using ICD-9 codes with manual review of some patients that did not match using a computer matching process.

Results

The audit found that approximately 7 percent of eligible patients had not been enrolled in the registry. Because of concerns that the missing patients may have had different outcomes than the patients who had been enrolled in the registry, the registry team asked participating hospitals to complete registry forms for all missing patients. This effort increased the percentage of eligible patients enrolled in the registry to over 99 percent. The team also compared the discharge status of the missing patients to the enrolled patients and found no significant differences in outcomes; the team concluded that the patients had been missed at random and that there were no systematic enrollment issues. Discussions with the hospitals identified the reasons for not enrolling patients as confusion around eligibility requirements, training issues, and questions about informed consent requirements.

The first audit was completed in 2003. Additional audits were completed in 2006 and 2008.

Key Point

For many registries, audits are an important tool for ensuring that the data are reliable and valid. However, registries that rely on voluntary site participation must be cautious to avoid overburdening sites during the audit process. A remote audit using readily available electronic files, such as claims files, provided a reasonable assessment of the percentage of eligible patients that had been enrolled in the registry, without requiring large amounts of time or resources from participating sites.

For More Information

Cronenwett JL, Likosky DS, Russell MT, Eldrup-Jorgensen J, Stanley AC, Nolan BW; A regional registry for quality assurance and improvement: The Vascular Study Group of Northern New England (VSGNNE). J Vasc Surg 2007;46: 1093-1102.

Chapter 11: Interfacing Registries with Electronic Health Records (EHRs)

With national efforts to both invest in electronic health record (EHR) systems and to advance the evidence base in areas such as effectiveness, safety, and quality through registries and other studies, it is clear that interfacing registries with EHRs will become increasingly important over the next few years. As described below, while both EHRs and registries utilize clinical information at the patient level, registries are population focused, purpose-driven, and designed to derive outcomes information defined before collecting and analyzing the data. EHRs are focused on the collection and use of health-related information on and for an individual. While in practice there may be some overlap of functionalities between the two, their roles are distinct, and both are very important to the health care system. This chapter explores issues of interoperability and a pragmatic 'building-block approach' towards a functional, open-standards[B] based solution. An important value of this approach is that EHR vendors can implement it without major effort or impact on their current systems. While the focus of this handbook is on patient registries, the same approach described in this chapter is applicable to clinical research studies, safety reporting, biosurveillance, public health, and quality reporting. This chapter also includes case examples (see Case Examples 33, 34, 35, and 36) describing some of the challenges and approaches to interfacing registries with EHRs.

Background

As recently as 2007, only 13 percent of U.S. physicians were estimated to have adopted partial electronic health record (EHR) systems, with only 4 percent adopting more complete EHR systems.[463,464,465] With the passage of the American Recovery and Reinvestment Act of 2009 (ARRA), a rapid and transformative change is now in process. ARRA set aside approximately $19 billion in incentives to providers to adopt EHR systems over the next several years.

An electronic health record refers to an individual patient's medical record in digital format. EHRs can be comprehensive systems that manage both clinical and administrative data; for example, an EHR may collect medical histories, lab data, and physician notes and assist with billing, inter-practice referrals, appointment scheduling, and prescription refills. They can also be targeted in their capabilities; many practices choose to implement EHRs that offer a subset of these capabilities, or they may implement multiple systems to fulfill different needs. According to the Institute of Medicine, there are four core functionalities of an EHR: health information and data, results management, order entry and support, and decision support.[466]

The current U.S. EHR market is highly fragmented.[467] Until recently, the term EHR was broadly applied to systems that fall within a range of capabilities. In 2004, a certification process was established by an industry coalition of the American Health Information Management Association (AHIMA), the Health Information Management Systems Society (HIMSS), and the National Alliance for Health Information Technology. The Certification Commission for Health Information Technology (CCHIT) is a private

[B] In this context, "open standards" means that the standards are developed through a transparent process, with participation from many stakeholders, and are not proprietary. "Open standards" in this context does not mean that the standards are available free of charge; there may be fees associated with the use of certain standards.

nonprofit organization with the 'sole public mission of accelerating the adoption of robust, interoperable health information technology by creating a credible, efficient certification process.'[468] Each year, CCHIT publishes criteria, against which vendors voluntarily submit to a certification process. The numbers of certifying EHRs is gradually increasing.[469]

Even with increasing standardization of EHRs, there are many issues and obstacles to achieving interoperability (meaningful communication between systems -- as described further below) between EHRs and registries or other clinical research activities. Among these obstacles are information interoperability and exchange; issues in confidentiality, privacy, security, and data access; and issues in regulatory compliance. For example, in terms of information interoperability and exchange, it has been observed (by the Clinical Research Value Case Workgroup) that clinical research data standards are developing independently from certain standards being developed for clinical care data; that currently the interface between the EHR and clinical research data is ad hoc and can be prone to errors and redundancy; that there is a wide variety of modes of research and medical specialties involved in clinical studies, thus making standards difficult to identify; and that there are differences among standards developing organizations around healthcare data standards and how they are designed and implemented (including some proprietary standards for clinical research within certain organizations). With respect to confidentiality, privacy, security and data access it is pointed out that secondary use of data may violate patient privacy, and protections need to be put in place before data access can be automated. In the area of regulatory compliance, it is noted that for some research purposes there is a need to comply with regulations for electronic systems (e.g., 21 CFR Part 11) and other rules (e.g., Common Rule).[470]

Since the passage of ARRA, the office of the Secretary of HHS has been charged with setting standards and certification criteria for EHRs with interoperability being a core goal. The Office of the National Coordinator of Health Information Technology (now commonly referred to as the ONC) within HHS promotes the development of a nationwide interoperable HIT infrastructure, and establishes HIT Policy and Standards Committees that are comprised of public and private stakeholders (e.g., physicians) to provide recommendations on the HIT policy framework, standards, implementation specifications, and certification criteria for electronic exchange and use of health information.

The new Federal oversight of EHR standards is clearly guided by the need for EHRs that benefit from the market-building impact of $19 billion in provider incentives to serve the broader public purposes for which the ARRA funds are intended.[471] Specifically, the elusive goal that has not been satisfied in the current paradigm is the creation of an interoperable HIT infrastructure. Without interoperability, the HIT investment under ARRA may actually be counterproductive to other ARRA goals, including the ability to generate and disseminate information on the comparative effectiveness of alternative therapies and the goal of measuring quality in the healthcare system efficiently and transparently. Ideally, EHR standards will facilitate the groundwork for what the Institute of Medicine has called, the 'learning healthcare system.'[472] The goal of a learning healthcare system is to transform the way evidence is generated and used to improve health and healthcare -- a system in which patient registries and similar, real-world study methods are expected to play a very important role. Ultimately, the HIT standards that are adopted, including standardized vocabularies, data elements, data sets and technical standards, may have a far reaching impact on how transformative ARRA will be from an HIT perspective.

EHRs and Patient Registries

Prior to exploring how EHRs and registries might interface, it is useful to clearly differentiate one from the other. While EHRs may assist in certain functions that a patient registry requires (e.g., data collection, data cleaning, data storage, etc.), and a registry may augment the value of the information collected in an EHR (e.g., population views, quality reporting, etc.), an EHR is not a registry, and a registry is not an EHR. Simply stated, an EHR is an electronic record of health-related information on an individual that conforms to nationally recognized interoperability standards, and that can be created, managed, and consulted by authorized clinicians and staff, across more than one health care organization.[473] As defined in Chapter 1, a registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical or policy purposes. Registries are population focused and designed to fulfill specific purposes defined before collecting and analyzing the data. EHRs are individual focused and designed to collect, share, and use that information for the benefit of that individual.

EHRs and Evidence Development

The true promise of EHRs in evidence development is in facilitating the achievement of a practical, scalable, and efficient means of collecting, analyzing, and disseminating evidence. By digitizing information, many of the scalability constraints of patient registries and other clinical research activities can be dramatically reduced. Paper records are inherently limited because of the difficulties in systematically finding or sampling eligible patients for research activities and the effort required to re-enter information into a database. Digitizing information has the capacity to improve both of these requirements for registries, enabling larger, more diverse patient populations, and avoiding duplication of effort for participating clinicians and patients. Reducing duplication of effort only occurs to the extent to which EHRs capture data elements and outcomes with specific, consistent, and interoperable definitions — or to the extent that data can be found and transformed by other processes and technologies, (e.g., natural language processing) into standardized formats that match registry specifications. In addition to enabling health care information to be more readily available for registries and other evidence development purposes, bidirectionally interoperable EHRs may also serve an efferent role of delivering relevant information back, from a registry, to a clinician, (e.g., natural history, safety, effectiveness, quality).

Current Challenges in a Pre-Interoperable Environment

As it turns out, data capture for research purposes, in general, can be challenging for physicians. Of the many hospitals, health care facilities, and doctor's offices that participate in studies, most have more than one data capture system; an estimated 17 percent have 5 or more.[474] In other words, hospitals and practices are changing their workflow to accommodate non-harmonized research demands. As a result, data capture, especially for a registry in which a large number of patients may fit into a broad set of enrollment criteria, can be awkward and time-consuming for clinicians and their staff. While some of this can be overcome with uploads from these systems to registries of certain standard file formats, such as hospital or physician office billing files, without interoperable systems, the need to re-enter data from one system to another, train staff on new systems, and juggle multiple user names, passwords, and devices, presents a high barrier to participation, especially for physicians whose primary interest is patient care and who are often, themselves, resistant to change. The widespread implementation of EHRs that are not truly interoperable (as discussed below), coupled with the growth in current and future evidence

development activities, such as patient registries, may ironically create significant barriers to achieving the vision of a national, learning healthcare system. In many respects, physicians are part of the problem as they seek EHRs with highly customized interfaces and database schema rather than those that may be more amenable to interoperability.

Most EHRs are not fully interoperable in the core functions that would enable them to participate in the learning healthcare system that is envisioned by the IOM. This is directly related to a combination of technical and economic barriers to adoption and deployment of standards-based, interoperability solutions by EHRs. There are over 40 well-established EHR vendors, many of which provide heavily customized versions of their systems for each separate client. For some time, there was significant interest in adding clinical research capabilities to the already-implemented EHR systems,[475] but this so-called "Swiss Army Knife" approach did not prove to be technically or commercially effective. Issues encountered ranged from standardization of core data sets, to achieving compliance with FDA requirements for electronic systems used in clinical research. And, because there is no single, national EHR, even if this were achievable, it would not meet many registry purposes, which seek data across large, generalizable populations. In recent years, the industry has primarily turned back to pursuing an open standards approach to interacting with, rather than becoming, specialized systems.[476] Appendix C describes many of the relevant standards and standards-setting organizations.

Even though many EHR systems are technically uniform, in many ways due to the CCHIT EHR certification process, the actual software implementations are very different. As a result, achieving interoperability goals (across the myriad of installed EHRs, and current and future registries) through custom interfaces is a mathematical, and therefore, economic impossibility (see further below). An open standards approach seems to be the most viable. In addition, as tested in many demonstrations and as is slowly being incorporated by some vendors into commercial offerings, a user-configurable mechanism to enable the provider to link to any number of registries without requiring customization by the EHR vendor also is an important aspect of a scalable solution.

The Vision of EHR-Registry Interoperability

As EHRs become the primary desktop interface for physicians and other healthcare workers, it is clear that registries must work through the EHR in order for interoperability to be feasible. At the same time, the need for physicians to participate in registries to manage safety, evaluate effectiveness and to measure and improve quality of care is growing rapidly. As a result, EHRs will need to serve as an interface for more than one registry, simultaneously. In considering the need for interfacing EHRs with patient registries, it is a useful construct to consider the specific purpose that the patient registry is designed for, and then how an EHR that is interoperable with one or more registries might lessen the burden, barriers or costs of managing registries and other data collection programs. These potential functions can be thought of with respect to the registry purpose.

- Natural history of disease: identify patients (and alert clinicians) who meet eligibility criteria; present the relevant forms and instructions; capture uniform data; review the data prior to transmission; transmit data to the registry; receive and present information from the registry (e.g. population views).

- Effectiveness: identify patients (and alert clinicians) who meet eligibility criteria; execute sampling algorithms; present the relevant forms and instructions; capture uniform data; review the data prior to transmission; transmit data or analytics; receive and present information from the registry (followup schedules; registry wide results).

- Safety: identify events for reporting through triggers; capture uniform data; review the data prior to transmission; transmit data; receive and present requests for additional information; receive and present safety information from the registry.

- Quality: identify patients who meet eligibility; present the relevant forms and instructions; capture uniform data; review the data prior to transmission; transmit data to a registry for reporting; receive and present quality measure information and comparators from the registry.

In a truly interoperable system, registry-specific functionality could be presented in a software-as-service or middleware model, interacting with the EHR as the presentation layer on one end and the registry database on the other. In this model, the EHR is a gateway to multiple registries and clinical research activities through an open architecture that leverages best-in-class functionality and connectivity. Registries interact across multiple EHRs and EHRs interact with multiple registries.

Interoperability Challenges

Interoperability for health information systems requires communication; accurate and consistent data exchange; and use of the information that has been exchanged. The two core constructs, around communication and content, are often called syntactic and semantic interoperability.

Syntactic interoperability: Syntactic interoperability is the ability of heterogeneous health information systems to exchange data. There are several layers of syntactic interoperability. First, the wiring must be in place and the TCP/IP (internet) is the defacto standard. On top of this, an application protocol is needed such as HTTP or SMTP. The third layer is a standard messaging protocol such as SOAP (Simple Object Access Protocol).[477] The message must have a standard sequence, structure and data items in order to be processed correctly by the receiving system.

When proprietary systems and formats are used, the complexity of the task grows dramatically. For n systems, n(n-1)/2 interfaces are needed for each system to communicate with every other one.[478] For this reason, message standards are preferred. While this seems straightforward, an example portrays how, even for EHR to EHR communication, barriers still exist. Currently, the Health Level Seven (HL-7) Version 2 message standard (HL-7 v2.5) is the most widely implemented standard among EHRs, but this version has no explicit information model; instead, it rather vaguely defines many data fields and has many optional fields. To address this problem, the Reference Information Model (RIM) was developed as part of HL-7 v3, but v3 is not fully adopted and there is no well-defined mapping between v2.x and v3 messages.

Syntactic interoperability assures that the message will be delivered. Of the challenges to interoperability, this is the one most frequently solved. However, solving the delivery problem does not guarantee that the content of the message can be processed and interpreted at the receiving end with the meaning for which it was intended.

Semantic interoperability: Semantic interoperability implies that the systems understand the data that has been exchanged at the level of defined domain concepts. This "understanding" requires shared data models that, in turn, depend on standard vocabularies and common data elements.[479]

The National Cancer Institute (NCI)'s Cancer Bioinformatics Grid (caBIG) breaks down the core components of semantic interoperability into information or data models, which describe the relationships between common data elements in a domain: controlled vocabularies, which are an agreed upon set of standard terminology; and common data elements, which use shared vocabularies and standard values and formats to define how data are to be collected.

The standardization of what is collected, how it is collected, and what it means is a vast undertaking across healthcare. Yet, piece by piece, much work has, and is currently, being done, although the effort is not centralized nor is it equally represented across different medical conditions. One effort, called the CDASH Initiative, is led by the Clinical Data Interchange Standards Consortium (CDISC) and aims to describe recommended basic standards for the collection of clinical trial data.[480] It provides guidance for the creation of data collection instruments, including recommended case report form (CRF) data points, classified by domain (adverse events, inclusion/exclusion criteria, vital signs, etc.) and a core designation (highly recommended, recommended/conditional or optional). The first version of CDASH was published in October 2008, and it remains to be seen how widely this standard will be implemented in the planning and operation of registries, clinical trials and post-marketing studies, but is, nonetheless, an excellent step in defining a common set of data elements to be used in registries and clinical research.

Other examples of information models used for data exchange are the ASTM Continuity of Care Record (CCR) and HL7's Continuity of Care Document (CCD) which have standardized certain commonly reported components of a medical encounter, including diagnoses, allergies, medications, and procedures. The CCD standard is particularly relevant because it is one that has been adopted as part of CCHIT certification. The Biomedical Research Integrated Domain Group (BRIDG) model is an effort to bridge healthcare and clinical research standards and organizations with stakeholders from CDISC, HL7, NCI, and the FDA. Participating organizations are collaborating to produce a shared view of the dynamic and static semantics that collectively define a shared domain-of-interest, (i.e., the domain of clinical and pre-clinical protocol-driven research and its associated regulatory artifacts).[481]

Even with some standardization in the structure and content of the message, issues exist in the use of common coding systems. For any EHR and any registry system to be able to semantically interoperate, there need to be greater uniformity around which coding systems are to be used. At this time, there are some differences between coding systems adopted by EHR vendors and registry vendors. While it is still possible to translate these coding systems, and/or 're-code' them, it limits the possibility for achieving full semantic interoperability until this is achieved.

The collection of uniform data, including data elements for risk factors and outcomes, is a core characteristic for patient registries. If a functionally complete, standard 'dictionary' existed, it would also greatly improve the value of the information contained within the EHR. But, while tremendous progress has been made in some areas, such as cancer[482] and cardiology,[483] the reality is that full semantic interoperability will not be achieved in the near future.

Beyond syntactic and semantic interoperability, there are other issues that require robust, standardized solutions. One of the key issues is managing patient identifiers among different healthcare applications. Different healthcare entities, even departments within institutions, may use different identifiers for the same patient. Consider the example of a longitudinal patient registry that begins with a hospital admission but moves to followup in an ambulatory practice with a different EHR and a different identifier. There are several specific solutions, such as master patient indexes, patient record pointers, and patient controlled access mechanisms, yet none is universal.

A second issue is how best to authenticate users across multiple applications. A third issue is permission or authorization management. At a high level, how does the system enforce and implement varying levels of authorization? A healthcare authorization is specific to authorized purposes. A particular patient may have provided different authorizations to disclose information differently to different registries interacting with a single EHR at the same time, and the specificity of that permission needs to be retained, and in some way linked with the data, as it transits between applications. For privacy purposes, an audit trail also needs to be maintained and viewable across all the paths through which the data moves. In addition to privacy, security must also be ensured across all of the nodes in the interoperable system.

Partial and Potential Solutions

Achieving true, bidirectional interoperability for all of the required functions for EHRs and patient registries to function seamlessly with one another is unlikely to be accomplished for many years. However, as noted above, it is critical that a level of interoperability be achieved so that silos of information within proprietary informatics systems are not created that make it difficult or impossible to conduct large registries or other evidence development research across diverse practices and populations. Given the lack of a holistic and definitive interoperability model, an incremental approach to the successive development, testing, and adoption of open, standard building blocks towards an interoperable solution is likely the path forward. In fact, much has been done in the area of interoperability, and if fully leveraged, these advances can already provide at least a level of 'functional interoperability,' that could significantly ameliorate this potential problem.

From an EHR-registry perspective, functional interoperability could be described as a standards-based solution that achieves the following requirements:

> *The ability of any EHR to exchange valid and useful information with any registry, on behalf of any willing provider, at any time, in a manner that improves the efficiency of registry participation for the provider and the patient, and does not require significant customization to the EHR or the registry system.*

What constitutes 'useful' information exchange includes both general activities (e.g., patient identification, accurate/uniform data collection and processing), and specific additional elements, depending on the purpose of the registry (e.g., quality reporting). Such a definition implies an open standards approach where participation is controlled by the provider/investigator. To be viable, such a model would require that EHRs 'certify' to meet open standards for basic functional interoperability (the requirements advance over time), but have the opportunity to further differentiate their services by how much they can improve the efficiency of participation.

While the goal of functional interoperability likely requires the creation and adoption of effective open standards, there have been several approaches to partially addressing these same issues in the absence of a unified approach. HIT systems, including some EHRs, have been used to populate registry databases for some time. The Society of Thoracic Surgeons (STS), the American College of Cardiology (ACC), and others utilize models that are based on a central data repository that receives data from multiple conforming systems, on a periodic basis, through batch transfers. Syntactic interoperability is achieved through a clear specification that is custom programmed by the HIT systems vendor. Semantic interoperability is achieved by the publication of specifications for the data collection elements and definitions, on a regular cycle, and incorporation of such by the systems vendors. Each systems vendor pays a fee for the specifications and for testing their implementation following custom programming. In some cases, an additional fee is levied for the ongoing use of the interface by the systems vendor. Periodically, as data elements are modified, new specifications are published and the cycle of custom programming and testing is repeated. While there is incremental benefit to the provider organizations by not having to use multiple systems to participate in these registries, the initial and periodic custom programming efforts and the need to support custom interface requirements makes this approach not scalable. Furthermore, participation in one registry actually makes participation in other, similar registries more difficult, since the data elements are customized and not usable in the next program.

The American Heart Association's Get With The Guidelines® program uses a web services model for a similar purpose. The advantage of the web services model is that the data are transferred to the patient registry database on a transactional basis (immediately). But, the other drawbacks in custom programming and change management still apply. This program also offers an open standards approach through IHE RFD[484] or HITSP TP50 (described below). These examples describe two models for using EHRs to populate registry databases; other models exist.

