Medical Device-Based Registries

Draft White Paper for Third Edition of
"Registries for Evaluating Patient Outcomes: A User's Guide"

Introduction

Medical device registries are critical for the identification and study of medical devices outcomes. Device registries are used for many purposes, including long-term surveillance, fulfillment of postmarket commitments for regulatory bodies, comparative effectiveness assessments, and demonstration of effectiveness in under-studied subpopulations (see Chapter 1: Patient Registries for extensive discussion on the definition and purposes of registries in general[i]). Medical device registries play an increasingly important role in bridging the gap between device performance in clinical trials and their use in routine practice over time. Unlike clinical trials, device registries allow assessment of medical device performance in a real world setting. Registries contain data on large numbers of patients receiving care in diverse clinical settings and include clinical outcomes over time, thus providing a critical platform for capturing the experience with a medical device throughout the device and patient lifecycle. Moreover, by linking device exposures and long-term outcomes, registries permit follow-up that can span decades.

While devices share some similarities with drugs, several major issues unique to devices require special consideration in order to construct and use a medical device registry successfully. Outcomes associated with medical devices can be affected not only by underlying patient factors and device factors (such as biomaterials), but also by user interface (e.g., surgical technique or surgical preference and experience). Adverse effects of devices can be localized (e.g., stent thrombosis), but may be more systemic (e.g., toxic, allergic, autoimmune effects). Furthermore, additional hazards may be related to human factors and interactions. Finally, device malfunctions may be very diverse, ranging from manufacturing problems, design-induced errors, and anatomic or engineering effects.

Special challenges related to registry design, data collection, and analysis include the need for unique identification or overall identification of devices; detection of device failure; the need for follow-up; the

[i] Chapters referenced in this document can be found in the second edition of "Registries for Evaluating Patient Outcomes: A User's Guide," available at: http://www.effectivehealthcare.ahrq.gov/ehc/products/74/531/Registries%202nd%20ed%20final%20to%20Eisenberg%209-15-10.pdf.

ability to capture and take into account combinations of device and drug or of multiple components within a device; device modifications; and healthcare provider experience and learning.

This chapter will address two topics related to medical device registries: challenges in design and data collection and potential uses of emerging technology. The chapter begins with a discussion of the major considerations that influence the design of device registries and the data that must be collected. Potential approaches to address a variety of design challenges are described. The chapter then discusses emerging technologies that will potentially allow integration of automated device data capture into registry datasets.

Different Lifecycles between Drugs and Devices

Many medical device registries are similar in purpose to the key aims of drug registries, but, because the United States regulatory process differs between drug and device development, device registries require some special features and considerations. For example, the approximately 1,700 different types of devices requires three regulatory device classes with different submission processes, which highlights the complexity involved with evaluation of device safety and effectiveness. The U.S. Food and Drug Administration (FDA) classes I, II, and III are differentiated by the intended use of the device, and class then determines the type of premarketing submission required for FDA approval.[1] In addition, the current paradigm encouraged by the Total Product Life Cycle (TPLC) model[2] aims to apply knowledge acquired during product development to future generations of products. This useful framework establishes a solid baseline for understanding effectiveness and safety in devices, but much more information is necessary to fully understand these products during the lifecycle of innovation.

Differences between drugs and devices persist throughout TPLC. For example, drug modifications occur slowly, whereas device technologies often experience rapid changes over time.[3] Device registries must capture experiences with modifications of an individual and/or class of devices over time. In addition, device performance is affected by factors beyond the device itself. Sedrakyan and colleagues provide a comprehensive summary of the critical components of device evaluation, with a specific focus on implantable medical devices (IMD).[4] The observational data builds on randomized controlled trial (RCT) data to include both on and off-label use of the IMD and highlights the impact that insurance, distance to qualified providers, and geographic location have on both device use and outcomes.

Design and Data Collection Considerations

As with all registries, the primary purpose of a medical device registry will guide design options. Many factors related to registry design are similar to those discussed in Chapter 3: Designing a Registry, such

as selection of a study design and sample size considerations. However, some distinctive features of a medical device registry require additional planning. It is critical that the registry is adaptable to various needs that arise during the lifecycle of device innovation. Some challenges include device identification/lack of unique device identifiers; variation in the ways a device can fail; combination of devices or components from similar and different manufacturers; device changes over time; the need for longer follow-up; and impact of provider experience, training, and choice of device. Moreover, unique device failure modes may be identified that precede consequential clinical signs and symptoms, allowing for remedies before harms are experienced by the patient. This chapter will provide general suggestions for addressing these challenges, but each device registry is unique and will require a solution appropriate for its specific purpose.

Device Identification

Currently, Unique Device Identifiers (UDI) are largely unavailable – this is in sharp contrast to drugs, where National Drug Codes permit universal drug identification in billing claims data and in registries. The inability to identify specific devices affects registry design and data collection and poses challenges for researchers and regulators. Compounding the problem is the fact that device modifications are frequent and part of the business model for manufacturing and innovation. Researchers may connect safety and effectiveness to a class/subset of devices, rather than to the device generally. Hence, it is critically important to identify an individual device accurately. Related challenges include the lack of standardized definitions and attribute (descriptor) creation based on specific device product codes; difficulties in data collection, such as transmitting information from electronic medical records (EMR) to registries or automated data capture such as those related to barcode scanning accuracy;[5] and hurdles in maintaining master product lists.

Section 519(f) of the Federal Food, Drug, and Cosmetic Act (based on a 2007 amendment) directs the FDA to promulgate regulations establishing a unique device identification system for medical devices. This FDA initiative eventually will assist with many of the challenges posed by the current lack of standard identifiers for medical devices. In the meantime, several approaches may be used to capture identity in the absence of a UDI that is unique across all devices. For example, some devices have identifiers, such as catalogue, serial, and lot numbers, that are unique to device class or manufacturer. While these are not standardized and there may be several components from different manufacturers with similar serial numbers, these numbers can facilitate device identification and tracking when combined.

Thus, prior to UDI implementation, researchers must be creative in collecting device information and taking advantage of UDI-like data to fill the gap created by the lack of identifiers. For example, the

Society of Thoracic Surgeons Adult Cardiac Database developed a data collection form with an exhaustive list of various heart valve devices. This checklist enables registry participants to collect any information that could be relevant to their practice. Orthopedic registries worldwide are taking advantage of serial number, lot number, or catalogue numbers in order to classify and uniquely identify products. An inefficient but at times appropriate solution is to include device photos in the registry. This strategy is most applicable in settings with few devices on the market that have marked differences in design that can be captured with photographs.

Device Failure

There are numerous types of device failures, making it difficult to capture all potential failure modes and adverse events in a single device registry. For example, a device can squeak, break, rupture, or become infected. Importantly, the propensity to develop these failures is often unknown during the registry design phase. While the discussion of adverse event reporting requirements for device registries is outside the scope of this chapter, careful consideration of anticipated categories of failure modes is important in registry design. Researchers should consider methods of adjudication and verification of device failure during the design phase in order to ensure collection of all data elements needed to inform those discussions. It is also important to consider how potential failures will be detected for the particular device.

Automated surveillance within the registry is an advanced approach to identifying device failure; when implemented correctly, it can permit real-time evaluation of failure within a large sample/population. Surveillance, however, is a complex endeavor, and standardized data elements and collection procedures are required, likely across multiple institutions or registries. There are several examples of successful registry implementations for surveillance in cardiovascular disease. The Data Extraction and Longitudinal Trend Analysis (DELTA) network study was the first computerized safety surveillance study for cardiovascular medical devices. This multicenter prospective observational study was designed for safety evaluation of drug eluting coronary stents, embolic protection devices, and vascular closure devices used during percutaneous coronary intervention.[6] It used standard data elements from the American College of Cardiology National Cardiovascular Data Registry (NCDR), which facilitated aggregation of safety events across institutions.

Device Systems and Components

In many cases, the device of interest for a registry is either part of a larger system of devices or contains multiple components that are considered devices themselves. Issues around the lack of unique identifiers persist and are accompanied by the additional challenge of determining which component is responsible for failure. Sometimes, device components are cleared or approved separately by the FDA. When a

registry is designed to understand effectiveness and safety and the device of interest is dependent on its accompanying devices, information on all components must be captured in enough detail to assess how well the device of interest is functioning. If an adverse event occurs, regulators must be able to pinpoint which component of the system of devices requires action.

In most instances, devices are approved by the FDA as full systems rather than singular components. However, surgeons may 'mix and match' multiple manufactures or multiple brands into one system. Such mixing presents a data collection issue as well as an analytical challenge. Heterogeneous devices may need to be grouped together in order to perform analysis, and assumptions about homogeneity may not hold. Components of the newly created system may have different stages of expiration, which could alter the effectiveness or long-term safety of the overall system. Because there are different lifecycles for components in the same system, components may be replaced at different rates. Registries can address this by collecting data on the system as a whole and then attempting to obtain the expiration dates for each component.