Momentum towards a Functional Interoperability Solution

Significant momentum is already building towards adopting open standard building blocks that will incrementally lead to functional interoperability solutions. For example, the EHR Clinical Research Value Case Workgroup has focused its use cases on two activities: (1) the ability to communicate study parameters (e.g., eligibility information, CRFs), and (2) the ability to exchange a core dataset from the EHR.[485] Others in the standards development community have taken a stepwise approach to create the components for a first generation, functional interoperability solution. As described below, this solution has already overcome several of the key barriers to creating an open, scalable, model that can work simultaneously between multiple EHR systems and registries. Some of the issues that have been addressed through these efforts include: flexibility in presenting a uniform data collection set that can be modified from time to time, without custom programming by the EHR vendor; the ability to leverage existing, standardized EHR data to populate portions of the data collection set; and the ability to submit the data on a transactional basis to a registry, clinical trial or other data recipients in a standard format.

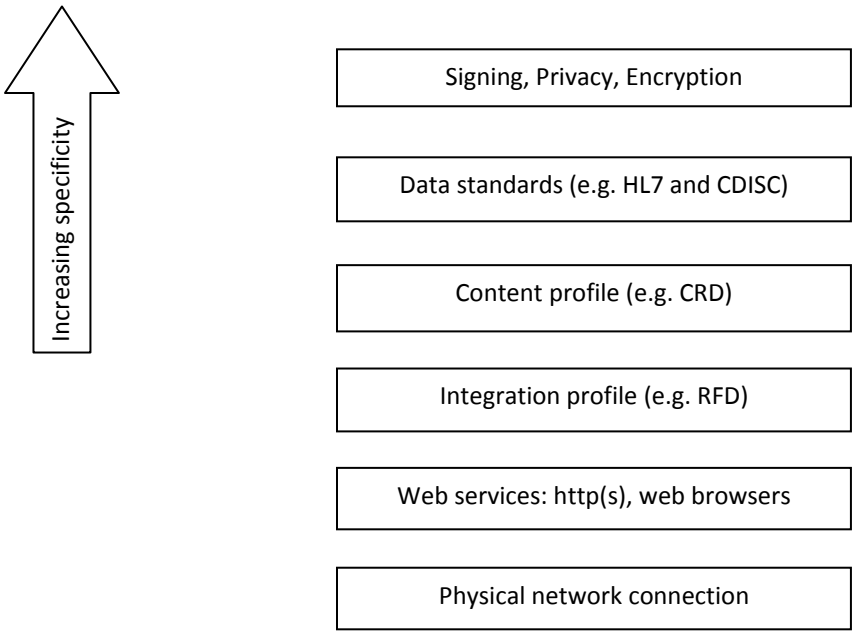
Building-Block Approach

A building-block approach to the technical side of this issue is an effective and pragmatic way to build in increments, and allow all players in the industry to focus on specific components of interoperability; early successes can then be recognized and used to form the next step in the solution. This is a change from the earlier approaches to this issue, where the problem (and the solution) was defined so broadly that complete semantic interoperability seemed to be the only way to solve the problem; this proved

overwhelming and unsupportable. Instead, a working set of industry-accepted standards and specifications that already exist can focus tightly on one aspect of interfacing multiple data capture systems, rather than considering the entire spread of issues that confound the seamless interchange between healthcare and research systems.

There are many different standards focused on different levels of this interface, and several different key stakeholders that create, work with, and depend on these standards. A useful way to visualize these technical standards is to consider a stack where each building block is designed to facilitate one aspect of the technical interface between an EHR and a data collection system (Figure 3). The building blocks are modest but incremental changes that move two specific systems towards interoperability, and are scalable to different platforms.

Figure 3. Building Block Approach



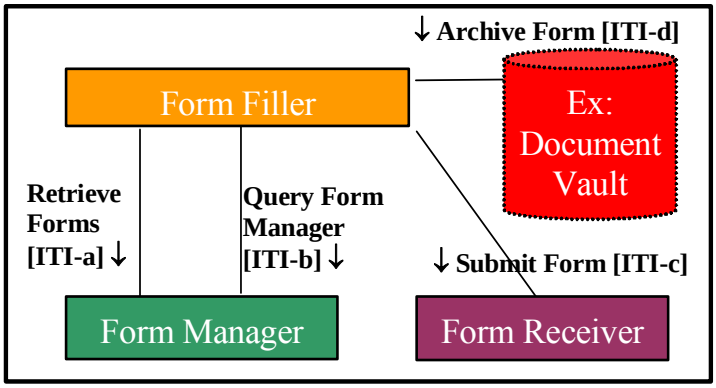
This theoretical stack starts with the most basic technical components as the ground layers. Physical network connections, followed by web services, secure hypertext transfer protocol (https), using secure socket layer (SSL) communications protocol, and web browsers create the foundation of the interoperability structure. These standard technologies are compatible across most systems already, as part of the World Wide Web.

A standard integration profile, Retrieve Form for Data Capture (RFD), sits as the base of specific interoperability for health care data transfer, and takes advantage of the Web standards as a way to integrate between EHRs and registry systems. RFD is a generic way for systems to interact. In a sense, RFD opens a circuit or provides a 'dial tone' to allow an EHR to exchange information with a registry or other clinical research system. RFD was created and is maintained by Integrating the Healthcare Enterprise (IHE). It is also accepted under HITSP as TP50. Specifically, RFD provides a method for gathering data within a user's current application to meet the requirements of an external system (e.g., a

Registry). In RFD, as Figure 4 below shows, this is accomplished by retrieving a registry or other data collection form from a source (Form Manager), displaying it within the EHR system (Form Filler) to allow completion of the form (with data validation checks), either through direct user entry or automated population from the EHR database, and then returning an instance of the data back to the registry system (Form Receiver). Of importance, the EHR initiates the transaction.

Once an EHR is RFD enabled, it can be used for multiple use-cases. RFD opens a circuit, and allows for information exchanges of different purposes including registries and clinical trials, quality initiatives, safety, and public health reporting.

Figure 4. RFD Diagram



Content profiles such as Clinical Research Data Capture (CRD) build the next level, allowing standard content defined within an EHR to be mapped into the data collection elements for the registry, eliminating duplicate entry for these defined elements. CRD and the Drug Safety Content (DSC) profiles, managed by IHE, build upon the IHE RFD integration profile. Correspondingly, HITSP C76, or Case Report Pre-Populate Component (for Drug Safety), leverages the HITSP TP50 retrieve form for data capture transaction package.

CRD allows the functional interoperability solution to leverage standardized content as it becomes defined and available within EHRs. In other words, it is an incremental approach to leveraging whatever content has been rigorously defined and resident within the EHR, and that is also usable and acceptable to the registry (i.e., matching some portion of its defined data elements and definitions). To the extent that these data reside in a common format, they can be used for auto-population of the registry forms without custom programming. CRD leverages the Continuity of Care Document (CCD), an HL7 standard that is also a current requirement for CCHIT EHR certification. In this scenario, the CCD is generated by the EHR to populate a case report form. Only the relevant data from the CCD are used by the registry as is determined by the registry system that is presenting the form. Alternatively, CRD specifies that CDASH, a CDISC standard for data collection elements, may optionally be used as the content message to pre-populate the case report form.

The Next Increment

As the basic components of functional interoperability are being tested and implemented, more attention is focusing on the next increments of the building block approach. The important challenges to be addressed include: patient identification/privacy protection, the potential and appropriate use of digital

signatures, other related and emerging profiles, such as querying the EHR for existing data [Query for Existing Data (QED)], and transferring process related study information as captured in the study protocol [Retrieve Protocol for Execution (RPE)]. More extensive work in data mapping and the development of use cases around content are also needed.

Patient identification/privacy protection:

Patients within the context of clinical care are identified by a patient identifier, usually referred to as a medical record number. When those patients participate in a registry, they will also have a patient identifier within the context of those programs. In some cases, where explicit authorization has been obtained, the medical record number may be shared across programs and can be used as a common identifier that links the patient across systems. In other cases, there is a need to anonymize the patient identifier. In the latter situation, infrastructure can be deployed to create unique, anonymized patient identifiers that serve to protect the patients' identity and facilitate secure, patient identity management [e.g. Patient Identifier Cross-Referencing (PIX)].[486]

Beyond anonymizing, it also may be desirable to maintain a cross-referencing of patient identifiers or aliases across multiple systems so that the medical record number within the EHR can be linked back to the identifier within the registry or clinical trial, without revealing the patient identity. Pseudonymization is a procedure by which all person-related data is replaced with one artificial identifier that maps one-to-one to the person.[487] Pseudonymization allows for additional use cases where it is necessary to link a patient seen in different settings (such as linking back to source records for additional information or monitoring).[488]

Digital signatures:

Certain registry purposes (such as regulatory reporting) require electronic signatures, such as when the clinician or investigator attests to the completeness and accuracy of information being submitted for a research purpose. The current paradigm is the physical or electronic signature of a paper or electronic CRF by the investigator. The potential and appropriate use of digital signatures may further broaden the set of use cases by which EHRs may be utilized for secondary purposes. Other approaches to facilitating identity management, signing, and verification, such as Private Key Infrastructure (PKI), provide advantages in terms of non-repudiation and detection to tampering. In the next wave of the interoperability effort, it will be important to define those scenarios that will require the strength of an enhanced digital signature.

Other related and emerging efforts:

As the building blocks of interoperability develop, additional flexibility will be gained as the registry and EHR can more fully communicate in a common language to both request more clinical data, and to provide the EHR with more information on the workflow requirements of the registry or other study protocol. These requirements point to other work being done to address these issues. Below are two examples from IHE profiles:

- Query for Existing Data (QED) – This integration profile allows a clinical data consumer, such as a registry, clinical trial, or quality reporting system, to query a clinical data source for a variety of relevant study data, such as vital signs, diagnostic results, problems and allergies, medications, and immunizations. With this model, the registry data consumer plays an active role in querying an EHR for real-time clinical information relevant to the study protocol.

- Retrieve Protocol for Execution (RPE) – This profile intends to allow an EHR to retrieve a protocol or a complex set of clinical research instructions which are necessary to fulfill the specified requirements of the protocol. The objective of this effort is to leverage existing standards, such as the Trial Design Model, and efforts underway by the CDISC and HL7 standards organizations, in order to further advance these definitions. The availability of these definitions and a set of transactions defined by RPE will: provide an EHR with content which may be used to identify patients for a research program based on defined inclusion/exclusion criteria; or manage the patient visit schedule and appropriate case report forms or assessments which need to be completed in the appropriate sequence; or even to assist with other clinical activities such as ordering protocol specified tests or labs.

Data mapping and constraints:

While the efforts described above continue to expand the use of electronic medical record data for a variety of secondary purposes, it is clear that clinical and research teams, standards, and terminologies need to be further harmonized to maximize the benefits of information sharing across the variety of clinical and research systems. Effectively and efficiently managing this requires that harmonization efforts are furthered among vendors and among standards organizations. It also requires that use cases continue to be honed and explicitly defined so that new clinical document *constraints* can be applied, as necessary for each specified use case. Use cases will range across study types and across purposes, including drug safety, biosurveillance, public health, and so forth. Each clinical document constraint should strive to capture and deliver the necessary information so as to fully support the level of information sharing which is required by the scenario that maximizes both the efficiency of the clinical care/research workflow, as well as the value of previously collected relevant data.

What Has Been Done

A number of efforts have demonstrated successful implementations of several of the aforementioned building block standards, for the purpose of achieving functional interoperability for registry purposes, including safety, effectiveness, and quality measurement. In one case, a registry focused on effectiveness in pain management was made interoperable with a commercial EHR using RFD communication.[489] In a second case, the **A**dverse Drug Event **S**pontaneous **T**riggered **E**vent **R**eporting (ASTER) project,[490] interoperability was achieved for the purpose of reporting adverse event information to the Food and Drug Administration (FDA) (See Case Example 36). In a third case, a commercial EHR was made interoperable with a quality reporting initiative for the American College of Rheumatology (ACR),[491] and to a Physician Quality Reporting Initiative (PQRI) Registry for reporting data to the Centers for Medicare and Medicaid Services.[492] In each case, both the registry and the EHRs were able to exchange useful information and decrease the effort required by the participating physicians.

Distributed Networks

It should be noted that the models of interoperability discussed above presume that data is shared between a distributed EHR and a patient registry (or another recipient such as a regulatory authority or a study sponsor). Alternative models may leave all data within the EHR but execute analyses in a distributed fashion and aggregate only results. To effectively accomplish distributed analyses requires either semantic interoperability or the ability to map to a conforming database structure and content, as well as the sophistication of a large number of EHR systems to run those types of queries in a manner that does not require providers to customize or program their systems. Several groups are advancing these concepts

(e.g., i2b2.org), and they may eventually prove to be very suitable for particular registry purposes (e.g., safety or public health surveillance). To our knowledge, they have not yet been subject to the rigors of a standard setting process, but they do provide an interesting alternative or complementary framework for further investigation.

Conclusions

Achieving EHR–registry interoperability will be increasingly important as adoption of EHRs and the use of patient registries for many purposes both grow significantly. The linkage of registries with health information exchanges (HIEs) is also important, as HIEs may serve as data collection assistants with which registries may need to interact.[493] Achieving Interoperability between these data sources is critical to ensuring that the massive HIT investment under ARRA does not create silos of information that cannot be joined for the public good. Such interoperability should be based on open standards that enable any willing provider to interface with any applicable registry, without requiring customization or permission by the EHR vendor. Interoperability for health information systems requires accurate and consistent data exchange, along with use of the information that has been exchanged. In addition, care must be taken to ensure that integration efforts comply with legal and regulatory requirements for the protection of patient privacy. While we remain a long way from full semantic interoperability, a great deal of useful work has and is being done. For example, the adoption of open standards, such as HITSP TP50, C76 and IHE RFD, CRD, and DSC alone, greatly enhance the ability for EHRs and registries to function together and reduce duplication of effort. 'Functional interoperability' provides a goal that can be achieved in the near term with significant gains in improving workflow and reducing duplication of effort for providers and patients participating in registries. The successive development, testing, and adoption of open standard building blocks, which improve functional interoperability and move us incrementally towards a fully interoperable solution, is a bridging strategy that provides benefits to providers, patients, EHR vendors, and registry developers today.

Case Example 33: Challenges in creating electronic interfaces between registries and EHRs

Description:	The IC3 Registry is a practice-based quality improvement program that aims to improve adherence with established, evidence-based, best practices for the management of CV patients, as codified by nationally-accepted performance measures for the treatment of patients with coronary artery disease, heart failure, hypertension, and atrial fibrillation. Data are collected by multiple means, including paper, web-based data collection tool, and via electronic medical records.
Sponsor:	Bristol-Myers Squibb/Sanofi Pharmaceuticals and the American College of Cardiology
Year Started:	2008
Year Ended:	Ongoing
No. of Sites	173 practices in 48 states and 2 U.S. territories
No. of Patients:	107,500 patient encounters

Challenge

Nearly half of the registry sites have some type of EHR in place, and the creation of electronic interfaces between the EHRs and the registry would reduce the burden of data entry on participating sites. However, the creation of electronic interfaces between the registry and EHRs is hampered by the lack of generally adopted standards for data definitions, structure, and exchange. In addition, the inability to create robust interfaces is exacerbated by the fact that clinicians use EHRs in an ad hoc manner that is inconsistent across practices. EHR data collection is subject to data accuracy issues, largely arising from data entry errors that are not readily identifiable, as there are very few mechanisms for data validation. Lastly, the EHR environment is constantly evolving, resulting in frequent modifications to how the data are captured. Effective interfaces between the registry and EHRs are needed to reduce duplication of provider effort.

Proposed Solution

The IC3 registry was developed with these technological challenges in mind. The registry uses a standard set of 153 defined data elements and a structured XML format developed to facilitate export from various EHR systems. To address the EHR implementation issue, the registry has implemented robust data quality processes to review the data.

Results

The integration of EHR data into the registry has proven enormously challenging due to both syntax and semantics issues. Because integration is not based on an open, adopted standard, each integration must be customized to the individual practice's EHR, and the amount of IT support at the practice varies significantly between sites. Data elements are also difficult to collect in a standard manner. For example, myocardial infarction may be defined differently within different vendors' EHRs, and sometimes even within EHRs from the same vendor. The IC3 Registry took the approach of working directly with EHR vendors to certify that certain EHRs collect the registry data elements consistently according to registry definitions. Four EHRs are currently certified, meaning that they have embedded the prescribed data elements and definitions into their EHR. Unfortunately, this involves both custom effort by the EHR and inability to easily update the data dictionary.

The next issue involved transporting the data from the EHR to the registry. The registry tried using the continuity of care record (CCR) format, but found that this format is too often customized to meet the individual practices' needs. Currently, the registry is working with a third party company that provides data transfer services to physicians who wish to move from one EHR to another. This company has provided a data mapping technology that the registry can use to map data from an EHR to the registry.

Even when the data have been successfully mapped and transferred to the registry, there may still be issues with using the data in performance measures if the data are not from a certified EHR. Data from certified EHRs are still questionable, as it is difficult to assess whether changes made in the EHR were appropriately communicated to physicians, and whether physicians changed their documentation as a result. For example, an EHR may modify its definition of atrial fibrillation to conform to IC3 standards. But, if the physicians do not change how they record the data, the data will still be inconsistent with the registry definitions. Data validation is difficult in these cases because there is no source documentation. Traditional methods of data validation are not feasible here, and there are few alternatives currently available.

These challenges demonstrate the need for generally adopted, open standards to facilitate both data consistency and validation, and interchange between EHRs and registries. At the time of this case study, such standards were not broadly adopted in the EHR community.

Key Point

Effective integration of registries and EHRs requires standards for data definitions, structure, and exchange. These standards are critical for integration to become a viable method of reducing duplicate data entry.

For More Information

https://www.improvingcardiaccare.org

Case Example 34: Creating a registry interface to incorporate data from multiple EHRs

Description:	The MaineHealth Clinical Improvement Registry (CIR) is a secure, web-based database system that provides a tool for primary care physicians in the outpatient setting to consolidate and track key clinical information for preventative health measures and patients with common chronic illnesses.
Sponsor:	The project is the result of a collaboration between Maine Medical Center (MMC) Physician-Hospital Organization, MaineHealth, and MMC Information Services.
Year Started:	2003
Year Ended:	Ongoing
No. of Sites	106 primary care practices (450 providers)
No. of Patients:	Over 200,000

Challenge

A physician-hospital organization (PHO) developed a web-based patient registry to improve quality of care and track patient outcomes across a large network of physicians. Many practices in the network used

electronic health records (EHRs) and did not have sufficient staff to enter patient data a second time into a registry. In addition, the practices used a wide range of EHRs, and each had unique technical specifications. The registry needed a technical integration solution to reduce the data entry burden on practices that used EHRs, but, due to resource limitations, it could not develop customized interfaces for each of the many different EHRs in use.

Proposed Solution

The registry elected to allow practices to submit data from their EHRs to the registry, in a one-way data transfer. An interface was written against an XML specification. Practices wishing to participate in the registry without doing direct data entry must be able to export their data in a file that conforms to this specification (although HL7 files are accepted when necessary). Data transfers occur on a schedule determined by each site – some send their data in real time, while others send on a monthly basis.

Once data files are received by the registry, registry staff members review each portion of the data (demographics, vaccinations, office visits, etc.) before signing off on the file and incorporating the data into the registry. Extensive error checking and validation are completed during the initial specification phase to minimize the amount of manual data checking needed during each transfer. The validation phase involves both technical staff and quality improvement staff at the practices to ensure that the data are transferred and mapped correctly into the registry database.

Results

Of the 106 primary care practices participating in the registry, about 60 percent enter data directly into the registry, and about 40 percent contribute data via XML transfer. The organization and management of this initiative has required strong internal support from the registry and from participating practices. Management teams and technical resources were needed during the startup phase and continue to be essential as more practices contribute data via XML transfer.

Key Point

Technical interface solutions between registries and EHRs can be successful, but require a robust organizational commitment from the registry sponsor and participating sites to provide the necessary resources during the set-up and launch phases.

For More Information

http://www.mmcpho.org/technology/mainehealth_clinical_improvement_registry_cir/

Case Example 35: Technical and security issues of creating a health information exchange

Description:	The Oakland Southfield Physicians Quality Registry is a practice-based registry designed to promote health outcomes and office efficiencies, and to identify early interventions and best practices in primary care practices. The registry integrates and exchanges health information from many sources through the Oakland Southfield Physicians Health Information Exchange (OSPHIE).
Sponsor:	Oakland Southfield Physicians
Year Started:	2006

Year Ended:	Ongoing
No. of Sites	150 practices
No. of Patients:	Network covers over 250,000 patients

Challenge

In 2006, the practice association launched a registry to improve quality of care in its primary care practices. However, the association quickly realized that it needed to integrate and exchange health information with multiple sources, such as payer claims, pharmacy claims, practice management systems, laboratory databases, and other registry systems, on behalf of over 150 primary care practices.

Proposed Solution

To support this requirement, the practice association constructed a health information exchange (HIE). The HIE is a data warehouse made up of multiple data sources that facilitate the collaborative exchange of health information with a network of trading partners and then integrates the patient disease registry data with a wide range of supplemental clinical information. The HIE allows the registry to securely exchange data with trading partners (i.e., third party payers, laboratories, hospitals, registry systems, etc.) via a variety of methods and in a variety of structures. By pushing information both to the registry system and other systems, the HIE eliminates duplicate data entry in two or more systems. Data transfers occur at established intervals, based on record updates or availability of information.

A key aspect of the system is the master patient and physician index, which allows data from various sources to be linked to the proper patient. Prior to import, data received in the registry is validated against a master patient and physician index for accuracy.

Results

Through data sharing with the OSP registry, the team has been able to facilitate the alignment of multiple data sources, with evidence based care guidelines available at point of care – a value partnership striving to improve health outcomes as well as the efficient access to key health care data points. This solution is reliant on building trust between trading partners in support of both the secure transfer of information and recommended use.

The HIE has successfully incorporated data from practice management systems, laboratory providers, an e-prescribing system, a registry system, and third party payers (medical and pharmacy claims detail). Relevant data is currently transmitting in a real-time capacity from the HIE to both the registry system and e-prescribing system on behalf of the participating physicians. The data warehouse also generates monthly 'gaps-in-care reports' for physician clinical quality review and patient outreach.

Key Point

An HIE may be a useful tool for integrating and exchanging data between registries and other systems. When integrating data from many sources, a master patient and physician index can be a critically important tool for ensuring that the incoming data are linked to the appropriate patient.

For More Information

http://www.ospdocs.com/OSP+Advantage/Clinical+Quality+Registry-21.html

Case Example 36: Developing a new model for gathering and reporting adverse events

Description:	The "Adverse Drug Event Spontaneous Triggered Event Reporting" (ASTER) study uses a new approach for gathering and reporting spontaneous adverse drug events (AEs). The study was developed as a proof of concept for the model of using data from electronic health records to generate automated safety reports, replacing the current system of manual AE reporting. The goals are to reduce the burden of reporting and provide timely reporting of AEs to regulators.
Sponsor:	Brigham and Women's Hospital, Partners Healthcare, CDISC, CRIX International, and Pfizer Inc.
Year Started:	Pilot launched in 2008
Year Ended:	Ongoing
No. of Sites	N/A
No. of Patients:	N/A

Challenge

Health care data is rapidly being translated into electronic formats, but, to date, safety reporting has not taken full advantage of these electronic data sources. The spontaneous adverse event reporting system, which relies on reports submitted manually by health care professionals, is still the primary source of data on potential adverse events (AEs). However, the availability of large amounts of data in electronic formats presents the opportunity to rethink the spontaneous adverse event reporting system. A new model could take advantage of the increasing availability of electronic data and improving technology to automate the process of gathering and reporting adverse events (AEs). The goals of automated AE reporting are to reduce the burden of reporting on physicians, improve the frequency with which AEs are reported, and increase the timeliness and quality of AE reports.

An automated model, however, must overcome many challenges. The system must be scalable, must incorporate data from many sources, and must be flexible enough to adapt to the needs of many diverse groups. The model must address point of care issues (such as burden of reporting), data exchange standards (so that the data are interpretable and valid), and processes for reviewing for the AE reports.

Proposed Solution

The Adverse Drug Event Spontaneous Triggered Event Reporting" (ASTER) study attempts to address these challenges and demonstrate the potential viability of an automated model for facilitating the gathering and reporting of AEs. ASTER allows data to be transferred from an electronic health record (EHR) to an adverse event case report form and submitted directly to the Food and Drug Administration (FDA) in the format of an individual case safety report (ICSR).

The process of gathering and reporting AEs through ASTER involves four steps based on the open standard "Retrieve Form for Data Capture (RFD)":

1. A physician indicates in the EHR that a drug was discontinued due to an AE.
2. The system immediately generates a pre-populated AE report form. The physician sees the form in the EHR.
3. The physician enters a small amount of additional data to complete the AE report form.
4. The form is then processed by a third party forms manager, who sends it to the FDA as a reported spontaneous adverse event from the physician, in a standard format.

Results

The pilot phase of ASTER began in 2008. The goal of this phase was to demonstrate proof of concept for the new model. Specifically, it was hypothesized that 1) if an EHR could help a clinician identify potential adverse events and, 2) if the burden of completion of an adverse event form were significantly reduced, then the rate of reporting of spontaneous adverse events to the FDA could be significantly increased. ASTER recruited 26 physicians, 91% of whom had not reported an adverse event to the FDA in the prior year. Following implementation, over 200 events were reported over a period of 3 months.

There are still many questions that need to be answered before the ASTER model could become more widely used in the United States. For example, initial findings from ASTER suggest that an increased number of events are reporting using this model; this creates a need for the receiver of the reports (e.g., the FDA) to have sufficient capacity to respond to the reports. Also, the fields that are captured in the ASTER model are based on the paper form fields. Moving to a truly digital system may require a change in the data collected to better align with the way data are collected in electronic formats.

Key Point

New models for gathering and reporting AEs may be able to leverage electronic health data and emerging technologies to both improve the timeliness of reporting and reduce the burden of reporting on health care professionals.

For More Information

http://www.asterstudy.com

Rockoff, Jonathan D. "Pfizer Project Looks at Side Effects." The Wall Street Journal. January 2, 2009.

Chapter 12: Adverse Event Detection, Processing, and Reporting

Registries that collect information on specific drugs and medical devices need to anticipate the need for adverse event detection, processing, and reporting. Figure 5 provides a broad overview of the reporting requirements for AEs and shows how the reporting differs according to whether the registry has direct patient interaction, whether the product under study is a drug or medical device, and whether the registry receives sponsorship and/or financial support from a "regulated industry."[494] These industries may include entities with products subject to FDA regulation, including products with FDA approval, an FDA granted license, and investigational products, and others, such as manufacturers, user facilities, and distributors.

The U.S. Food and Drug Administration (FDA) defines an adverse drug experience as any adverse event (AE) associated with the use of a drug in humans, whether or not considered drug related,[495] while the International Conference on Harmonisation guideline ICH E2A similarly defines an AE as an untoward medical occurrence in a patient administered a pharmaceutical product, whether or not related or considered to have a causal relationship with the treatment.[496]

For marketed products regulated by the FDA, AEs are categorized for reporting purposes according to the seriousness and expectedness (i.e., previously observed and included in local product labeling) of the event, as it is presumed that all spontaneously reported events are potentially related to the product for the purposes of FDA reporting. Prior to marketing approval, "relatedness" is an additional determinant of reportability for events occurring during clinical trials or preclinical studies associated with investigational new drugs and biologics. For AEs occurring during post-approval studies and reported during planned contacts and active solicitation of information from patients, such as registries collecting data regarding one or more FDA-approved products,[497,498] the requirements for mandatory reporting also include whether or not there is a reasonable possibility that the drug caused the adverse experience.[499] For registries that do not actively solicit AEs, incidentally reported events (e.g., those reported during clinician or consumer contact for another purpose) should be handled and evaluated as spontaneously reported events.

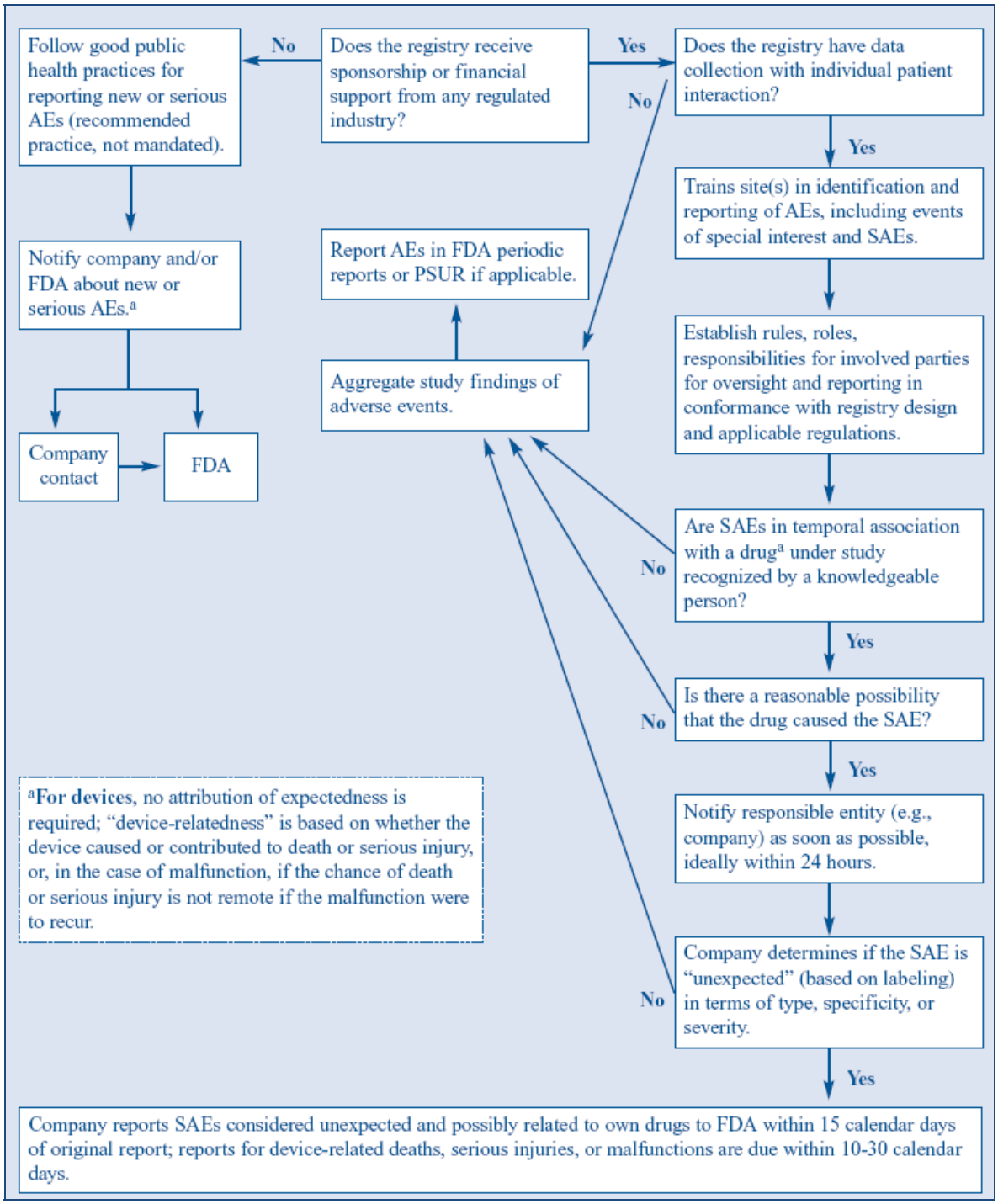
The medical device reporting (MDR) regulations differ from those for drugs and biologics, in that reportable events include both AEs and problems with the device itself.[500] MDR reporting is required for incidents in which the device may have caused or contributed to a death or serious injury, or may have malfunctioned, and would likely cause or contribute to death or serious injury if the malfunction were to recur.[501,502]

Most registries have the opportunity to identify and capture information on AEs for biopharmaceutical products and/or medical devices. With the passing of the FDA Amendments Act (FDAAA) in September 2007 and the increased emphasis on monitoring of ongoing safety profiles, evaluation of risks unknown at the time of product approval, and proactive detection of potential safety issues, registries increasingly continue to be used to fulfill safety-related objectives.[503] Although there are no regulations in the United States that specifically require registries to capture and process AE reports (aside from reporting requirements for registries that are sponsored by regulated industries), there is an implicit requirement from the perspective of systematic data collection and promoting public health: any individual who

believes a serious risk may be associated with exposure to a medical product should be encouraged to report that AE either to the product sponsor or directly to the FDA through the MedWatch system.

The minimum dataset required to consider information as a reportable AE is indeed minimal, namely (1) an identifiable patient, (2) an identifiable reporter, (3) an event, and (4) product exposure. However, in addition to direct data collection, AEs can be detected through retrospective analysis of a population database where direct patient or healthcare provider contact does not occur. Patient interactions may include clinical interactions or data collection by phone, Internet, or other means; perusal of electronic medical records or insurance claims data would not be considered direct patient interactions. Reporting is rarely required for individual AEs observed in aggregate population data, since there is no direct patient interaction where an association might be suggested or inferred. Nevertheless, if aggregate or epidemiologic analyses suggest an AE is associated with exposure to a drug or medical product, it is desirable that this information be forwarded to the manufacturer of that product, who will determine any need for, and timing of, reporting of study results to the relevant regulatory authorities. Figure 5 provides a broad overview of the reporting requirements for AEs and shows how the reporting differs according to whether the registry has direct patient interaction, and whether it receives sponsorship and/or financial support from a "regulated industry."[504] These industries may include entities with products subject to FDA regulation, including products with FDA approval, an FDA granted license, and investigational products, and others, such as manufacturers, user facilities, and distributors.

Figure 5. Best Practices for Adverse Event Reporting to FDA in Registries of Postmarket Products



This chapter addresses the identification, processing, and reporting of AEs that are detected in situations in which a registry has individual patient contact. This document is not a formal regulatory or legal document; therefore, any information or suggestions presented herein do not supersede, replace, or otherwise interpret federal guidance documents that touch on these subjects. Registry sponsors are

encouraged to discuss plans for AE collection and processing with local health authorities when planning a registry.

Medical devices are significantly different from pharmaceuticals in the manner in which AEs and product problems (complaints) present themselves, in the etiology of their occurrence, and in the regulation governing defining, and reporting of these occurrences, as well as post-approval study requirements. This chapter is focused on AEs related to pharmaceutical products. Other sources provide more information about defining and reporting of device-related AEs and product problems and about post-marketing studies (including those involving registries).[505,506,507]

AE Detection and Recording by the Registry

All AE reporting begins with a suspicion by the physician (or responsible person who obtains or receives information) that a patient exposed to a medicinal product experienced some adverse event and that the event has a reasonable possibility of being causally related to the product being used; this is referred to as the "becoming aware" principle. It is important to develop a plan for detecting, processing, and reporting AEs for any registry that has direct patient contact. If the registry receives sponsorship in whole or part from a regulated industry (for drugs or devices), then the sponsor has mandated reporting requirements, including stringent timelines. (See AE reporting requirements for registry sponsors later in this chapter.)

The process for detecting and reporting AEs should be established in collaboration with the sponsor and any oversight committees. (See Chapter 2.) Once the plans have been developed, sites should be trained on how to identify AEs and to whom they should be reported. AE reporting is based on categorization of the adverse event according to the seriousness of the event, expectedness of the event based on labeling, and presumed causality or possible association with use of the product, as follows:

- *Seriousness:* Serious AEs (SAEs) include events that result in death, are life threatening (an event in which the patient was at risk of death at the time of the event), require or prolong inpatient hospitalization, result in persistent or significant disability or incapacity, or result in a congenital anomaly. Important medical events may also be considered serious when, based on medical judgment, they may jeopardize the person exposed and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., death, prolonged hospitalization).

- *Expectedness:* All AEs that are previously unobserved or undocumented are referred to as "unexpected," in that the nature and severity are not consistent with information provided in the relevant product information (e.g., approved professional package insert or product label). Determination of expectedness is made on a case-by-case basis by the sponsor. Expected events typically do not require expedited reporting to the regulatory authorities.

- *Relatedness:* Relatedness is intended to indicate that an evaluation has been made in which it was determined that the event had a reasonable possibility of being related to exposure to the product. This assessment of causality is based on factors such as biological plausibility, prior experience with the product, and temporal relationship between product exposure and onset of the event, as well as de-challenge (discontinuation of product to determine if the adverse event resolves) and rechallenge (re-introduction of the product to determine if the adverse event reoccurs). Many terms and scales are used to describe the degree of causality, including terms such as "certainly,"

"definitely," "probably," "possibly," or "likely" related or not related, but there is no standard nomenclature.[508]

AE reports for a pharmaceutical or biological product should provide information about the four basic elements of an AE report: (1) an identifiable patient, (2) an identifiable reporter, (3) a suspect drug or biological product, and (4) an adverse event or fatal outcome. Typically, forms such as a questionnaire or an AE case report form may be used to collect information regarding an AE. When solicitation of specific AEs is not pre-specified, it is good practice, although not required, to permit AE detection by asking general questions, such as "Have you had any problems since your last visit or since we last spoke?" and then following up any such reports with probes as to what happened, diagnoses, and other documentation.

Collecting AE Data in a Registry

There are two key considerations regarding AE collection as part of a registry: (1) what data need to be collected to meet the registry's safety-related objectives and (2) what processes need to be in place to ensure that the registry is in compliance with regulations regarding expedited and periodic adverse event reporting, if applicable. The data fields needed for registry analysis purposes may be minimal (e.g., event and onset date), whereas a complete SAE form for a subset of events reported to the registry may be required to fulfill sponsor reporting requirements. Due to the nature of registries, the balance of collecting enough data to meet registry objectives must constantly be balanced with limiting the burden on sites. To this end, the processes for AE reporting should be streamlined as much as possible, but not at the risk of non-compliance.

The collection of AE data by a registry is generally either intentionally solicited (meaning that the data are part of the uniform collection of information in the registry), or unsolicited (meaning that the AE information is volunteered or noted in an unsolicited manner and not as a required data element through a case report form). As described further below, it is good practice for a registry to specify when and how AE information, and any other events of special interest, should and should not be solicited from patients by physicians or other responsible parties (referred to as "sites" hereafter) and, if that information has been obtained, how and when the site should inform the appropriate persons.

While an AE may be reported to the manufacturer, FDA (via MedWatch), or the registry itself (and then from the registry to the manufacturer), it is strongly encouraged that the protocol document the procedures that should be followed and that the sites be trained in these procedures, as well as general obligations and public health considerations. A separate safety reporting plan may also be considered that fully describes the responsible parties and the operational considerations for ensuring that potentially reportable information is evaluated in an appropriate time frame, and, for manufacturer-sponsored registries, in accordance with any applicable standard operating procedures. This type of plan should also describe how deviations or systemic failures in detection and reporting processes will be identified, addressed, and considered for corrective action.

Determining whether the registry should use the case report form to collect AEs should be based on the principles described in Chapter 5, which refer to the scientific importance of the information for evaluating the specified outcomes of interest. This may mean that all, some, or no adverse events are collected on the case report forms. However, if some AEs are collected in an intentional solicited manner (such as routine collection of a primary or secondary outcome via an AE case report form), and others

come to attention in an unsolicited, "spontaneous" way (e.g., reporting an AE in the course of registry contact, such as a call to the sponsor or registry support staff), then from a practical perspective it is even more important to have a clear process so that sites are not confused and AEs that require reporting are identified. In this scenario, one best practice that has been introduced in electronic registry studies is to have a notification sent promptly to the sponsor's safety group when a case report form is submitted that contains specific or potential information indicating that a serious AE has occurred. This process allows for rapid followup by the sponsor, as needed.

AE Reporting by the Registry

Once suspicion has been aroused that an unexpected serious event has a reasonable possibility of being causally related to a drug, the AE should be reported to FDA through MedWatch, to the company that manufactures the product, or to the registry-coordinating center. A system needs to be developed such that all appropriate events are captured and duplicate reporting is avoided to the extent possible. Generally, AE reports are submitted directly to the manufacturer, since they are often most efficient at evaluating, processing, and reporting for regulatory purposes within the required time periods. Alternatively, sites could be instructed to report AEs directly to FDA, according to their normal practices for marketed products; however, this often means companies are not notified of the AE and are not able to followup or evaluate the event in the context of their safety database. In fact, companies are not necessarily notified by the FDA if an AE report comes directly to FDA, since only certain reports are shared with industry, and reporters have an option to request that the information not be shared directly with the company.[509] When sites report AEs directly to FDA, this process can also risk inadvertent duplication of information for events recorded both by the registry and the company.

Ideally, the practice for handling AEs and serious adverse events (SAEs) should be applied to all treatments (including comparators) recorded in the registry, so that all subjects are treated similarly. Systematic collection of all AEs provides a unique resource of consistent and contemporaneously collected comparison information that can be used at a later date to conduct epidemiologic assessments. In fact, a strong advantage of registries with systematic data collection and internal comparators is that they provide both numerators and denominators for safety events; thus, reporting of known AE rates in the context of a safety evaluation provides useful information on real-world performance. The contrast with comparators helps to promote clarity about whether the observed effects are unique to the product, to a class, or are common to the condition being treated. Reporting AEs without denominator information is less useful from a surveillance perspective. The reliability of the denominator should always be judged, however, by considering the likelihood that all events were reported appropriately.

For post-approval registries that are not financially supported by pharmaceutical companies, health care providers at registry sites should be instructed that if they suspect, or otherwise become aware of a serious AE that has a reasonable possibility of being causally related to a drug or product, they should report the event directly to the product manufacturer (who must then report to FDA under regulation) or to FDA's MedWatch program (or local health authority if the study is conducted outside of the United States). Reporting can be facilitated by providing the MedWatch Form 3500,[510] as well as information regarding the process for submission, and MedWatch contact information.

For registries that are sponsored or financially supported in full or part by a regulated industry, and that study a single product, the most efficient monitoring system is one in which all physicians participating in

the registry report all AEs (or SAEs only) directly to the sponsor or centralized designated responsible personnel, who then reports to the regulatory authorities, in order to avoid duplicate reporting. However, when products other than those exclusively manufactured by the sponsor are involved, sponsors will need to determine how to process AE reports that are received for comparator products. Sponsors are not generally obligated to report AEs for their competitors, but from a public health perspective, specifying how the site should address those AEs (e.g., report directly to the comparator product's manufacturer or to FDA) is good practice. Options for the sponsor include (1) recommending that the AEs of comparators be reported directly to the manufacturer or to FDA; (2) collecting all AEs and forwarding the AE report directly to the comparator's manufacturer (who would then, in turn, report to FDA); and (3) actually reporting the AE for the comparator product directly to FDA. Many sponsors, as standard practice in pharmacovigilance, report events potentially associated with another manufacturer's drug to that manufacturer's safety department as a courtesy, rather than report events directly to the FDA, and choose to continue that practice when conducting a registry or other observational study.