In addition to the actual device, some implantable devices require assistance from procedural devices, including other commodity devices or operative instruments. In these cases, additional information must be collected. For example, in hernia repair, information on the method of mesh adhesion, such as staples, glue, or sutures, may be necessary for collection, as these adhesives could interact with a specific type of mesh and cause failures. Researchers should consider the role of these factors and how they can be captured in the data collection process.

Drug / Device Combinations

Device/drug combinations have become increasingly common over the past decade. Because the development processes for drugs and devices differ, combination products face different challenges. For example, drug-eluting stents (DES) are an example of a product where the device, a bare-metal stent, has been enhanced by the addition of an immunosuppressant or mitotic inhibitor[7] and its elution polymer coating. In 2003, the FDA approved the addition of drug to stents for a subset of cardiac patients with uncomplicated coronary lesions.[8] In these patients, there was a decrease in coronary restenosis causing repeat revascularization 9 months after stent implantation compared with bare-metal stents. However, as the adoption rate of DES increased, the population of patients in which they were implanted changed – they tended be sicker patients. Moreover, stent thrombosis, a rare but serious adverse event, was higher in DES patients at one-year compared to bare metal stent patients.[9,10,11] In cases like this, registries are a critical tool for understanding the long-term safety and effectiveness of the technology.[12,13,14] Special considerations in registry design include separate collection of concomitant drug dosing information and

attention to the medications that the patient is taking during implantation in order to flag possible drug interactions. It is also important to prospectively collect concurrent medications that the patient is using over time, again in order to understand potential interactions.

Obtaining Sufficient Follow-up Information

Obtaining sufficient follow-up is an issue for all studies, and many of these challenges are addressed in Chapter 3: Registry Design and Chapter 7: Patient and Provider Recruitment and Management. However, long-term follow-up is a particular concern with implantable devices. Clinical trials have relatively short follow-up for implantable devices that are expected to stay in the body indefinitely or until replaced with similar device. These devices may be studied for less than 5 years but are intended to work for decades. While follow-up time in the initial period of implantation is useful, an indefinite follow-up registry imbedded within a clinical practice has the ability to answer questions concerning device safety and effectiveness for as long as it is required. Few registries have sufficient follow-up for endpoints of device performance, continuous effectiveness, and safety. One of the best examples is the National Joint Replacement Registry of Australia,[4] which has follow-up of greater than 10 years.

A unique challenge for device registries is that once a device is implanted, a patient does not have to return to the doctor if they do not have any issues, as opposed to a therapeutic situation where patients return for prescription refills. As a result, collecting follow-up data both directly from patients and through the healthcare provider is a useful tool for patient retention. Loss to follow-up differentially for patients that do not experience complications is a risk and underscores the importance of achieving reasonably complete follow-up on all patients through well-designed continuity of care delivery settings[15]. Long- term data on medical devices can also be obtained through linking registries with administrative billing data or other clinically rich data sources.

Provider Experience and Training

Provider experience and training can influence the selection of device, device performance, and patient outcomes, particularly for implantable devices. Surgeons generally have a preference in terms of selection of devices, and although sometimes this is based on clinical appropriateness, it can also be based on marketing or familiarity with a particular brand. Group purchasing organizations may also influence selection, and, in these cases, surgeons may not have a choice of device. Additionally, provider experience and surgical/procedural skill can greatly influence effectiveness and safety of devices.[16]

Because of the impact that the healthcare provider can have on device performance, collection of a provider identifier, identifiable or synthetic, may be an important component of a registry. The collection of identifiable provider codes raise concerns about data security and may present a deterrent for physician

participation. Novel methods of using synthetic identifiers, such as those that integrate provider characteristics, may need to be considered.