Some disease registries do not involve a specific product, such as natural history studies or registries evaluating treatment patterns and outcomes in a particular patient population prior to marketing approval of the sponsor's product. It is recommended in this situation that sites be instructed to follow their own standard practices for spontaneous adverse event reporting, including reporting any events associated with a product known to be manufactured by the sponsor.

In most circumstances where a serious drug-associated AE is suspected, sites are encouraged to submit to sponsors supportive data, such as lab values, vital signs, and examinations, along with the SAE report form. If determined to be an AE, the sponsor will include the event in the safety database, internally evaluate the event, and transfer the adverse event report to the regulatory authorities, if required. It should be noted that the regulations represent minimum requirements for compliance; in some cases special circumstances for a particular product may result in additional events being reportable (e.g., expected events of particular interest to regulators). It should not be expected that registry participants be aware of all the reporting nuances associated with a particular product. To the extent possible, guidance on reporting events of special interest should be provided in the protocol and in safety training, if performed.

Serious AEs that are potentially related to drug exposure should be submitted to the sponsors as quickly as possible after becoming aware of the event so that the sponsor may, in turn, comply with 15-calendar-day reporting requirements as needed. This submission can be accomplished by phone or fax, or by means of automated rules built into the vehicle used for data collection (such as automatic triggers that can be designed into electronic data capture programs). For direct regulatory submissions, the MedWatch Form 3500A[511] should be used for post-approval reporting for drugs and therapeutic biologics; for vaccines, consult the Vaccine Adverse Event Reporting System (VAERS).[512] Foreign events may be submitted on a CIOMS form (the World Health Organization's Council for International Organizations of Medical Sciences),[513,514,515] or a letter can be generated that includes the relevant information in narrative format.

Coding

Coding AEs into a standard nomenclature should be done by trained experts to assure accuracy and consistency. Reporters, patients, health care providers, and registry personnel should do their best to

capture the primary data clearly, completely, and in as "natural" clinical language as possible. Since reporters may use different verbatim terms to describe the same event, it is recommended that sponsors apply coding conventions to code the verbatim terms. The Medical Dictionary for Regulatory Activities (MedDRA®) is customarily used throughout the product development cycle and as part of Pharmacovigilance; however, other coding systems are also used. For example, SNO-MED is used instead of MedDRA in some electronic health records. Coding the different verbatim language to preferred terms allows similar events to be appropriately grouped. This also creates consistency among the terms for evaluation and maximizes the likelihood that safety signals will be detected.

Sponsors should review the accuracy of the coding of verbatim AEs into appropriate terms. If coding is performed by someone other than the sponsor, any applicable coding conventions associated with the underlying condition or product should be shared. Review of the coding process should focus on the use of terms that do not accurately communicate the severity or magnitude of the AE or possibly mischaracterize the AE. Review of the coded terms compared with reported verbatim terms should be performed in order to ensure consistency and accuracy of the AE reporting and to minimize variability of coding of similar adverse event terms. Attention to consistency is especially important, as many different individuals may code AEs over time and this contributes to variability in the coding process. In addition to monitoring AEs individually for complete clinical evaluation of the safety data, sponsors should consider grouping and analyzing clinically relevant coded terms that could represent similar toxicities or syndromes. Combining terms may provide a method to detect less common and serious events that would otherwise be obscured. However, sponsors should be careful when combining related terms to avoid amplifying a weak signal or obscuring important overall findings. In addition to monitoring individual AEs, sites and registry personnel should be attentive to toxicities that may cluster into syndromes.

AE Management

In some cases, such as a safety registry created as a condition of approval, a Data Safety Monitoring Board (DSMB), Data Monitoring Committee (DMC), or Adjudication Committee may be established with the primary role of periodically reviewing the data as they are generated by the registry. Such activities are generally discussed directly with the regulatory authorities, such as FDA. These authorities are typically involved in the design and critique of protocols for post-approval studies. Ultimately, registry planning and the registry protocol should anticipate and clearly delineate the roles, responsibilities, process, forms, and lines of communication about AE reporting for sites; registry personnel; the DSMB or Adjudication Committee, if one exists; and the sponsoring organization. Definitions and approaches should be documented for determining what is considered unexpected and possibly related to drug or device exposure. Management of AE reporting should be clearly stated in the registry protocol, including the roles, responsibilities, processes, and methods for handling AE reports by the various parties conducting the registry, and responsibilities to perform followup activities with the site to ensure that complete information is obtained. Sponsors who are stakeholders in a registry should have a representative of their internal drug safety or pharmacovigilance group participate in the design and review of the registry protocol and have a role in the data collection and reporting process (discussed in Chapter 2) to facilitate appropriate and timely reporting and communication.

For post-approval studies financially sponsored by manufacturers, the overall company AE monitoring systems are usually operated by personnel experienced in drug safety (also known as pharmacovigilance, regulatory safety, product safety, and safety and risk management). If sites need to report or discuss an

AE, they can call the contact number provided for the registry and are then prompted to press a number if reporting an AE. This number then transfers them to drug safety surveillance so they can interact directly with personnel in this division and bypass the registry-coordinating group. These calls may or may not be tracked by the registry. Alternatively, the registry system can provide instructions to the site on how to report AEs directly to the sponsor's drug safety surveillance division. Through this method, the sponsor provides a separate contact number for AE reporting (independent of the registry support staff), which places the site in direct contact with drug safety personnel. This process minimizes the possibility of duplicate AE reports and the potentially complicated reconciliation of two different systems collecting AE information. Use of this process is critical when dealing with products that are available via a registry system, as well as outside of a registry system, and it allows sites to have one designated drug safety representative for interaction.

Sponsors are strongly encouraged to hold discussions with the regulatory authorities when considering the design of the AE monitoring system for a registry that is designed specifically for surveillance of product safety. These discussions should be focused on the purpose of the registry, the "best fit" model for AE monitoring, and the timing of routine registry updates. With respect to internal operations chosen by the sponsor to support the requirements of an AE monitoring system, anecdotal feedback suggests that health authorities expect compliance with the agreed-upon requirements. Details regarding the implementation are the responsibility of the sponsor.

It should also be noted that the FDA's Proposed Rule for Safety Reporting Requirements for Human Drug and Biologics Products (68 FR 12406, 14 March 2003) suggests that the responsible point of contact for the FDA should be provided for all expedited and periodic AE reports, and preferably, this individual should be a licensed physician. Although this proposed rule has never been finalized, the principle is similar to the Qualified Person for Pharmacovigilance (QPPV) in Europe, whereby a specific, qualified individual is identified to provide responses to health authorities, upon request, including those regarding AEs reported via the registry system.

AE Required Reporting for Registry Sponsors

Understanding the reporting requirements of the sponsor directly affects how registries collect and report AEs. Sponsors that are regulated industries are subject to the requirements shown in Table 17. ICH guidelines describe standards for expedited reporting[516,517] and provide recommendations for periodic safety update reports[518] that are generally accepted globally.

Table 17. Overview of Serious Adverse Event Reporting Requirements for Marketed Products

Note: International Conference on Harmonisation (ICH) guidances describe standards for expedited reporting[279,280] and provide recommendations for periodic safety update reports[281] that are generally accepted globally.

Type of Requirement	Drugs and Biologics	Devices
U.S. post-marketing regulations	Primary: 21 CFR 314.80 (drugs), 21 CFR 600.80 (biologics) Other: 21 CFR 310.305, 21 CFR 314.98	21 CFR 803.20
Required reporting source	Regulated industries	Manufacturer, importer, user facility
Required reports	Serious, unexpected, and with a reasonable	Death or serious injury; device

Type of Requirement	Drugs and Biologics	Devices
	possibility of being related to drug exposure (some exceptions apply)	malfunction
Alternative reports	Not applicable	Summary reports (periodic line-listing of reports of well-known events)
Timeframe for reporting	15 calendar days for expedited reports	5 work days, 10 work days or 30 calendar days, depending on source and action required
Reporting form	MedWatch 3500A (for mandatory reporting required of a regulated industry) MedWatch 3500 (for voluntary reporting by healthcare professionals, consumers and patients)	
Web sites	www.fda.gov/medwatch	www.fda.gov/cdrh/mdr

Requirements for regulated industries that sponsor or financially support a registry include expedited reporting of serious and unexpected AEs made known to them via spontaneous reports. For studies such as registries, the 15-calendar-day notification applies if the regulated industry believes there is a reasonable possibility that the unexpected SAE was causally related to product exposure. Best practices for international reporting are that all "affiliates" of a sponsor report serious, unexpected, and possibly related events to the sponsor in a timely fashion, ideally within 2 calendar days; this allows the sponsor, in turn, to complete notification to the responsible regulatory authority within a total of 15 calendar days. Events that do not meet the requirements of expedited reporting (such as nonserious events or serious events considered expected or not related) may require submission through inclusion in an appropriate safety update, such as the New Drug Application (NDA) or Biologic Licensing Application (BLA) Annual Report, Periodic Report, or Periodic Safety Update Report (PSUR), as applicable.[519] In many cases, sponsors are also required to provide registry safety updates to the health authority. Thus, sponsors may coordinate registry safety updates (i.e., determining the date for creating the data set [data cut off dates]) with the timing of the NDA Annual Report, Periodic Report, PSUR, or other agreed-upon periodic reporting format. Devices, however, have different reporting requirements (see www.fda.gov/cdrh/mdr) . In any event, sponsors should discuss safety reporting requirements for their specific registries with the applicable health authorities (such as FDA and European Medicines Agency [EMEA]) before finalizing their registry protocol.

In some cases, a registry sponsor may encourage the site to systematically report all potential SAEs to the sponsor. Given the potential for various interpretations by different sites in assessing the seriousness and relatedness of a particular AE—and therefore, inconsistency across sites in the evaluation of a particular adverse event—this method has certain advantages. In addition, expectedness is not always a straightforward assessment, and serious events can have significant variability depending on the local approved product labeling. For this reason, it is important that this determination be made by the sponsor and not the reporter of the event. Although this approach may result in substantially greater demands on the sponsor to evaluate all reports, it helps to ensure compliance and to avoid, to the extent possible, a source of underreporting. Furthermore, sponsors must make their own assessment regarding the causality of individual events, and U.S. and international regulations differ as to whether the reporter or the sponsor

prevails when there is a disagreement about causality. For these reasons, planning for high-quality and consistent training in AE reporting requirements across sites is the preferred approach for a patient registry.

Regardless of who assesses presumed relatedness, sponsors should be prepared to manage the increased volume of AE reports, and sponsor registry staff should be trained to understand company policy and regulations on AE reporting in order to ensure compliance with local regulations. This training includes the ability to identify and evaluate the attributes of each adverse event and determine the reportability status to the health authority in keeping with local regulation. Sponsors are encouraged to appoint a health care practitioner to this role in order to ensure appropriate assessment of the characteristics of an AE.

When biopharmaceutical or device companies are not sponsoring, financially supporting, or participating in a registry in any way, AE reporting is dependent upon the "become aware" principle. If any agent or employee of the company receives information regarding an AE report, the agent or employee must document receipt and comply with internal company policy and regulatory requirements regarding AE reporting, to assure compliance with applicable drug and device regulations.

Special Case: Risk Evaluation and Mitigation Strategies (REMS)

Under FDAAA (2007), the FDA established an enforceable new framework for risk management of products with known safety concerns, called Risk Evaluation and Mitigation Strategies (REMS).[520] These programs can be imposed during clinical development, as part of the approval process, or at any time post-approval, should a new safety signal be identified. Although each REMS is customized depending on the product and associated issues, typical components include marketing or labeling restrictions, post-approval study commitments, targeted education and outreach for physicians, pharmacists and patients, and in some cases, a performance-linked access system (PLAS), also known as a restricted access or limited distribution system. A PLAS can be described as a special application of a registry. Unlike the less structured disease or exposure registries discussed above, a PLAS is designed to ensure the safe use of an approved product that has a particular risk-benefit profile that requires more careful controls. The purpose of a PLAS is to mitigate a certain known drug-associated risk by ensuring that product access is tightly linked to some preventive and/or monitoring measure. Examples include systems that monitor laboratory values, such as white blood cell counts during clozapine administration to prevent severe leukopenia or routine pregnancy testing during thalidomide administration to prevent in utero exposure of this known teratogenic compound. Although different in the structured nature of their protocols, both PLAS and other registries collect a battery of information using standardized instruments in a prospective manner.

A PLAS may carry special AE reporting requirements, and as a result of the extensive contact with a variety of potential sources of safety information (i.e., pharmacists, patients), care should be taken to identify all possible routes of reporting. If special requirements do exist, they should be made explicit in the registry protocol, with clear definitions of roles, responsibilities, and processes. Training of involved health care providers, such as physicians, nurses, and pharmacists, can be undertaken with written instructions or via telephone and/or face-to-face counseling. Training of these health care providers should also extend beyond AE reporting to the specific requirements of the program in question. Such training may include the intended use and associated risk of the product, appropriate patient enrollment,

and specific patient monitoring requirements, including guidelines for product discontinuation and management of AEs, as well as topics to cover during comprehensive counseling of patients. The objectives of the PLAS system and overall REMS should be clearly stated (e.g., prevention of in utero exposure during therapy via routine pregnancy testing), and registration forms that document the physician's and pharmacist's attestation of their commitment to requirements of the patient registry system that should be completed prior to prescribing or dispensing the product.

Chapter 13: Analysis and Interpretation of Registry Data to Evaluate Outcomes

Registries have the potential to produce databases that are an important source of information regarding health care patterns, decisionmaking, and delivery, and their subsequent association with patient outcomes. Registries, for example, can provide valuable insight into the safety and/or effectiveness of an intervention, or the efficiency, timeliness, quality, and patient-centeredness of a health care system. The utility and applicability of registry data rely heavily on the quality of the data analysis plan and the ability to interpret the results. Analysis and interpretation of registry data begin with a series of core questions:

- *Study purpose:* Were the objectives/hypotheses predefined or post hoc?
- *Patient population:* Who was studied?
- *Data quality:* How were the data collected, reviewed, and verified?
- *Data completeness:* How were missing data handled?
- *Data analysis:* How were the analyses chosen and performed?

While the scientific opportunities that may result from using data from a well-designed registry are clear, there are inherent challenges to making appropriate inferences. A principal concern with registries is that of making inferences without regard to the quality of data, since quality standards have not been previously well established or consistently reported. In some registries, comparison groups may be less robustly defined than in more formal observational designs (e.g., cohort, case-control studies). Information provided about the external validity of a registry sample is often limited, as well.

This chapter explains how analysis plans are constructed for registries, how they differ depending on their purpose, and how registry design and conduct can affect analysis and interpretation. The analytic techniques generally used for registry data are presented, addressing how conclusions may be drawn from the data and what caveats are appropriate. The chapter also describes how timelines for data analysis can be built in at registry inception and how to determine when the registry data are complete enough to begin analysis.

Hypotheses and Purposes of the Registry

While it may be relatively straightforward to develop hypotheses for registries intended to evaluate safety and effectiveness, not all registries have specific, testable, or simple hypotheses. Disease registries commonly have aims that are primarily descriptive, such as describing the typical clinical features of individuals with the disease, variations in phenotype, and the clinical progression of the disease over time (natural history). These registries play a particularly important role in the study of rare diseases.

In the case of registries where the aim is to study the association between specific exposure(s) and outcome(s), pre-specification of the study methodology and presence or absence of a priori hypotheses or research questions may affect the interpretation of registry data.

The many possible scenarios are well illustrated by examples at the theoretical extremes.

On one extreme, a study may evolve out of a clear and explicit pre-specified research question and hypothesis. In such a study, there may have been preliminary scientific work that laid the conceptual foundation and plausibility of the proposed study. The investigators fully articulate the objectives and analytic plan before embarking on any analysis. The outcome is clearly defined and the statistical approach documented. Secondary analyses are identified and may be highlighted as hypothesis generating. The investigators have no prior knowledge of analyses in this database that would bias them in the formulation of their study objective. The study is conducted and published regardless of the result. The paper states clearly that the objective and hypothesis were pre-specified. For registries that are intended to support national coverage determinations with data collection as a condition of coverage, the specific coverage decision question may be specified a priori as the research question, in lieu of a hypothesis.

On the other extreme, a study may evolve out of an unexpected observation in a database in the course of doing analyses for another purpose. A study could also evolve from a concerted effort to discover associations—for example, as part of a large effort to understand disease causation. In such a study, the foundation for the study is developed post hoc, or after making the observation. Because of the way in which the observation was found, the rationale for the study is developed retrospectively. The paper does not clearly state that the objective and hypothesis were not pre-specified.

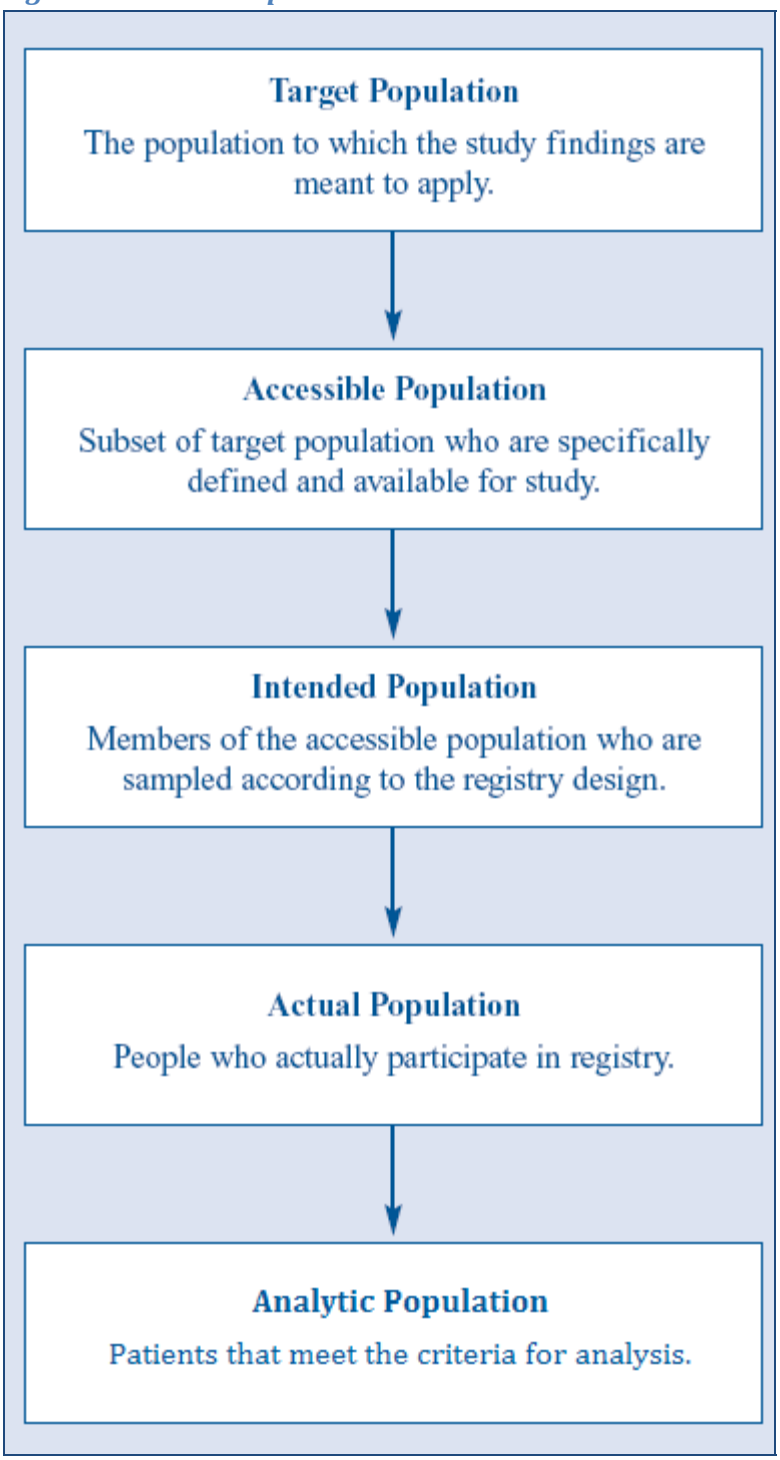
Of course, there are many examples that fall between these extremes. An investigator may suspect an association for many variables, but find the relationship for only one of them. The investigator decides to pursue only the positive finding and develop a rationale for a study or grant. The association was sought, but it was sought along with associations for many other variables and outcomes.

Thus, while there is substantial debate about the importance of pre-specified hypotheses,[521,522] there is general agreement that it is informative to reveal how the study was developed. Transparency in the methods is needed so that readers may know whether these studies are the result of hypotheses developed independently of the study database, or whether the question and analyses evolved from experience with the database and multiple iterations of exploratory analyses. Both types of studies have value.

Patient Population

The purpose of a registry is to provide information about a specific patient population to which all study results are meant to apply. To determine how well the study results apply to the target population, five populations, each of which is a subset of the preceding population, need to be considered, along with how well each population represents the preceding population. These five sub-populations are shown in Figure 6.