Device-specific training is an important element of a medical device registry that is not an issue in a drug registry. Device premarket studies are typically smaller than drugs studies Post-approval, regulatory agencies are concerned about training program quality. Often, an observational study is required to formally evaluate the appropriateness of physician training. Regardless of whether regulators have mandated this type of study, the integration of training information into data collection is recommended by regulators. The importance of this varies based on device type. For example, in the case of the introduction of a new carotid stent, experience with similar stent types, such as balloon-expandable or self-expanding, can be translated to observed patient outcomes. However, if a percutaneous valve is being studied, specific training on the delivery technique required by that specific valve is important. The amount of training required to ensure safe application of technology is often unclear.[9]

Beyond training, there are experience-oriented factors that should be considered in analyses and training evaluation: practitioner training; practitioner annual volume; practitioner lifetime volume; facility volume; and facility characteristics such as academic teaching status. It is important to distinguish between these factors because there is a threshold effect for each. Some factors, particularly lifetime volume, have not been well documented or analyzed. For this reason, registries should consider capturing this data despite the challenges. For others, such as hospital volume and academic teaching status, the relationships with complications, revision surgery, length of hospital stay, and mortality are well documented.[17,18,19] It is ideal to have training and volume information in the registry, but this may not always be realistic. If this is deemed critical, information needs to be collected on provider experience and training at registry initiation and supplemented if any training programs occur during the registry development.

Registry design teams should consider how provider training and learning curves could be handled during analysis. Particularly for devices with few qualified surgeons, clustering may be an issue in analysis. Sample size may need to increase, and statistical methods that account for clustering such as generalized estimating equations should be utilized. Adjustment by surgical volume, either on the hospital or provider level, might also be appropriate.[20] For example, some studies have shown that categories integrating both of these components as one adjustment variable (e.g., high volume hospital and surgeon; high volume hospital with low volume surgeon; low volume hospital with high volume surgeon; both low volume) are useful.[21]

Summary of Design and Data Collection Considerations

Although device registries are similar to other registries operationally, the challenges outlined above are critical to consider during the registry design phase. Careful review of the unique features of medical device registries can result in high quality, useful studies of device performance. Medical devices must be identified accurately and their attributes classified according to standard nomenclature. Minimum recommended identity variables include manufacturer, product name, lot number (where applicable), catalog number, serial number (where applicable), description of device, and device attributes. These implant characteristics can then be linked to patient, surgeon, hospital, and procedural data along with outcomes of interest. Device identification and attribute classification require constant maintenance as new devices are introduced into the market. In the future, UDIs will significantly facilitate this process. A standard minimum dataset targeted toward device registries would be useful for supporting strong registry designs and to facilitate linkages with other data sources.

The definition and validity of device failures is another important element. In developing a device registry, the modes of failures and definitions must be clearly defined. Device failures should be adjudicated and verified for accuracy. It is also crucial to track all device components. Device systems such as leads and generators in implantable cardioverter defibrillators (ICDs) must both be tracked in case either component fails. Collecting information to track drug/device interactions is also critical. Finally, sufficient follow-up of patients must be established for registries to provide longitudinal outcomes.

Over time, various stakeholder communities have increased their efforts to foster the development of clinical registries as a valuable postmarket tool for capturing utilization of devices, identifying early signals, and studying postmarket performance of medical technology. Examples of long-standing collaborative efforts include those between FDA and professional society databases such as the American College of Cardiology NCDR.[22] This collaboration resulted in one of the largest observational studies on hemostasis devices using NCDR registry data.[23] In addition, the FDA collaborated with Duke University and the Society of Thoracic Surgeons to study the outcomes of transmyocardial revascularization procedures using the Adult Cardio Thoracic Database.[62] More recently, the national multi-stakeholder community, including professional societies, the FDA, and the Centers for Medicare and Medicaid Services worked together to establish the first national transcatheter valve therapy (TVT) registry to capture transcathether aortic valve replacement therapies.[24] In the orthopedic arena, the FDA led the development of International Consortium of Orthopedic Registries to advance the methodological infrastructure for studying performance and clinical outcomes of orthopedic implants.[25]

Potential Uses of Emerging Technology

Registries may soon be able to take advantage of emerging technology for data transmission. New technologies can enable medical devices to transmit data directly to electronic medical records and other patient management systems. Ultimately, this type of data may be sent directly to a patient registry, reducing the burden of data entry and increasing the timeliness of registry data.

These new technologies are currently at various stages of development. Automatic measurement and adjustment of programming to provide optimal settings is a potential area of innovation that would provide efficiencies in the use of pacemakers and other implantable devices. Feasibility for this has been demonstrated by the Automaticity registry, which aims to evaluate physician's acceptance of automatic algorithms for ventricular capture, automatic sensing, and automatic optimization of sensor settings. [26,27] The Automaticity team concluded that project team follow-up and avoidance of reprogramming due to the automated programming can increase effective use of hospital time and resources. This would be a useful technology for registries because all automated changes can be collected at one follow-up time point, rather than collecting each change ad-hoc as it occurs.