Figure 6. Patient Populations



The *target population* is defined by the study's purpose. To assess the appropriateness of the target population, one must ask the question, Is this really the population that we need to know about? For example, the target population for a registry of oral contraceptive users would include women of childbearing age who could become pregnant and are seeking to prevent pregnancy. Studies often miss important segments of the population in an effort to make the study population more homogeneous. For

example, it is less informative than desirable if a study to assess a medical device that is used to treat patients for cardiac arrhythmias defines only men as its target population, because the device is designed for use in both men and women.

The *accessible population* is defined using inclusion criteria and exclusion criteria. The inclusion criteria define the population that will be used for the study, and generally include geographic (e.g., hospitals or clinics in the New England region), demographic, disease-specific, and temporal (e.g., specification of the included dates of hospital or clinic admission), as well as other criteria. Conversely, the exclusion criteria seek to eliminate specific patients from study and may be driven by an effort to assure an adequate-sized population of interest for analysis. The same goals may be said of inclusion criteria, since it is difficult to separate inclusion from exclusion criteria (e.g., inclusion of adults aged 18 and over vs. exclusion of children under age 18).

The accessible population may lose representativeness to the extent that convenience plays a part in its determination, because people who are easy to enroll in the registry may differ in some critical respects from the population at large. Similarly, to the extent that homogeneity plays a part in determining the accessible population, it is less likely to be representative of the entire population because certain population subgroups will be excluded.

Factors to be considered in assessing the accessible population's representativeness of the target population include all the factors mentioned above that are used as inclusion and exclusion criteria. One method of evaluating representativeness is to describe the demographics and other key descriptors of the registry study population and to contrast its composition with patients with similar characteristics who are identified from an external database, such as might be obtained from health insurers, health maintenance organizations, and the Surveillance Epidemiology and End Results (SEER) cancer registries.

However, simple numerical/statistical representativeness is not the main issue. Representativeness should be evaluated in the context of the purpose of the study; that is, whether the study results can reasonably be generalized or extrapolated to other populations of interest outside of those included in the accessible population. (See Case Example 37.) For example, suppose that the purpose of the study is to assess the effectiveness of a drug in U.S. residents with diabetes. If the accessible population includes no children, then the study results very well may not apply to children, since children often metabolize drugs very differently than adults.

On the other hand, consider the possibility that the accessible population is generally drawn from a geographically isolated region, whereas the target population may be the entire United States or the world. In that case, the accessible population is not geographically representative of the target population, but that would have little or no impact on the representativeness of the study findings to the target population if the action of the drug (or its delivery) does not vary geographically (which we would generally expect to be the case, unless pertinent racial/genetic or dietary factors were involved). Therefore, in this example, the lack of geographical representativeness would not affect interpretation of results.

The reason for using an *intended population*, rather than using the whole accessible population for the study, is simply a matter of convenience and practicality. The issues to consider in assessing how well the intended population represents the accessible population are similar to those for assessing how well

the accessible population represents the target population. The main difference is that the intended population may be specified by a sampling scheme, which often tries to strike a balance among representativeness, convenience, and budget. If the intended population is a random sample of the accessible population, it may be reasonably assumed that it will represent the accessible population; however, for many, if not most, registries, a complete roster of the accessible population does not exist. More commonly, the intended population is compared with the accessible population in terms of pertinent variables.

On the other hand, to the extent that convenience or other design (e.g., stratified random sample) is used to choose the intended population, one must consider the extent to which the sampling of the accessible population—by means other than random sampling—has decreased the representativeness of the intended population. For example, suppose that, for the sake of convenience, only patients who attend clinic on Mondays are included in the study. If patients who attend clinic on Monday are similar in every relevant respect to other patients, that may not constitute a limitation. But if Monday patients are substantially different from patients who attend clinic on other days of the week (e.g., well-baby clinics are held on Mondays) and if those differences affect the outcome that is being studied (e.g., proportion of baby visits for "well babies"), then that sampling strategy would substantially alter the interpretations from the registry and would be considered a meaningful limitation.

The extent to which the *actual population* is not fully representative of the intended population is generally a matter of real-world issues that prevent the initial inclusion of study subjects or adequate followup. In assessing representativeness, one must consider the likely underlying factors that caused those subjects not to be included in the analysis of study results and how that might affect the interpretations from the registry. For example, consider a study of a newly introduced medication, such as an antiinflammatory drug that is thought to be as effective as other products with fewer side effects, but it is more costly. Inclusion in the actual population may be influenced by prescribing practices governed by a health insurer (such as the new drug being approved for reimbursement only for patients who have "failed" treatment with other antiinflammatory products, resulting in an actual population that is systematically different from the target population of potential antiinflammatory drug users). The actual population may be refractory to treatment or have more comorbidities (e.g., gastrointestinal problems), and may be specifically selected for treatment beyond the intention of the study-specified inclusion criteria. In fact, registries of newly introduced drugs and devices may often include patients who are different from the ultimate target population.

Finally, the *analytic population* includes all those patients that meet the criteria for analysis. In some cases, it becomes apparent that there are too few cases of a particular type, or patients with certain attributes, such that these subgroups do not contribute enough information for meaningful analysis. Patients also may be excluded from the analysis population because their conditions are so rare that to include them could be considered a breach of patient confidentiality. Analytic populations are also created to meet specific needs, e.g., an investigator may request a dataset that will be used to analyze a subset of the registry population, such as those who had a specific treatment or condition.

A related issue is that of "early adopters," in which practitioners who are quick to use a novel health care intervention or therapy differ from those who use it only once it is well established. For example, a registry of the use of a new surgical technique may initially enroll largely academic physicians and only

much later enroll community-based surgeons. If the outcomes of the technique differ between the academic surgeons (early adopters) and community-based surgeons (later adopters), then the initial results of the registry may not reflect the true effectiveness of the technique in widespread use. Patients selected for treatment with a novel therapy may also differ with regard to factors such as severity or duration of disease and prior treatment history, including treatment failures, (e.g., patients with more severe or late stage disease, who have failed on other treatments might be more likely to use a newly approved product that has shown efficacy in treating their condition soon after approval); later on, patients with less severe disease may start using the product.

Finally, patients who are included in the *analytic population* for a given analysis of registry data may also be subject to selection or inclusion criteria, and these may also affect interpretation of the resulting analyses. For example, if only patients who remain enrolled and attend followup visits through two years after study initiation are included in an analysis of adherence to therapy, it is possible or likely that adherence may be different among those who remain enrolled in the study and have multiple followup visits than those who do not. Differential loss to followup, whereby patients who are lost may be more likely to experience adverse outcomes, such as mortality, than those who remain under observation, is a related issue that may lead to biased results, and is discussed further in Chapter 3.

Data Quality Issues

In addition to a full understanding of study design and methodology, analysis of registry events and outcomes requires an assessment of data quality. One must consider whether most (or all) important covariates were collected, whether the data were complete, and whether missing data were handled correctly, as well as whether the data is accurate.

Collection of All Important Covariates

While registries are generally constructed for a particular purpose or purposes, registry information may be collected for one purpose (e.g., provider performance feedback) but then used for another (e.g., addressing a specific clinical research question). When using an available database for additional purposes, one needs to be sure that all the information necessary to address a specific research question was collected in a manner that is sufficient to answer the question.

For example, suppose the research question addresses the comparative effectiveness of two treatments for a given disease using an existing registry. To be meaningful, the registry should have accurate, well-defined, and complete information, including potential confounding factors, population characteristics (of those with disease X); exposures (whether patients received treatment A or B); and patient outcome(s) of interest. Confounding factors are variables that influence both the exposure (treatment selection) and the outcome in the analyses. These factors can include patient factors (age, gender, race, socioeconomic factors, disease severity, or comorbid illness); provider factors (experience, skills); and system factors (type of care setting, quality of care, or regional effects). While it is not possible to identify all confounding factors in planning a registry, it is desirable to give serious thought to what will be important and how the necessary data can be collected. Analysis of registries requires information about such variables so that the confounding covariates can be accounted for, using one of several analytic techniques covered in upcoming sections of this chapter. In addition, as described in Chapter 3, eligibility for entry into the registry may be restricted to individuals within a certain range of values for potential

confounding factors, to reduce their effects. Such restrictions may also affect the generalizability of the registry.

Data Completeness

Assuming a registry has the necessary data elements, the next step is to be assured that the data are complete. Missing data can be a challenge for any registry-based analysis. Missing data include situations where a variable is directly reported as missing or unavailable, where a variable is "non-reported" (i.e., the observation is blank), where the reported data may not be interpretable, or where the value must be imputed to be missing because of data inconsistency or out-of-range results. Before analyzing a registry database, the database should be "cleaned" (discussed in Chapter 10), and attempts should be made to obtain as much missing data as realistically possible from source documents. Inconsistent data (e.g., answer yes to a question at one point and no to the same question at another) and out-of-range data (a 500- year-old patient) should be corrected when possible. Finally, the degree of data completeness should be summarized for the researcher and eventual consumer of analyses from the registry.

Handling Missing Data

The intent of any analysis is to make valid inferences from the data. Missing data can threaten this goal by both reducing the information yield of the study and, in many cases, introducing bias. The first step in knowing how to handle missing data is to understand why the data are missing. Missing data fall into three classic categories.[523]

- *Missing completely at random (MCAR):* Instances where there are no differences between subjects with missing data and those with complete data. In such random instances, missing data only reduce study power without introducing bias.

- *Missing at random (MAR):* Instances where missing data depend on known or observed values, but not unmeasured data. In such cases, accounting for these known factors in the analysis will produce unbiased results.

- *Missing not at random (MNAR):* Here, missing data depend on events or factors not measured by the researcher and thus, potentially introduce bias.

To gain insight into which of the three categories of missing data are in play, one can compare the distribution of observed variables for patients with specific missing data, to the distribution of those variables for patients for whom those same data are present. Alternatively, one can attempt to "predict a missing variable", also called imputation, using logistic regression analysis where the dependent variable is a dummy variable representing the missing data.

While pragmatically it is difficult todetermine whether data are MCAR or MAR, there are, nonetheless, several means of managing missing data within an analysis. For example, a "complete case" strategy limits the analysis to patients with complete information for all variables. This is the default strategy used in many standard analytic packages (e.g., SAS, Cary, NC). A simple deletion of all incomplete observations, however, is not appropriate or efficient in all circumstances, and it may introduce significant bias if the deleted cases are substantively different from the retained, complete cases (i.e., not MCAR). In observational studies with prospective, structured data collection, missing data are not

uncommon, and the "complete case" strategy is inefficient and not generally used. For example, patients with diabetes who were hospitalized because of inadequate glucose control might not return for a scheduled followup visit, at which HbA1c was to be measured. Those missing values for HbA1c, then, would probably differ from the measured values because of the reason for which they were missing, and they would be categorized as MNAR. In an example of MAR, the availability of the results of certain tests or measurements may depend on what is covered by patients' health insurance (a known value), since registries do not typically pay for testing. Patients without this particular measurement may still contribute meaningfully to the analysis. In order to not exclude patients with missing data, one of several imputation techniques may be used to estimate the missing data.

Imputation is a common strategy in which average values are substituted for missing data, using strategies such as unconditional and conditional mean, multiple hot-deck, and expectation maximum, among others.[524,525] For data that are captured at multiple time points, investigators often "carry forward" a last observation. However, such a technique can be problematic if early dropouts occur and a response variable is expected to change over time. "Worst-case" imputation is another means of substitution in which investigators test the sensitivity of a finding by substituting a "worst case" value for all missing results. While this is conservative, it offers a "lower bounds" on an association rather than an accurate assessment. One particular imputation method that has received significant attention in recent analyses has been termed "multiple imputations." Rubin first proposed the idea to impute more than one value for a missing variable as a means of reflecting the uncertainty around this value.[526] The general strategy is to replace a missing value with multiple values from an approximate distribution for missing values. This produces multiple "complete data sets" for analysis from which a single summary finding is estimated.

There are several issues in how prognostic models for decisionmaking can be influenced by data completeness and missing data.[527] Burton and Altman reviewed 100 published multivariable, cancer prognostic models published in seven leading cancer journals in 2002. They found that the proportion of complete cases was reported in only 39 studies, while the percentage missing for important prognostic variables was reported in 52 studies. Comparison of complete cases with incomplete cases was provided in 10 studies, and the methods used to handle missing data were summarized in 32 studies. The most common techniques used for handling missing data were complete case analysis (12), dropping variables with high numbers of missing cases from model consideration (6), and some simple author imputation rule (6). One article used multiple imputation techniques. The reviewers concluded there was room for improvement in the reporting and handling of missing data within registry studies.[528]

Readers interested in learning more about methods for handling missing data and the potential for bias are directed to two other useful reviews, one by Greenland and Finkle[529] and the other by Hernan and colleagues.[530]

It is important to keep in mind that the impact of data completeness will differ, depending on the extent of missing data and the intended use of the registry; it may be less problematic with regard to descriptive research, than research that is intended to support decisionmaking. For all registries, it is important to have a strategy on how to handle missing data and how to explicitly report on data completeness to facilitate interpretation of study results.

Data Accuracy and Validation

While observational registry studies are usually not required to meet FDA and ICH standards of Good Clinical Practice (GCP) developed for clinical trials, sponsors and contract research organizations who conduct registry studies are responsible for ensuring the accuracy of study data to the extent possible. Detailed plans for site monitoring, quality assurance, and data verification should be developed at the beginning of a study and adhered to throughout the lifespan of the study. Chapter 10 discusses in detail approaches to Data Collection and Quality Assurance, including data management, site monitoring, and source data verification.

Additional consideration needs to be given to ensuring the accuracy and validity of data and programming at the stage of analysis. The Office of Surveillance and Epidemiology (OSE) of the FDA's Center for Drug Evaluation and Research uses a manual of "Standards of Data Management and Analytic Process in the Office of Surveillance and Epidemiology" for analyses of databases conducted within OSE, that addresses many of these issues and may be consulted for further elaboration on these topics.[531] Topics addressed that pertain to ensuring the accuracy of data just prior to, and during analysis include: developing a clear understanding of the data at the structural level of the database and variable attributes; creating analytic programs with careful documentation and an approach to variable creation and naming conventions that is straightforward, and, when possible, consistent with the Clinical Data Interchange Standards Consortium (CDISC) initiative; and verification of programming and analytic dataset creation by a second analyst, in whole or in part.[532]

Data Analysis

This section provides an overview of practical considerations for analysis of data from a registry. As the name suggests, a descriptive study focuses on describing frequency and patterns of various elements of a patient population, whereas an analytical study focuses on examining associations between patients or treatment characteristics and health outcomes of interest (e.g., comparative effectiveness).

Statistical methods commonly used for descriptive purposes include those that summarize information from continuous variables (e.g., mean, median) or from categorical variables (e.g., proportions, rates). Registries may use incidence (the proportion of the population that develops the condition over a specified time interval), and prevalence (the proportion of the population that has the condition at a specific point in time) to describe the population. Another summary estimate that is often used is an incidence rate. The incidence rate (also known as absolute risk) takes into account both the number of people in a population who develop the outcome of interest, and the person-time at risk, or the length of time contributed by all people during the period when they were in the population and the events were counted.

For studies that include patient followup, an important part of the description of study conduct is characterization of how many patients are "lost," or drop out, during the course of conducting a registry, and at what point they are "lost." Figure 4 illustrates key points of information that provide a useful description of losses to followup and study dropouts.

For analytical studies, the association between a risk factor and outcome may be expressed as attributable risk, relative risk, odds ratio, or hazard ratio, depending on the nature of data collected, the duration of the study, and the frequency of the outcome. Attributable risk, a concept developed in the field of public health and preventive medicine, is defined as the proportion of disease incidence that can be attributed to

a specific exposure, and it may be used to indicate the impact of a particular exposure at a population level. The standard textbooks cited here have detailed discussions regarding epidemiologic and statistical methods commonly used for the various analyses supported by registries.[533,534,535,536,537]

For analytic studies of data derived from observational studies, like registries, it is important to consider the role of confounding. When planning a study, it is possible to try to collect as much data as possible to address known confounders; however, there is always the possibility that unknown confounders will affect the interpretation of analyses derived from observational studies. It is important to consider the extent to which bias (systematic error stemming from factors that are related both to the decision to treat and to the outcome(s) of interest [confounders]) could have distorted the results. For example, selective prescribing (confounding by indication) results when people with more severe disease or those who have "failed" other treatments are more likely receive newer treatments; these patients are systematically different from other patients who may be treated with the product under study. Misclassification in treatment can result from the patient's incorrect recall of dose or poor adherence or treatment compliance. Other types of bias include detection bias[538] (e.g., when comparison groups are assessed at different points in time or by different methods), selective loss to followup where patients with the outcomes of most interest (e.g., sickest) may be more likely to drop-out of one treatment group than another, and performance bias (e.g., systematic differences in care other than the intervention under study, such as a public health initiative promoting healthy lifestyles directed at patients who receive a particular class of treatments).

Confounding may be evaluated using stratified analysis and through sensitivity analyses. The extensive information and large sample sizes available in some registries also support use of more advanced modeling techniques for addressing confounding by indication, such as the use of propensity scores to create matched comparison groups, or for stratification or inclusion in multivariate risk modeling.[539,540,541,542] The uptake of these approaches in the medical literature in recent years has been extremely rapid, and their application to analyses of registry data has also been broad. Examples are too numerous for a few selections to be fully representative, but registries in nearly every therapeutic area, including cancer,[543] cardiac devices,[544] organ transplantation,[545] and rare diseases,[546] have published the results of analyses incorporating propensity-score based approaches. As also noted in Chapter 3, instrumental variables, when a valid instrument is found that may be incorporated into analysis, also present opportunities for assessing and reducing the effects of confounding by indication through adjustment in the analysis.[547]

Groupings within a study population, such as patients seen by a single doctor or practice, residents of a neighborhood, or other "clusters", may, in themselves, impact or predict health outcomes of interest. Such groupings may be accounted for in analysis through use of analytic methods including ANOVA, and hierarchical or multilevel modeling.[548,549,550,551]

For economic analyses, the analytic approaches often encountered are cost-effectiveness analyses and cost-utility studies. To examine cost effectiveness, costs are compared with clinical outcomes measured in units such as life expectancy or years of disease avoided.[552] Cost-utility analysis, a closely related technique, compares costs with outcomes adjusted for quality of life (utility) using measures known as quality-adjusted life years (QALYs). Since most new interventions are more effective but also more expensive, another analytic approach examines the incremental cost-effectiveness ratio (ICER) and

contrasts that to the willingness to pay. (Willingness-to-pay analyses are generally conducted on a country-by-country basis, since various factors relating to national health insurance practices and cultural issues affect willingness to pay.) The use of registries for cost-effectiveness evaluations is a fairly recent development, and consequently, the methods are evolving rapidly. More information about economic analyses can be found in standard textbooks.[553,554,555,556,557,558]

It is important to emphasize that cost-effectiveness analyses, much like safety and clinical-effectiveness analyses, require prospective collection of specific data elements suited to the purpose. Although cost-effectiveness- type analyses are becoming more important, and registries can play a key role in such analyses, traditionally registries have not collected much information on quality of life or resource use that can be linked to cost data.[559] To be used for cost-effectiveness analysis, registries must be developed with that purpose in mind.

Developing a Statistical Analysis Plan

It is important to develop a statistical analysis plan (SAP) that describes the analytical principles and statistical techniques to be employed, in order to address the primary and secondary objectives, as specified in the study protocol or plan. Generally, the SAP for a registry study that is intended to support decisionmaking, such as a safety registry, is likely to be more detailed than the SAP for a descriptive study or health economics study. A registry may require a primary "master SAP," as well as subsequent, supplemental SAPs. Supplemental SAPs might be triggered by new research questions emerging after the initial "master SAP" was developed or because the registry evolved over time (e.g., additional data collected, data elements revised). Although the evolving nature of data collection practices in some registries poses challenges for data analysis and interpretation, it is important to keep in mind that the ability to answer questions emerging during the course of the study is one of the advantages (as well as challenges) of a registry. In the specific case of long-term, rare disease registries, many of the relevant research questions of interest cannot be defined a priori, but arise over time as disease knowledge and treatment experience are accrued. Supplemental SAPs can be developed only when enough data become available to analyze a particular research question. At times, the method of statistical analysis may have to be modified to accommodate the amount and quality of data available. To the extent that the research question and SAP are formulated *before* the data analyses are conducted, and results are used to answer specific questions or hypotheses, such supplemental analysis retains much of the intent of pre-specification, rather than wide-ranging exploratory analyses (sometimes referred to as “fishing expeditions”). The key to success is to provide sufficient details in the SAP that, together with the study protocol and the case report form(s), they describe the overall process of the data analysis and reporting.

Preliminary descriptive analysis to assist SAP development. During SAP development, one particular aspect of a registry that is somewhat different from a randomized controlled study is the necessity to understand the "shape" of the data collected in the study. This may be crucial for a number of reasons.

Given the broad inclusion criteria that most registries tend to propose, there might be a wide distribution of patients, treatment, and/or outcome characteristics. The distribution of age, for example, may help to determine if more detailed analyses should be conducted in the "oldest old" age group (80 years and over) to help understand health outcomes in this subgroup that might be different from outcomes for their younger counterparts.

Unless a registry is designed to limit data collection to a fixed number of regimens, the study population may experience many "regimens," considering the combination of various dose levels, drug names, frequency and timing of medication use (e.g., acute, chronic, intermittent), and sequencing of therapies. The scope and complexity of these variations constitute one of the most challenging aspects of analyzing a registry, since treatment is given at each individual physician's discretion. Grouping of treatment into "regimens" should be carefully conducted, guided by clinical experts in that therapeutic area. The full picture of treatment patterns may become clear only after a sizable number of the patients have been enrolled. Consequently, the treatment definition in a SAP may be refined during the course of the study. Furthermore, there may be occasions where a particular therapeutic regimen is used in a much smaller number of patients than anticipated, so specific study objectives focusing on this group of patients might become unfeasible. Also, the registry might have enrolled many patients who would normally be excluded from a clinical trial because of significant contraindications related to comorbidity or concomitant medication use; in this case, the SAP may need to define how these patients will be analyzed (either as a separate group or as part of the overall study population) and how these different approaches might affect the interpretation of the study results.

There is a need to evaluate the presence of potential sources of bias and, to the extent feasible, utilize appropriate statistical measures to address such biases. For example, the bias known as "confounding by indication"[560] results from the fact that physicians do not prescribe medicine at random: the reason a patient is put on a particular regimen is often associated with his/her underlying disease severity and may, in turn, affect treatment outcome. To detect such a bias, the distribution of various prognostic factors at baseline is compared for patients who receive a treatment of interest and those who do not. A related concept is "channeling bias," where drugs with similar therapeutic indications are prescribed to groups of patients who may differ with regard to factors influencing prognosis.[561] To detect such a bias, registry developers and users must document the characteristics of the exposed and nonexposed participants, and either demonstrate their comparability, or use statistical techniques to adjust for differences. (Additional information about biases often found in registries is detailed in Chapter 3.) In addition to such biases, analyses need to account for factors that are interrelated, also known as interaction terms.[562] The presence of interaction terms may also be identified after the data are collected. All of these issues should be taken into account in an SAP, based on understanding of the patient population in the registry.

Timing of Analyses during the Study

Unlike a typical clinical trial, registry-based studies, especially those that take several years to complete, may conduct "intermediate" analyses before all patients have been enrolled and/or all data collection has been completed. Such midcourse analyses may be undertaken for several reasons. First, many of these registries focus on serious safety outcomes. For such safety studies, it is important for all parties involved to actively monitor the frequency of such events at regular predefined intervals so that further risk assessment or risk management can be considered. The timing of such analyses may be influenced by regulatory requirements. Second, it may be of interest to examine treatment practices or health outcomes during the study to capture any emerging trends. Finally, it may also be important to provide intermediate or periodic analysis to document progress, often as a requirement for continued funding.

While it is useful to conduct such periodic analysis, careful planning should be given to the process and timing. The first questions are whether a sufficient number of patients have been enrolled and whether a sufficient number of events have occurred. Both can be estimated based on the speed of enrollment and

rate of patient retention, as well as the expected incidence rate of the event of interest. The second issue is whether sufficient time has elapsed after the initial treatment with a product that, biologically speaking, it is plausible for events to have occurred. (For example, some events can be observed after a relatively short duration, such as site reactions to injections, compared with cancers, which may have a long induction or latency.) If there are too few patients or insufficient time has elapsed, premature analyses may lead to the inappropriate conclusion that there is no occurrence of a particular event. Similarly, uncommon events, occurring by random chance in a limited sample, may be incorrectly construed as a safety signal. On the other hand, it is inappropriate to delay analysis so long that an opportunity might be missed to observe emerging (safety) outcomes. Investigators should use sound clinical and epidemiological judgment when planning intermediate analysis and, whenever possible, use data from previous studies to help to determine the feasibility and utility of such an analysis.

When planning the timing of the analysis, it may be helpful to consider substudies if emerging questions require data that were not collected originally. Substudies often involve data collection based on biological specimens or specific laboratory procedures. They may, for example, take the form of nested case-control studies. In other situations, a research question may be applicable only to a subset of patients, such as patients who become pregnant while in the study. It may also be desirable to conduct substudies among patients in a selected site or patient group to confirm the validity of study measurement. In such instances, a supplemental SAP may be a useful tool to describe the statistical principles and methods.

Factors to Be Considered in the Analysis

Registry results are most interpretable when they are specific to well-defined endpoints or outcomes in a specific patient population with a specific treatment status. Registry analyses may be more meaningful if variations of study results across patient groups, treatment methods, or subgroups of endpoints are reported. In other words, analysis of a registry should explicitly provide the following information:

- *Patient:* What are the characteristics of the patient population in terms of demographics, such as age, gender, race/ethnicity, insurance status, and clinical and treatment characteristics (e.g., past history of significant medical conditions, disease status at baseline, and prior treatment history)?

- *Exposure (or treatment):* Exposure could be therapeutic treatment such as medication or surgery, a diagnostic or screening tool, behavioral factors, such as alcohol, smoking habits and diet, or other factors, such as genetic predisposition or environmental factors. What are the distributions of the exposure in the population? Is the study objective specific to any one form of treatment?

- *Endpoints (or outcomes):* Outcomes of interest may encompass both "effectiveness" (or comparative-effectiveness), the benefits of a health care intervention under "real-world" circumstances,[563] and "safety," the risks or harm that may be associated with an intervention. Examples of effectiveness outcomes include survival, disease recurrence, symptom severity, quality of life, and cost effectiveness. Safety outcomes may include infection, sensitivity reactions, cancer, organ rejection, and mortality. Endpoints must be precisely defined at the steps of data collection and analysis. Are the study data on all-cause mortality or cause-specific mortality? Is information available on pathogen-specific infection (bacterial vs. viral, for example)? (See Case Example 38.)

- *Time:* For valid analysis of risk or benefit that occurs over a period of time following therapy, detailed accounting for time factors is required. In regard to exposures, dates of starting and stopping a treatment, or switching therapies should be recorded. In regard to outcomes, the dates when followup visits occur, whether or not they lead to a diagnosis of an outcome of interest, are required in order to take into account how long and how frequently patients were followed. Dates of diagnosis of outcomes or interest, or dates when patients complete a screening tool or survey, should be recorded. At the stage of analysis, results must also be described in a "time-appropriate" fashion. For example, is an observed risk consistent over time (in relation to initiation of treatment) in a long-term study? If not, what time-related risk measures should be reported in addition to (or instead of) cumulative risk? When exposure status changes frequently, what is the method of capturing the population at risk? Many observational studies of intermittent exposures (e.g., use of nonsteroidal antiinflammatory drugs or pain medications) use time windows of analysis, such as looking at events following first use of a drug after a prescribed interval (e.g., 2 weeks) without drug use. Different analytic approaches may be required to address issues of patients enrolling in a registry at different times and/or having different lengths of observation during the study period. Consideration of how to address different lengths of observation for people who enroll in a registry at different times is necessary.

- Successful analysis of observational studies also depends, to a large extent, on the ability to measure and analytically address the potential for bias.[564] Refer to Chapter 3 for a description of potential sources of bias.

Choice of comparator. An example of a troublesome source of bias is the choice of comparator. When participants of a cohort are classified into two or more groups of individuals, according to certain study characteristics (such as treatment status, with the "standard of care" group as the comparator), the registry is said to have an internal, or concurrent, comparator. The advantage to an internal comparator design is that patients are likely to be more similar to, than different from, each other (in contrast to comparisons between registry subjects and external groups of subjects), except for their treatment status. In addition, consistency in measurement of specific variables and data collection methods may also make the comparison more valid. Internal comparators are particularly useful for treatment practices that change over time. Comparative effectiveness studies may often necessitate use of an internal comparator in order to maximize the comparability of patients receiving different treatments within a given study, and to ensure that variables required for multivariate analysis are available and measured in an equivalent manner for all patients to be analyzed.

Unfortunately, it is not always possible to have, or to sustain, a valid internal comparator. For example, there may be significant medical differences between patients who receive a particularly effective therapy and those who do not (e.g., underlying disease severity or contraindications), or it may not be feasible to maintain a long-term cohort of patients who are not treated with such a medication. It is known that external information about treatment practices (such as scientific publications or presentations) can result in physicians changing their practice of medicine, such that they no longer prescribe the previously accepted standard of care. There may be a systematic difference between physicians who are early adopters and those who start using the drug or device after its effectiveness has been more widely accepted. Early adopters may also share other practices that differentiate them from their later adopting colleagues.

In the absence of a good internal comparator, one may have to leverage external comparators to provide critical context to help interpret data revealed by a registry. An external or historical comparison may involve another study or another database that has similar disease or treatment characteristics compared with registry subjects. Such data may be viewed as a context for anticipating the rate of an event. One widely used comparator is the SEER cancer registry data, because SEER provides detailed annual incidence rates of cancer, stratified by cancer site, age group, gender, and tumor staging at diagnosis. A procedure for formalizing comparisons with external data is known as standardized incidence rate or ratio;[565] when used appropriately, it can be interpreted as a proxy measure of risk or relative risk.

Use of an external comparator, however, may present significant challenges. For example, SEER and a given registry population may differ from each other for a number of reasons. The SEER data cover the general population, and have no exclusion criteria pertaining to history of smoking or cancer screening, for example. On the other hand, a given registry may consist of patients who have an inherently different risk of cancer than the general population, resulting from the registry having excluded smokers and others known to be at high risk of developing a particular cancer. This registry would be expected to have a lower overall incidence rate of cancer, which, if SEER incidence rates are used as a comparator, may complicate or confound assessments of the impact of treatment on cancer incidence in the registry.

Regardless of the choice of comparator, similarity between the groups under comparison should not be assumed without careful examination of the study patients. Different comparator groups may potentially result in very different inferences for safety and effectiveness evaluations; therefore, analysis of registry findings using different comparator groups may be used in sensitivity analyses to determine the robustness of a registry's findings. Sensitivity analysis refers to a procedure used to determine the sensitivity of the study result, to alterations of a parameter. If a small parameter alteration leads to a relatively large change in the results, the results are said to be sensitive to that parameter. This procedure may be used to determine how the final study results might change when taking into account those lost to followup. A simple hypothetical example is presented in Table 18.

Table 18 illustrates the extent of change in the incidence rate of a hypothetical outcome, assuming varying degrees of loss to followup, and differences in incidence between those for whom there is information and those for whom there is no information due to loss to followup. In the first example, where 10 percent of the patients are lost to followup, the estimated incidence rate of 111/1,000 people is reasonably stable; it does not change too much when the (unknown) incidence in those lost to followup changed from 0.5 times the observed to 5 times the observed, with the corresponding incidence rate that would have been observed ranging from 106 to 156 per 1,000. On the other hand, when the loss to followup increases to 30 percent, the corresponding incidence rates that would have been observed range from 94 to 242. This procedure could be extended to a study where there is more than one cohort of patients, with one being exposed and the other being nonexposed. In that case, the impact of loss to followup on the relative risk could be estimated by using sensitivity analysis.

Patient censoring. At the time of a registry analysis, events may not have occurred for all patients. For these patients, the data (e.g., survival) are said to be "censored," indicating that the observation period of the registry was stopped before all events occurred. In these situations, it is unclear when the event will occur, if at all. In addition, a registry may enroll patients until a set stop date, and patients entered into the registry earlier will have a greater probability of having an event than those entered more recently

because of the longer followup. An important assumption (and one that needs to be assessed in a registry) is how patient prognosis varies with the time of entrance into the registry. This may be a particularly problematic issue in registries that assess innovative (and changing) therapies. Patients and outcomes initially observed in the registry may differ from patients and outcomes observed later in the registry timeframe (or not at all). Patients with censored data, however, contribute important information to the registry analysis and should not be excluded from the SAP. One method of analyzing censored data to estimate the conditional probability of the event occurring is to use the Kaplan-Meier method.[566] In this method, for each time period, the probability is calculated so that those who have not experienced an event before the beginning of the period will still not have experienced it by the end of the period. The probability of an event occurring at any given time is then calculated from the product of the conditional probabilities of each time interval.

In summary, the development of a good SAP requires careful considerations of study design features and the nature of the data collected. Most typical, cohort study, analytical methods can be applied, and there is no one-size-fits-all approach. Efforts should be made to carefully evaluate the presence of biases and to control for identified potential biases during data analysis. This requires close collaboration among clinicians, epidemiologists, statisticians, study coordinators, and others involved in the design, conduct, and interpretation of the registry.

A number of biostatistics and epidemiology textbooks cover, in depth, the issues raised in this section and the appropriate analytic approaches for addressing them; for example, "time-to-event" or survival analyses,[567] and issues of recurrent outcomes and repeated measures, with or without missing data[568] in longitudinal cohort studies. Other texts address a range of regression and non-regression approaches to analysis of case-control and cohort study designs[569] that may be applied to registries.

Table 18. A Hypothetical Simple Sensitivity Analysis
[Impact of loss to followup on incidence rates per 1,000 in a study of 1,000 patients in a registry]

Various assumptions of the observed incidence rate	Assuming a 10-percent loss to followup	Assuming a 30-percent loss to followup
Incidence rates based on patients who stayed in the registry	111 (100/900)	110 (77/700)
Assuming the incidence of patients lost to followup is X times the rate of incidence estimated in those who stayed in the registry:		
X=0.5	106	94
X=1	111	110
X=2	122	143
X=5	156	242

Interpretation of Registry Data

Interpretation of registry data is needed so that the lessons from the registry can be applied to the target population and used to change future health care and patient outcomes. Proper interpretation of registry data allows users to understand the precision of the observed risk or incidence estimates, to evaluate the hypotheses tested in the current registry, and often also to generate new hypotheses to be examined in

future registries or randomized controlled trials. If the purpose of the registry is explicit, the actual population studied is reasonably representative of the target population, the data quality monitored, and the analyses performed so as to reduce potential biases, then the interpretation of the registry data should allow a realistic picture of the safety, effectiveness, or value of a clinical evaluation, the quality of medical care, or the natural history of the disease process studied. Each of these topics needs to be discussed in the interpretation of the registry data, and potential shortcomings should be explored. Assumptions or biases that could have influenced the outcomes of the analyses should be highlighted and separated from those that do not affect the interpretation of the registry results. The use of a comparator that is of the highest reasonably possible quality is integral to the proper interpretation of the analysis.

Interpretation of registry results may also be aided by comparisons with "external" information. Examples would include rates, or prevalence, of the outcomes of interest in other studies and different data sources (taking into account reasons they may be similar or different), putting findings of registry analysis in context of other previous study results, and other pertinent clinical and biological considerations as the validity and generalizability of the results.

Once analyzed, registries provide important feedback to several groups. One group is the registry developers. Analysis and interpretation of the registry will demonstrate strengths and limitations of the original registry design and will allow the developers to make needed design changes for future versions of the registry. Another group comprises the study sponsors and related oversight/governance groups, such as the Scientific Committee and Data Monitoring Committee. (Refer to Chapter 2 for more information on registry governance and oversight.) Interpretation of the analyses allows the oversight committees to offer recommendations concerning continued use and/or adaptation of the registry and to evaluate patient safety. The final group is comprised of the end users of the registry output, such as patients or other health care consumers, health services researchers, health care providers, and policymakers. These are the people for whom the data were collected and who may use the results to choose a treatment or intervention to provide or undergo, to determine the need for additional research programs to change clinical practice, to develop clinical practice guidelines, or to determine policy. All three user groups work toward the ultimate goal of each registry—improving patient outcomes.

Case Example 37: Using registry data to evaluate outcomes by practice

Description:	The Epidemiologic Study of Cystic Fibrosis (ESCF) Registry was a multicenter, encounter-based, observational, postmarketing study designed to monitor product safety, define clinical practice patterns, explore risks for pulmonary function decline, and facilitate quality improvement for cystic fibrosis (CF) patients. The registry collected comprehensive data on pulmonary function, microbiology, growth, pulmonary exacerbations, CF-associated medical conditions, and chronic and acute treatments for children and adult CF patients at each visit to the clinical site.
Sponsor:	Genentech, Inc.
Year Started:	1993
Year Ended:	Patient enrollment completed in 2005; followup complete
No. of Sites	215 sites over the life of the registry
No. of Patients:	32,414 patients and 832,705 encounters recorded

Challenge

Although guidelines for managing cystic fibrosis patients have been widely available for many years, little is known about variations in practice patterns among care sites and their associated outcomes. To determine whether differences in lung health existed between groups of patients attending different CF care sites and to determine whether these differences were associated with differences in monitoring and intervention, data on a large number of CF patients from a wide variety of CF sites were necessary.

As a large, observational, prospective registry, ESCF collected data on a large number of patients from a range of participating sites. At the time of the outcomes study, the registry was estimated to have data on over 80 percent of CF patients in the United States, and it collected data from more than 90 percent of the sites accredited by the U.S. Cystic Fibrosis Foundation. Because the registry contained a representative population of CF patients, the registry database offered strong potential for analyzing the association between practice patterns and outcomes.

Proposed Solution

In designing the study, the team decided to compare CF sites using lung function (i.e., FEV1 values), a common surrogate outcome for respiratory studies. Data from 18,411 patients followed in 194 care sites were reviewed, and 8,125 patients from 132 sites (minimum of 50 patients per site) were included. Only sites with at least 10 patients in a specified age group (6-12, 13-17, 18 and older) were included for evaluation of that age group. For each age group, sites were ranked in quartiles based on the median FEV1 value at each site. The frequency of patient monitoring and use of therapeutic interventions were compared between upper and lower quartile sites after stratification for disease severity.

Results

Substantial differences in lung health across different CF care sites were observed. Within-site rankings tended to be consistent across the three age groups. Patients who were cared for at higher ranking sites had more frequent monitoring of their clinical status, measurements of lung function, and cultures for respiratory pathogens. These patients also received more interventions, particularly intravenous antibiotics for pulmonary exacerbations. The study concluded that frequent monitoring and increased use of appropriate medications in the management of CF are associated with improved outcomes.

Key Point

Stratifying patients by quartile of lung function, age, and disease severity allowed comparison of practices among sites and revealed practice patterns that were associated with better clinical status. The large numbers of patients and sites allowed for sufficient information to create meaningful and informative stratification, and resulted in sufficient information within those strata to reveal meaningful differences in site practices.

For More Information

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Case Example 38: Using registry data to study patterns of use and outcomes

Description:	The Palivizumab Outcomes Registry was designed to characterize the population of infants receiving prophylaxis for respiratory syncytial virus (RSV) disease, to describe the patterns and scope of the use of palivizumab, and to gather data on hospitalization outcomes.
Sponsor:	MedImmune, Inc.
Year Started:	2000
Year Ended:	2004
No. of Sites	256
No. of Patients:	19,548 infants

Challenge

RSV is the leading cause of serious lower respiratory tract disease in infants and children and the leading cause of hospitalizations nationwide for infants less than one year of age. Palivizumab was approved by the U.S. Food and Drug Administration (FDA) in 1998 and is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Two additional, large, retrospective surveys conducted after FDA approval studied the effectiveness of palivizumab in infants, again showing that it reduces the rate of RSV hospitalizations. To capture post-licensure patient demographic outcome information, the manufacturer wanted to create a prospective study to identify infants receiving palivizumab to better understand the population receiving the prophylaxis for RSV disease and to study the patterns of use and the hospitalization outcomes.

Proposed Solution

A multicenter registry study was created to collect data on infants receiving palivizumab injections. No control group was included. The registry was initiated during the 2000-01 RSV season. Over 4 consecutive years, 256 sites across the United States enrolled infants who had received palivizumab for RSV under their care, provided that the infant's parent or legally authorized representative gave informed consent for participation in the registry. Data were collected by the primary healthcare provider in the

office or clinic setting. The registry was limited to data collection related to subjects' usual medical care. Infants were enrolled at the time of their first injection, and data were obtained on palivizumab injections, demographics, and risk factors, as well as on medical and family history.

Followup forms were used to collect data on subsequent palivizumab injections, including dates and doses, during the RSV season. Compliance with the prescribed injection schedule was determined by comparing the number of injections actually received with the number of expected doses, based on the month that the first injection was administered. Infants who received their first injection in November were expected to receive five injections, whereas infants receiving their first injection in February would be expected to only receive two doses through March. Data were also collected for all enrolled infants hospitalized for RSV and were directly reported to an on-site registry coordinator. Testing for RSV was performed locally, at the discretion of the healthcare provider. Adverse events were not collected and analyzed separately for purposes of this registry. In clinical trials, the most common adverse events occurring at least 1 percent more frequently in palivizumab-treated patients than controls, were upper respiratory infection, otitis media, fever, and rhinitis. Cyanosis and arrhythmia were seen in children with congenital heart disease (CHD). There have also been post-marketing reports of injection site reactions.

Results

From September 2000 through May 2004, the registry collected data on 19,548 infants. The analysis presented injection rates and hospitalization rates for all infants by month of injection and by site of first dose (pediatrician's office or hospital). The observed number of injections per infant was compared with the expected number of doses based on the month the first injection was given. Over 4 years of data collection, less than 2 percent (1.3 percent) of enrolled infants were hospitalized for RSV. This analysis confirmed a low hospitalization rate of palivizumab prophylaxis for RSV in a large nationwide cohort of infants from a geographically diverse group of practices and clinics. The registry data also showed that the use of palivizumab was mostly consistent with the 2003 guidelines of the American Academy of Pediatrics for use of palivizumab for prevention of RSV infections. As the registry was conducted prospectively, nearly complete demographic information and ~ 99 percent of followup information on all enrolled infants was captured, an improvement compared to previously completed retrospective studies.

Key Point

A simple stratified analysis was used to describe the characteristics of infants receiving injections for RSV. Infants in the registry had a low hospitalization rate, and these data support the effectiveness of this treatment outside of a controlled clinical study. Risk factors for RSV hospitalizations were described and quantified by presenting the number of infants with RSV hospitalization as a percentage of all enrolled infants who were hospitalized. These data supported an analysis of postlicensure effectiveness of RSV prophylaxis, in addition to describing the patient population and usage patterns.

For More Information

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Section III: Evaluating Registries

Chapter 14: Assessing Quality

Registries are undertaken for many purposes, ranging from descriptive studies intended to contribute to scientific understanding of patient outcomes, to studies used to inform policy decisions. Some are undertaken with great urgency, whereas others proceed with more deliberation. Budgetary support ranges from spartan to adequate. Most importantly, registries often serve multiple purposes and change over time to accommodate these various purposes—in fact, these are hallmarks of registries. Although all registries can provide useful information, there are levels of rigor that enhance validity and make the information from some registries more useful for guiding decisions than others.

Prior to the publication of the first edition of this handbook, no standards had been developed by which to guide evaluation of registries, and the research into quality aspects of registries still remains sparse.[570] Previous chapters of this handbook have described various attributes and characteristics that constitute good registries and "good registry practice." This chapter provides an overview of key components of the design, execution, and analysis of a registry that promote reliability and validity of data on patient outcomes.

The aim of this chapter is to provide a simple and user-friendly system that allows registries to be described and evaluated in the context of the purpose for which they are conducted. Information is presented to help distinguish between:

- Basic, good registry practices that are desirable to meet certain purposes.
- Future directions for practices that could enhance scientific rigor but may not be achievable because of practical constraints.

The items listed as "basic elements of good practice" are applicable to all patient registries. While it may not be practical or feasible to achieve all of the basic elements of good practice, it is useful to consider these characteristics in planning and evaluating registries. The information described in this handbook, and particularly in this chapter, is also designed to be used in reporting registry study results, much as CONSORT guidelines have been used to improve reporting of clinical trials[571] and STROBE guidelines are being similarly used for observational studies.[572,573]

It is also important to remind readers that some of the fundamental differences between clinical trials and registries will affect how quality is evaluated. For example, a clinical trial will have a schedule of visits and assessment that is rigorously maintained. A clinical trial patient who does not adhere to the schedule may be viewed as non-compliant with the protocol and could potentially be discontinued from the trial. In a registry, treatments and assessments may be recommended, but the registry participant who does not adhere to the schedule would typically be allowed to remain in the registry.

Defining Quality

This chapter has adapted a definition of "quality" that was developed for randomized controlled trials;[574,575] the term is used to refer to the confidence that the design, conduct, and analysis of the trial or registry can be shown to protect against bias (systematic error) and errors in inference—that is, erroneous conclusions drawn from a study.[576] As used here, quality refers to both the data and to the conclusions drawn from analyses of these data. For more information about the types of biases that can affect observational studies, as well as strategies for addressing, and even avoiding, these biases to the extent feasible, see Chapters 3 and 13. For more information about bias, validity, and inference, readers are encouraged to consult epidemiologic textbooks.[577,578,579,580]

Measuring Quality

There are two major difficulties with assessing quality in registries:

- It can often be difficult to differentiate between the quality of the design, the study conduct, and the information available.
- There is a lack of empirical evidence for evaluating parameters purported to indicate quality and impact on the evidence produced from registries.

In addition, registries vary widely in methodology, scope, and objectives, and therefore attributes that are important in one scenario may be less important in another. Furthermore, registries may be very useful vehicles for providing clinically relevant real-world information, even when they meet relatively few of the basic elements of good practice (typically because of budgetary limitations). In many cases, some data are better than no data, and even registries that fall short of including all the basic elements of good registry practice may still provide valuable insights about real-world medical and consumer practices and disease etiology, and may be particularly valuable for modeling exercises. Evaluations of the quality of any registry must therefore be done with respect to the specific purpose of the registry, must take into account both the internal and external validity of the data, and should be tempered by considerations of cost and feasibility.

The most commonly used method to assess quality of studies is a quality scale; there are numerous quality scales of varying length and complexity in existence, with strong views being expressed both for and against their use.[581,582,583] Different scales emphasize distinctive dimensions of quality and therefore can produce disparate results when applied to a given study. In most situations, a summary score is derived by adding individual item scores, with or without weighting. This method, however, ignores whether the various items may lead to a bias toward the null (suggesting the erroneous interpretation that there is no effect), or tend to exaggerate the appearance of an effect when none really exists, and the final score produced does not reflect individual components.[584]

Rather than develop a checklist, the approach suggested here is to undertake a quality component analysis- an investigation of the components that may affect the results obtained. In the quality component analysis, a differentiation is made between two domains: research quality, which pertains to the scientific process (in this instance, the design and operational aspects of the registry), and evidence quality, which relates to the data/findings emanating from the research process.[585,586,587] According to Lohr,[588,589,590,591] "The level of confidence one might have in evidence turns on the underlying robustness of the research and the analysis done to synthesize that research."

To select the quality components for analysis, several key elements identified in previous research studies, among many consulted, were Guidelines for Good Pharmacoepidemiology Practice,[592,593] the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Guideline on Good Clinical Practice,[594] the Council for International Organizations of Medical Sciences (CIOMS) International Guidelines for Ethical Review of Epidemiological Studies,[595] various reports on rating scientific evidence from observational studies[596,597] and surveillance systems,[598] Goldberg's review of registry evaluation methods,[599] the MOOSE proposal for reporting meta-analysis of observational studies,[600] the EULAR taskforce on biologic registers,[601] and Guidance for Reporting Observational Studies maintained by the Equator Network.[C]

The results of the quality component analysis must be considered in conjunction with context-specific substantive components that relate to the disease area, the type of registry, and the purpose of the registry. (See Table 19.) For example, a disease-specific registry that has been designed to look at natural history should not be deemed low quality simply because it is not large enough to detect rare treatment effects.

Quality Domains

The quality domains shown here are the domains described earlier in this handbook. For research, the quality domains are research design and processes and procedures, which address planning, design,; data elements and data sources, and ethics, privacy, and governance. For evidence, the quality domains are external validity, internal validity and analysis, and reporting.

Table 20 shows the basic elements of good registry practice for research, and Table 21 shows additional practices that have the potential to enhance scientific rigor, and thus, the validity and reliability of information resulting from registries. Similarly, Table 22 shows the basic elements of good registry practice for evidence, and Table 23 shows additional practices that may enhance the evidence quality. It is important to weigh efforts taken to promote the accuracy and completeness of evidence in balance with the public health urgency of a problem, the types of interventions that are available, and the risks to public health from coming to a wrong conclusion. These lists of components are most likely incomplete, but the level of detail provided should be useful for high-level quality distinctions.

Most importantly, the basic elements of good practice, as well as the potential enhancements to good practice, depend, to a great extent, on the resources and budget available to support registry-based research.

Table 19. Overview of Registry Purposes

- Determining clinical effectiveness, cost effectiveness, or comparative effectiveness of a test or treatment, including evaluating the acceptability of drugs, devices, or procedures for reimbursement.
- Measuring or monitoring safety and harm of specific products and treatments, including comparative evaluation of safety and effectiveness.
- Measuring or improving quality of care, including conducting programs to measure and/or improve the practice of medicine and/or public health.
- Assessing natural history, including estimating the magnitude of a problem; determining the

[C] http://www.equator-network.org/resource-centre/library-of-health-research-reporting/reporting-guidelines/observational-studies/#obse

underlying incidence or prevalence rate; examining trends of disease over time; conducting surveillance; assessing service delivery and identifying groups at high risk; documenting the types of patients served by a health provider; and describing and estimating survival.

Table 20. Research Quality—Basic Elements of Good Practice for Establishing and Operating Registries

Research Design

- Develop objectives (main and supporting, as needed)
- Identify the target population, eligibility, inclusion and exclusion criteria. For registries where practice characteristics may influence outcome, seek to include diverse clinical practices. Where possible, a broad range of patients is desirable (few exclusion criteria.)
- Identify important personal identifiers, exposures, risk factors, and mitigating (or protective) factors and seek those that are reasonably feasible to collect. Use the literature to inform the choice of data elements.
- Choose outcomes that are clinically meaningful and relevant to patients and to the medical community for decision-making. Define patient outcomes clearly, especially for complex conditions or outcomes that may not have uniformly established criteria (e.g., provide an operational definition for an "injection site reaction").
- Consider the most efficient and reliable means to collect data of sufficient quality to meet the registry's purpose , and whether existing data can be used to supplement or minimize active data collection
- Use validated scales and tests when such tools exist for the purpose needed.
- Understand the followup time required to detect events of interest, whether or not it is feasible to achieve, and assure that the followup time planned is adequate to address the main objective. Consider the size required to detect an effect, should one exist, or to achieve a desired level of precision, whether or not the sample size requirement can be achieved within the available time and budget.
- Plan to report safety events according to regulatory requirements.
- Plan the data analysis, including what comparative information, if any, will be used to support study hypotheses or objectives.

Processes and Procedures

- Key aspects of the registry should be agreed and documented at the outset, including the goals, design, target population, methods for data collection, data elements and sources, high-level data management and data quality review, and how human subjects will be protected. It may be helpful for stakeholders to have input to assure clinical relevance and feasibility.
- Establish a process for documenting any modifications to the plan. Note that the main objective may change over time as knowledge accumulates, and the plan for followup may need to be adapted (e.g., at the outset of a rare disease registry, there may be little knowledge to guide hypothesis development (and what data should be collected)and the timing needed to address such hypothesis).
- Carefully consider the issues of protection of human subjects—including privacy, informed consent, data security, and study ethics—and address in accordance with local, national, and international regulations. Obtain review and approval by any required oversight committees (e.g., ethics committee, privacy committee, or institutional review board, as applicable). Consider the additional

issues of protection of human subjects if registry data are planned to be linked with other data sources.

- Define the role of any external sponsor, including data access, use and presentation.
- Provide clear, operational definitions of outcomes and other data elements. Establish a data and coding dictionary to provide explicit definitions and to describe coding used. Whenever possible, use standardized data dictionaries, such as the International Classification of Diseases, where applicable, and use coding that is consistent with nationally or internationally approved coding systems to promote comparability of information among studies.
- If linkage of registry data to other sources is planned, consider any additional requirements that may influence selection of data elements, definitions and so forth for successful linkage.
- Plan for subject and physician recruitment methods and goals, and for monitoring enrollment and retention.
- Plan to expend reasonable efforts to assure that appropriate patients are enrolled systematically and followed in as unbiased a manner as possible.
- Identify appropriate personnel and facilities, including those for secure data storage. Identify the individual(s) responsible for the integrity of the data, computerized and hard copy, and have the training and experience to perform the assigned tasks.
- Develop standard instructions for use in training data collectors. For safety studies, create a process for identifying and reporting serious events that is consistent with regulatory requirements. Plan training for study personnel about how to identify serious events, including asking about complaints or adverse events in a manner that is clear and specific (e.g., solicited vs. unsolicited), and to know if and how information should be reported to manufacturers and health authorities.
- Create a quality assurance plan that addresses data editing and verification. Plan for how missing data will be handled.
- Anticipate how study results will be communicated on completion. Publication policies should be specified in advance of collecting data and should be re-evaluated at regular intervals (e.g., annually).
- Develop a plan for stopping the registry or transitioning the registry, including any archiving or transferring data and notifying participants, as appropriate.

Table 21. Research Quality—Potential Enhancements to Good Practice for Establishing and Operating Registries

Research Design

- The study plan should be formalized into a research protocol.
- Concurrent comparators should be considered as they may offer an advantage over historical or external comparison groups, especially in situations where treatments are evolving rapidly. The comparator cohort should be as similar as possible to the exposed cohort, aside from the exposure under study.
- Formal statistical calculations may be used to specify number of patients or patient-years of observation needed to measure an effect with a certain level of precision; or to meet a specified statistical power to detect an effect ,should one exist, although the desired size may not be achievable within the practical study constraints. Precision and power considerations must be tempered with budgetary and feasibility constraints, and in consideration of the importance of conducting research in areas where little exists.
- Safety and effectiveness studies can be enhanced by collecting enough information to permit linkage with external databases such as the National Death Index , electronic health records, or

claims datasets, as appropriate. The desire for long-term followup should be balanced by considerations relating to collecting (or re-identifying) individually identifiable data, especially with regard to institutional review policies and privacy laws.

Processes and Procedures

- A feasibility study or pilot test may be useful in certain situations, such as when studying hard-to-reach populations, when sensitive data are sought, and when critical registry methods are new or have not otherwise been tested.
- When capturing composite scores, collect and record core components, if possible.
- Collect start and stop dates of treatments of interest, and dose (if relevant) or other means to discriminate between high and low exposure.
- Data collection methods should not limit site participation to the extent that it compromises the representativeness of sites. Although single methods of data collection are most efficient, multiple methods of data collection may be desirable for some purposes.
- When health information systems are used for active data collection, open standard approaches to interoperability are preferred since they permit more efficient collection of data from multiple systems.
- Methods of followup should be as similar as possible between exposure and comparison cohorts, and for all subjects in each cohort.
- Rigor can be enhanced by review or monitoring of a sample of data and/or data review by an adjudication committee for complex conditions, or endpoints for which established procedures and/or coding are not used. A risk-based strategy for quality assurance focuses on detecting and quantifying the most likely causes of error and types of error most likely to affect the registry purpose. For example, a registry might compare a random sample of patient data (e.g., 5-20% of patients and specific data variables) with patient charts or with a sample of registry sites based on "for-cause" reasons, or a combination of these approaches. Levels of QA activities may be adapted based on observed performance (e.g., increase QA for sites that appear to be having difficulty in study conduct or data entry).
- Quality is enhanced through transparency, which is reinforced by use of an advisory board, particularly a board that includes members who are external to the clinician, center, or company that sponsors the research. An advisory board or steering committee can promote clinical and public health relevance, and may assist with governance and communication.
- Maintaining appropriate documentation, such as an audit trail, ensures proper handling of information and supports transparency. Also, since registry analyses may be performed on "live" data or data that have been locked and have undergone formal review and editing, it is essential to establish processes and standards for creating analytic data files and maintaining such files to support publications and presentations.
- Publishing results in the peer-reviewed literature is a desirable means of introducing information into the public domain, as is presenting results at scientific meetings. The quality of presentations and publications will be enhanced by review by knowledgeable parties in advance of presentation or submission for publication.
- Consider whether third parties will be allowed to access the data, either during active data collection or after the registry data collection has ended and results have been reported. If so, consider the process that will be used for others to access the data.

Table 22. Evidence Quality — Indicators of Good Evidence Quality for Registries

External validity

- Registry participants are similar to the target population and, to the extent feasible, efforts were devoted to minimizing selection bias (e.g., rules for sequential enrollment were developed and codified in a manner that worked for all sites).
- Completeness of information on eligible patients was evaluated and described. The external validity was described (e.g., registry subjects were shown to be typical of the target population).

Internal validity

- For safety studies, a clear and specific approach was used (e.g., solicited vs. unsolicited) to ask about complaints or adverse events.
- Necessary information was collected for relevant key exposures, risk factors, and mitigating or protective factors.
- Exposure data used to support the main research questions were as specific as possible. For example, a specific product, including manufacturer, was identified to the extent feasible.
- Followup period was reasonably sufficient to capture the main outcomes of interest.
- A sample of data was compared with patient records.
- Reasonable efforts were devoted to minimize losses to followup, and followup was reasonably complete for the registry purpose.
- Data checks were employed using range and consistency checks.

Analysis and Reporting

- The report describes the methods, including target population and selection of study subjects, compliance with applicable regulatory rules and regulations, data collection methods, any transformation of variables and/or construction of composite endpoints, how missing data were handled, statistical methods used for data analysis, and a description of any circumstances that may have affected the quality or integrity of the data. This information should be provided with enough detail to allow replication of the methods in another study.
- Results were reported for all the main objectives, including estimates of effect for each.
- Accepted analytic techniques were used; these may have been augmented by new or novel approaches.
- Followup time was described to enable assessment of the impact of the observation period on the conclusions drawn.
- The role and impact of missing data and potential confounding factors were considered.
- The report includes a clear statement of any conclusions drawn from the analysis of the registry's primary and secondary objectives and any implications of study results. Alternative explanations for the observed results should be considered. Inferences about causal effects were based on a variety of factors, including the strength of the association, biases, and temporal relations. The practice of making inferences about causation largely on the outcome of tests of statistical significance is discouraged.
- All authors had a meaningful role in the design, conduct, analysis, or interpretation of results.

Table 23: Evidence Quality— Further Indicators of Good Evidence Quality for Registries

External Validity

- Eligibility (inclusion and exclusion criteria) was confirmed on enrollment.
- Selection bias was evaluated by describing the representativeness of the actual population in terms of how it was selected, how well the characteristics of the actual population match those of the target population, and to whom the results apply.

Internal Validity

- Results that can be confirmed by an unbiased observer—such as death, test results, and scores from validated measures for patient-reported results or clinical rating scales—enhance accuracy and reliability.
- Potential sources of errors relating to accuracy and falsification were rigorously evaluated and quantified (e.g., through database and site reviews).
- Reproducibility of coding was evaluated.

Analysis and Reporting

- For safety studies, the risks and/or benefits of products, devices, or processes under study were quantitatively evaluated beyond simply evaluating statistical significance (e.g., rates, proportions, and/or relative risks are reported, along with confidence intervals to provide information about precision).
- For studies of comparative effectiveness and safety, contemporaneous data were collected for a comparison group, to the extent that this was ethical and feasible, and that other reasonably accurate and relevant comparative data were not available.
- Validated analytic tools were used for the main analysis (e.g., commercially available analytic packages are used). If models were used, the specific data elements that were included were described.
- Sensitivity analyses may be used to examine and quantify the effect of varying the definitions of exposure and outcome, and definitions of potential confounders and outcomes on the association between the a priori exposure of interest and the outcome(s).
- The consistency of results were compared and contrasted with other relevant research.

Appendix A: An Illustration of Sample Size Calculations

For concreteness, assume that the outcome of interest is a dichotomous variable measured on each patient, such as the presence/absence of a complication associated with carotid endarterectomy (CE). (Typically, this literature considers complications within 30 days of the procedure.) Nothing essential changes for outcome variables measured on other scales, such as continuous or survival data. The dichotomous outcome (i.e., presence or absence of a complication) is then aggregated across patients into a complication rate (e.g., 9 complications for 300 patients = 3-percent complication rate).

As a general principle, sample size calculations depend on the study design, the study question, and the scale of measurement of the variables being measured. Indeed, one of the benefits of performing a sample size calculation is the requirement that each of these be specified, thus increasing the likelihood that the proper variables will be measured on the proper patients in the proper manner.

For CE, some registry-based designs and study questions that might be of interest include the following.

Design 1: For patients at high risk of stroke, perhaps using an operational definition of "symptomatic with 70-99 percent stenosis of the carotid artery," the study question is whether the surgeons within a larger entity (e.g., a national chain of hospitals) are, in aggregate, achieving similar complication rates to those who participated in the randomized trials demonstrating the efficacy of CE. (The reason that this is an open question is that the surgeons and institutions in these randomized trials underwent a high degree of selection, thus raising the concern that surgical outcomes were better than could be expected in usual practice.) The patient inclusion criteria for the registry are selected to be as close as possible to those of the randomized trials; thus, while various characteristics might be collected on each patient, no formal adjustment for case mix is required. For the present purposes, "case-mix adjustment" is the inclusion of various patient characteristics believed to influence complications of CE into a mathematical model used to predict the likelihood of these complications. Here, the most natural such model is a logistic regression. In Design 1, it is assumed that the characteristics of the registry patients are so similar to those of patients in the original randomized trials that no such adjustment is required.

Further, suppose that the 30-day complication rate of CE in the randomized trials was 3 percent. The study question can then be translated into a statistical hypothesis of a one-sample comparison of an observed complication rate vs. a prespecified value. In other words, the null hypothesis is that surgeons within the larger entity are, in aggregate, achieving complication rates that are the same (3 percent) as those of surgeons who participated in the randomized trials. The final input required to perform the sample size calculation is the complication rate under the alternative hypothesis. For example, if it is determined that the goal of the registry is to have high power to flag results as statistically significant if the true complication rate is 6 percent or higher, then the complication rate under the alternative hypothesis is 6 percent.

In general, the value of the complication rate under the alternative hypothesis is derived using a combination of quantitative and qualitative reasoning. (The precise methods used to derive the alternative hypothesis are context dependent and thus, not discussed in detail here.) In the present example, a cost-

effectiveness analysis might suggest that complication rates of 6 percent and above would call into question the efficacy of CE. Given these inputs, it can be shown that the effect size is 0.21, and the sample size required for 80-percent power is approximately 370.

Design 2: Continuing to follow patients at high risk of stroke, now suppose that the goal of the registry is to compare complication rates across hospitals. For simplicity, we continue to assume that patients are sufficiently similar to the comparator patients that no explicit adjustment for case mix is required.

Design 2 is a simple form of benchmarking application. For example, the CE complication rates for each hospital might be reported to a regulatory agency and/or the general public, the presumption being that statistically significant differences between complication rates can be used to identify hospitals with differences in quality of care. The particular danger in this design is that the complication rate for any particular hospital might be estimated with relatively little precision, thus generating results that have more noise than signal. (Another danger, discussed later, is that case-mix adjustment is required and not performed, or performed, but not adequate.)

We assume that the benchmarking will focus on comparing specific hospitals—i.e., in the underlying statistical model, hospital will represent a "fixed" rather than "random" effect. The null hypothesis is that the complication rates for all the hospitals are identical, and the alternative hypothesis is that the complication rates follow some pattern other than being identical. In this design, specifying the alternative hypothesis of interest is a potentially formidable task. One way to formulate this hypothesis is to focus on outlier hospitals. For example, suppose that there are 10 hospitals in the registry, the overall complication rate among 9 of these is expected to be 3 percent, and the complication rate at the tenth hospital is 10 percent. This information, along with expected number of cases in each hospital, is sufficient to calculate an effect size and thus perform the sample size calculation.

When comparing complication rates among specific hospitals, some adjustment may be made for multiple comparisons—that is, in any group of hospitals, there will always be a hospital with the highest complication rate, and focusing on differences between the outcomes of this particular hospital vs. outcomes of the others will overstate the level of statistical significance. The initial statistical test used to assess the homogeneity of complication rates across all the hospitals in the registry implicitly takes this multiple-comparison problem into account. Subsequent tests, in particular those tests that compare apparent outlier hospitals with others, should include an explicit adjustment for multiple comparisons, and the sample size calculations should reflect the fact that an adjusted comparison is being made.

In practice, the approach to this design might reasonably depend on whether registry data are being collected electronically or manually. If data are being collected electronically, then the most sensible policy is to collect information on all CE procedures performed within each hospital and to use the sample size formula as an assessment of whether the registry as a whole is likely to produce results that are sufficiently accurate to support decisionmaking. This assessment can be framed in terms of statistical power (as discussed above) or precision.

Considering precision, a 95-percent confidence interval for a nonzero complication rate for any hospital is $p \pm 1.96 \text{ sqrt } (pq/n)$, where p is the observed complication rate, $q = 1- p$, and n is the sample size. Supposing that $p = 3$ percent and $n = 300$ per hospital, within any particular hospital, the width of this confidence interval is expected to be approximately ± 1.9 percent. If data are being collected manually,

and thus the marginal cost of data collection per patient is high, then a reasonable policy would be to collect data on enough patients per hospital so that the precision of estimates of the complication rate within that hospital is considered adequate.

As with hypothesis testing, in deriving the width of the confidence interval, the analysis usually applies a combination of qualitative and quantitative insights. In particular, the question can be reframed as the following: For what values of the complication rate will my decision (whether taken from the perspective of clinical medicine, public health, etc.) be the same? For example, if the decision is the same regardless of where the complication rate falls within the range of 2-4 percent, then an interval of this width is "sufficiently precise."

Unless sample sizes are large, using registries to compare individual hospitals is potentially quite problematic. Although determining the inputs to the power calculations is not always a straightforward task, performing this analysis is quite useful, even if the result is only to suggest extreme caution in the interpretation of between-hospital differences.

Design 3: Continuing to follow patients undergoing CE, now suppose that the goal of the registry is to compare two different versions of the surgical procedure. For simplicity, continue to assume that patients are sufficiently similar to the comparator patients that no explicit adjustment for case mix is required. The following discussion (after including an adjustment for case mix, if appropriate) also applies to comparing two different versions of a medical device and similar applications. The key distinction between this design and Design 2 is that the primary comparison or comparisons can be stated ahead of time and that the number of comparisons is relatively small, thus implying that the issue of multiple comparisons can be ignored.

The analytic approach to this design is a logistic regression, with the input file having one record per patient. The outcome variable is the presence or absence of a complication, the categorically scaled control variable is the hospital, and the primary predictor is the categorically scaled coding of the type of surgical procedure (i.e., CE using version A vs. CE using version B). The null hypothesis is that, after accounting for any differences in hospitals, the two different versions of the procedure have identical complication rates. The alternative hypothesis is that the rates differ by a specified amount, this amount being the "minimum clinically significant difference" interpreted to be of concern. Power calculations proceed in the same fashion as for logistic regression with multiple predictors.

The main pitfall in this design is that patients who receive version A of the surgical procedure might differ from those who receive version B of the procedure along some dimension that has an impact on outcomes. (This pitfall is discussed in more detail under Design 4.)

In this application, the null and alternative hypotheses are sometimes structured the same way as in an equivalence trial—that is, differences in complication rates are not expected, and the goal of the study is to demonstrate that complication rates for the two versions of the surgical procedure are similar within a certain level of precision. The structure of the analysis is not fundamentally different. Indeed, sample size calculations for equivalence trials are sometimes not performed within a hypothesis-testing framework but instead are performed by identifying a sample size of sufficient magnitude to make the confidence interval for the difference in the complication rates between the two versions of the surgical procedure a certain width. For simplicity of presentation, from now on, assume that any equivalence-

trial-type calculations can be reframed into confidence interval format, and thus need not be discussed separately.

Design 4: Continuing to follow patients at high risk of stroke, and continuing to assume that the goal of the registry is to compare two different versions of the surgical procedure, now additionally assume that this comparison will adjust for case mix. Within the logistic regression paradigm, variables used to adjust for case mix are accounted for as covariates (i.e., additional predictors). Alternatively, propensity-scoring methods could be used to adjust for those variables that predict the assignment of patients to particular versions of the procedure. For concreteness, focus on logistic regression. In order to perform a sample size calculation for a logistic regression, the analyst must specify the predictive ability of the covariates and the odds ratio associated with the predictor of interest. (For example, version B of the procedure might increase the odds of complications by a factor of 1.5.) Once these inputs are specified, the sample size calculation is straightforward.

Both the logistic regression and propensity-scoring approaches suffer from the fundamental drawback that they can adjust only for covariates that are observed. In particular, if there are variables that predict outcome that are unmeasured (e.g., physician's assessment of a patient's likelihood to comply with treatment or stroke in evolution not included in the administrative database used as the source of data for the registry), then the comparison between the two versions of the surgical procedure is potentially biased. Accordingly, before proposing to use a registry to compare complication rates (e.g., across different versions of a procedure or a device) or other outcomes, it is critical to determine that the following three conditions do not all hold: (1) a patient, provider, system or other characteristic affects the complication rate; (2) this characteristic is unmeasured within the registry; and (3) there is a reasonable likelihood that this characteristic might be differentially distributed across the different versions of the procedure or the device. If all three conditions (in epidemiologic terms, the conditions for "confounding") hold, use of the registry to compare outcomes is potentially dangerous.

Critical to Designs 1-4 is the assumption that the CE complication rate is stable over time. Thus, for example, it is appropriate to use the registry to estimate a single complication rate associated with version A of the procedure, estimate another single complication rate associated with version B of the procedure, and compare the rates. On the other hand, if the technology of CE (e.g., physical materials, surgical technique) is improving, then the registry should continue to monitor the performance of CE over time. Such an ongoing monitoring function seems particularly relevant for medical devices and similar applications.

Even when the associated technology is assumed stable, some registries are intended to provide ongoing assessments of outcomes. For example, in a quality assurance context, CE complication rates might be assessed at individual hospitals on an annual basis (e.g., in order to check for problems that have recently arisen). On the other hand, a registry whose purpose is to assess whether the complication rates that were observed in randomized trials could be achieved in usual practice could be designed with a sunset provision to cease operation once this question is answered. The latter type of registry might, for example, accompany a conditional coverage decision by the Centers for Medicare & Medicaid Services.

Having an ongoing monitoring function induces additional analytical complications, among others a multiple-comparisons problem. Traditional statistical power calculations are performed under the assumption that the sample size is fixed and that (unless otherwise noted) multiple comparisons are not a

major issue. Sequential testing methods associated with randomized trials (where, for example, the type I error of .05 is apportioned into an early test with alpha = .001 and a subsequent test with alpha = .499) do not apply to this particular design, since most of these methods assume that the maximum sample size is fixed. (Some methods assume that what is fixed is not the number of patients but the number of events, but these methods are not a good match for registry applications either.)

Design 5: Suppose the goal is to estimate the complication rate associated with CE at multiple time points for the foreseeable future.

Control chart methodology might reasonably be applied to this class of problems. This methodology, often used in the quality assurance and quality improvement context, was originally developed for industrial applications. In this example, the null hypothesis, under which the system in question is "in control," is that the CE complication rate remains at the desired value of 3 percent throughout the entire followup period. Samples are taken at each point in time (e.g., monthly). As an example, if these monthly samples are of size 100, then the standard error is approximately 1.7 percent. The analyst then creates a "control chart" by plotting these monthly complication rates over time and forming "channels" based on the standard error. In this example, the channel extending from the point estimate to 1 standard error above the point estimate is 3 percent to 4.7 percent.

Once the basic control chart (which goes by different names depending on the scale of measurement of the outcome variable) is formed, the plot is checked for various violations of the null hypothesis of constant complication rates. The set of possible violations to be flagged as statistically significant might include (1) any observation more than 3 standard errors from the mean; (2) two of three consecutive observations more than 2 standard errors from the mean; (3) eight observations in a row that increase or decrease; and (4) eight observations in a row on one side of the mean. These rules of thumb implicitly take into account the multiple-comparisons problem by requiring noteworthy departures from the null hypothesis in order to be flagged, and they are based on the observed properties of physical machines as they fall out of adjustment (suddenly breaking down and producing an extreme outlier, gradually heating and thus producing sequentially higher readings, etc.). Complication rates of CE might or might not follow the properties of physical machines, but the decision rules from control chart methodology are at least a good place to start.

Appendix B: Copyright Law

Copyright law confers exclusive legal rights to the owner of the copyright.[335] The exclusive rights of copyright may be sold, assigned (transferred), or licensed (limited transfer of rights for use on specific terms or conditions) to others; these rights may also be waived (quit claim). Licensing ordinarily consists of a private agreement governed by contract rather than copyright law.[336]

The exclusive rights conferred by copyright to prepare derivative works and distribute copies of a health information registry, however, may be limited by regulatory requirements. Privacy Rule restrictions may exist on data use, reuse, and disclosures or may require additional patient authorizations for subsequent research use. The conditions of institutional review board approval under the Common Rule may also limit reuse and further disclosure of registry data. The terms of patient authorization and consent, a data use agreement, or a business associate agreement may modify the scope and nature of rights protected by copyright law. These limitations can be avoided by the use of de-identified health information, as defined by the Privacy Rule, plus information that is not subject to the Common Rule, if they suffice for the scientific or other purposes of the registry. Without resort to copyright protections, State laws may directly restrict access to registry data, as well as the use and disclosure of data from registries developed by public health agencies.

Formal copyright registration[337] with the U.S. Copyright Office is not necessary but may be desirable for registries anticipated to have commercial value. The owner of a copyright is generally the author[338] or author's employer; ownership of the copyright for a compilation is not ownership of the underlying facts or data.[339] Copyright law presumes that an employer owns the copyright in materials created by an employee within the scope of his or her employment as a "work made for hire." Institutional policies and procedures frequently prescribe whether the registry developer, his or her employer, or a funding agency owns the copyright. Employee manuals often contain an employer's position on the intellectual property created by employees. Research institutions frequently reserve the right to the intellectual property produced by their employees. Intellectual property issues are explicitly negotiated in most sponsored research contracts. Authors of a joint work are co-owners of copyright in the work.[341]

Several factors determine whether the use of a registry protected by copyright for scholarship, research, or certain other purposes is within the statutory fair use limitation on copyright.[342] In general, these factors will support subsequent uses of registry data for research, even though it may be protected by copyright. In any given set of circumstances, a specific analysis of the statutory factors is necessary to determine whether use is likely to be viewed within the fair use limitation on copyright.[343]

Copyright law may provide some legal protections for compilations such as health information registries. The extent of this protection depends on the specific characteristics of the registry. In general, the concept of ownership does not comfortably apply to health information, even when limited to copyright. Nevertheless, some registry developers may want to consider adding the legal protections of copyright to reinforce controls on access to and use of registry data. Registry developers may also encounter copyright protections on health information held by health care providers. Use of health information protected by copyright for research purposes may constitute fair use under copyright law.

Appendix C: Relevant Entities in Health Information Technology Standards

The Clinical Data Interchange Standards Consortium, or CDISC, is a multidisciplinary non-profit organization that is focused specifically on medical research, and works toward developing and supporting global, platform-independent data standards that enable information system interoperability. It is a membership organization made up of more than 170 academic research centers, global biopharmaceutical companies, technology and service providers, and IRBs.[602] CDISC has established standards to support the acquisition, exchange, submission and archival of clinical research data and metadata, such as case report tabulation data definitions, submission data, and operational data modeling; these standards are intentionally vendor-neutral, platform-independent and freely available.[603] CDISC has formed key partnerships with other standards bodies, vendors and research groups to further the creation and use of these and other industry standards. CDISC's Healthcare Link project is a board-approved initiative that specifically focuses on the mission of interoperability between healthcare and clinical research.[604]

Health Level Seven, or HL7, is an American National Standards Institute (ANSI) -accredited organization that produces specifications and protocols for clinical and administrative health care data. HL7 is a global organization with corporate and individual membership consisting of providers, vendors, payers, consultants, and government groups. Like CDISC, HL7 does not develop software, but instead creates specifications. HL7's original specification was a messaging standard that enables disparate healthcare applications to exchange keys sets of clinical and administrative data.[605] This standard defines the structure and content of the messages that are exchanged between systems in either batch mode, which facilitates transfer of a collection of individual messages labeled by a single header, or interactive mode, which transmits a single message. HL7 then extended this idea to a Clinical Document Architecture (CDA), which is designed to support standards for storing and retrieving file-level information, such as electronic health records.[606] The Reference Information Model (RIM) then specifies the details, results, and contexts of clinical informatics by defining subject areas, classes, attributes, use cases, and trigger events, such as a followup clinical visit.[607] HL7 also houses important specifications and tools relating to electronic documentation of standards, for example, the Continuity of Care document (CCD).

The Healthcare Information and Management Systems Society, or HIMSS, is an industry membership organization that focuses on knowledge sharing, advocacy and collaboration among its members. HIMSS is a long-standing advocate of using information management systems to improve health care, and represents a large portion of the industry (over 20,000 individuals and 350 corporations).[608] HIMSS plays a critical role in this discussion through the HIMSS Electronic Health Record (EHR) Association, and also through its role in partnering with two other key standards groups: HITSP and IHE.

The HIMSS Electronic Health Record Association (EHRA) is a trade association specifically made up of Electronic Health Record (EHR) companies. This Association is a key player in the interoperability discussion. The HIMSS EHR Association focuses on creating interoperable EHRs in hospital and ambulatory care settings, by providing a forum and structure for EHR leaders to work toward standards

development, interoperability, the EHR certification process, performance and quality measures, HIT legislation, and other EHR issues.[609]

IHE, or Integrating the Healthcare Enterprise, is an initiative sponsored by HIMSS that is designed specifically to bridge the gap between existing standards and the implementation of integrated systems. IHE does this by creating Profiles, which specify precisely how standards are to be used in integration implementations. It is important to note that IHE does not develop standards; instead, it provides a link point between the standards that exist and the problems among the industry that need to be solved. The initiative is focused on eliminating ambiguities, reducing configuration and interfacing costs, and ensuring a higher level of practical interoperability for users and developers of health care information technology as they implement standards-based communication between systems and then perform tests to determine that the implementation conforms to the specifications.[610] Standards from different organizations that achieve the same goal can be inserted into an IHE profile and IHE will then produce technical specifications that can be used by developers and vendors to build products that are compliant with those standards. IHE's value has been recognized by other standards organizations, particularly CDISC, because of its practical approach. For example, IHE has defined a simple 4-step process that carries a specific problem from problem definition, through implementation and testing, to the real world:

1. Identify interoperability problem
2. Specify Integration profiles
3. Test systems at Connectathon (an annual weeklong interoperability-testing event); demo at HIMSS Interoperability Showcase
4. Implement in real world

The Healthcare Information Technology Standards Panel (HITSP) serves as a partnership between the public and private sectors with the purpose of identifying a widely accepted set of standards for interoperability of health care applications. HITSP is funded by HHS, administered by ANSI, and tightly partnered with HIMSS; Federal agencies are mandated to use interoperability standards that have been harmonized by HITSP.[611]

The Certification Commission for Health Information Technology (CCHIT) is a private nonprofit organization with the 'sole public mission of accelerating the adoption of robust, interoperable health information technology by creating a credible, efficient certification process'.[612] It is divided into workgroups that address the standards for specific functional areas such as ambulatory care, behavioral health, personal health records, and cardiovascular care. Since being recognized as a certifying body by the U.S. Department of Health and Human Services in 2006, it remains the only Federally approved organization to certify health IT products and systems.[613]

Table C-1. Relevant Entities in Health Information Technology Standards

Group	YearEst.	# Members	Mission	Relevant Standards/ Specifications
CDISC	2000	>170 (corporate)	Develop and support data standards	CDASH
HL7	1987	>2200 (individuals)	Produce specifications and protocols for clinical and administrative health care data	CDA, RIM, CCD
HIMSS	1961	>350 (corporate), >22,000 (individuals)	Knowledge sharing, advocacy and collaboration	
EHRA	2004	~40 (corporate)	Creating interoperability between existing EHRs	EHRA Interoperability Roadmap
IHE	1997	>230 (organizations)	Provide a link point between the standards that exist and the problems among the industry that need to be solved	RFD, CRD
HITSP	2005	>550 (corporate and organizations)	Partnering with public and private sectors to achieve standards to support interoperability among healthcare software applications	TP50, C76
CCHIT	2004	26 products certified under 08 CCHIT ambulatory EHR criteria	Defines the requirements for an EHR to be certified in the US	CCHIT certification criteria (available at www.cchit.org/certify)

Appendix D: Linking Clinical Registry Data with Insurance Claims Files

A research project is being designed to compare the effectiveness of one class, or specific generic medication within the class, to another for treating diabetes. The results should provide scientific evidence for patients, physicians, and policy makers on which to base decisions about the use of these drugs.

Registry developer A will collect limited data sets of information on patients discharged with a diagnosis of diabetes from hospitals in three states. These limited data sets do not include patient names or direct identifiers, so are not considered individually identifiable health information under the HIPAA Privacy Rule. The registry developer has institutional review board (IRB) approval to use this data for research purposes. The hospitals will provide the data sets to group B under a data use agreement that complies with the HIPAA Privacy Rule.

Group B intends to perform probabilistic matching of the registry data to a health insurance claims database to determine diabetes treatment outcomes. Registry developer A and the research group B entered into a formal collaboration for this research project.

The health insurance database will be derived from the claims data of multiple health plans operating in the same three states. The insurers' original data sets include direct beneficiary identifiers and constitute protected health information under the HIPAA Privacy Rule. Because the registry contains only limited data sets, the claims data collected in the insurance database will have to be linked to the registry data using probabilistic matching techniques.

Consequently, the research project will only use a limited data set of health insurance claims data to create the link with the registry data. The health insurance companies will provide the limited data sets of claims information to group B under data use agreements that comply with the HIPAA Privacy Rule.

The common data elements for the insurance database and the registry that will be used for linkage are date of birth, gender, race, hospital ID, state of hospital, date of admission, date of discharge, date of death (if patients died), ICD-9 code for primary diagnosis for the index hospitalization, primary procedure code for the index hospitalization, and the ZIP codes for patient addresses.

In order to protect the identity of the hospitals, the researchers were asked to sign a confidentiality agreement, which specifically defined the registry operator's proprietary information. Such proprietary information included the names or other identifiers of hospitals or other healthcare facilities participating in the registry. The researchers were precluded from using the names or other distinguishing characteristics of the hospitals in any public document, including publications or marketing materials. The confidentiality agreement did allow the researchers to retain an identifier number for each hospital, so long as that number only identified generic characteristics and excluded any information about the hospital that would enable anyone to identify the specific hospital. For example, the researchers could not retain information that classified a particular hospital with a number that identified it as an academic teaching hospital based in a particular state with a certain number of beds, since in many instances, the

identity of the hospital could be derived from such information. Due to the potential contractual liability that may arise, the possibility of identifying participating hospitals is a critical issue to address.

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[292] CIOMS Guidelines, supra note 2, at paragraphs 18-21.
[293] CIOMS Guidelines, supra note 2, at paragraph 26.
[294] CIOMS Guidelines, supra note 2, at paragraph 40.
[295] See generally CIOMS Guidelines, supra note 2, at paragraph 43.
[296] See, for example, Section III, Article 8 of Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.
[297] See, for example, U.S. Department of Health and Human Services (HHS) regulations at 45 CFR Part 46; 21 CFR Parts 50 and 56 for research conducted in support of products regulated by the Food and Drug Administration (FDA).
[298]Regulations identical to 45 CFR 46 Subpart A apply to research funded or conducted by a total of 17 Federal agencies, some of which may also require additional legal protections for human subjects.
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[328] The Common Rule as adopted by HHS contains special protections for certain defined "vulnerable" populations, i.e., women, human fetuses, neonates, prisoners, and children. See 45 CFR Part 46, Subparts B, C, D.

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[346] 45 CFR 46.111(a)(7).

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[348] See 45 CFR 164.514(a)-(c) and (e) on the deidentification of health information and limited data sets, respectively.
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[353] 45 CFR 164.514(c).
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[356] 45 CFR 164.514(e)(4).
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