Diagnostics for implantable devices are another area of technical improvement. Implantable devices, such as ICDs, pacemakers, and cardiac resynchronization therapy devices, can track heart rate, heart rate variability, respiration rate, atrial tachyarrhythmia and ventricular tachyarrhythmia recurrence and duration, intrathoracic impedance, symptom markers, and patient activity.[28] This diagnostic information can be provided directly to EMRs and feed into registries, in many cases continuously. Although the clinical application of this capability is still being examined, the benefits in efficient, timely data capture are clear.

The fascinating pace of emerging medical technologies and information science applications are expected to further shape the healthcare research. Further development and integration of device-based registries into national postmarket infrastructure creates opportunities for novel methodology developments, harmonization, sharing, and combining of data.

Conclusion

Medical device registries can be designed for a variety of purposes. They can provide useful information on long-term effectiveness and safety of drugs, as well as the impact of factors such as surgical technique, surgeon, hospital, and patient characteristics. Like all studies, medical device registries have some limitations. Failure to control for often-complex confounding variables and the inability to take into account device version changes, surgical technique, and other unique factors can lead to false or

misleading conclusions. In addition, medical device registries are limited in their ability to identify small differences in performance among relatively similar, well-designed devices.[29] However, careful consideration of the unique nature of medical devices in registry design and analysis will allow medical device registries to bridge the gap between device performance in clinical trials and use in routine practice over time.

References

[1] U.S. Food and Drug Administration. Device Classification. Available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm. Accessed May 7, 2012.
[2] U.S. Food and Drug Administration. Total Produce Life Cycle. Available at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm199906.htm. Accessed May 7, 2012.
[3] Boam AB. Innovative Systems for Delivery of Drugs and Biologics. PowerPoint Presentation. Available at: www.fda.gov/ohrms/dockets/dockets/03n0203/03n-0203-ts00010-Boam.ppt. Accessed May 17, 2012.
[4] Sedrakyan A, Marinac-Dabic D, Normand SL, et al. A framework for evidence evaluation and methodological issues in implantable device studies. Med Care. 2010 Jun;48(6 Suppl):S121-8.
[5] Paxton E. Kaiser Permanente Implant Registries. PowerPoint Presentation. Available at: http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM272080.pdf. Accessed May 17, 2012.
[6] Vidi VD, Matheny ME, Donnelly S, Resnic FS. An evaluation of a distributed medical device safety surveillance system: the DELTA network study. Contemp Clin Trials. 2011 May;32(3):309-17.
[7] Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet. 2007 Feb 24;369(9562):667-78.
[8] Serruys PW, Kutryk MJ, Ong AT. Coronary-artery stents. N Engl J Med. 2006 354 (5): 483–95.
[9] Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation. 2007 Mar 20;115(11):1440-55; discussion 1455.
[10] Bavry AA, Kumbhani DJ, Helton TJ, Bhatt DL. What is the risk of stent thrombosis associated with the use of paclitaxel-eluting stents for percutaneous coronary intervention? A meta-analysis. J Am Coll Cardiol 2005;45:941-946
[11] Babapulle MN, Joseph L, Belisle P, et al. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. Lancet 2004;364:583-591
[12] Abizaid A, Chan C, Kaul U, et al. "Real World" evaluation of slow-release, polymer-based, paclitaxel-eluting TAXUS™ stents in native coronary arteries: the WISDOM international registry. Circulation. 2003;108(Suppl IV):IV-534. Abstract 2436.
[13] Guagliumi G, Sousa E, Urban P, et al. Sirolimus-eluting stent in routine clinical practice: a 6-month follow-up report from the international e-CYPHER registry. Circulation. 2003;108(Suppl IV):IV-534. Abstract 2437.
[14] O'Malley AJ, Normand, SL, Kuntz RE. Models for multivariate mixed outcomes application to the estimation of the objective performance: coronary-artery stenting. Stat Med 2003;22:313-36.
[15] Kuntz RE, Keaney KM, Senerchia C, Baim DS. Estimating the late results of coronary intervention from incomplete angiographic follow-up. Circulation 1993;87:815-30.

[16] Barker FG 2nd, Amin-Hanjani S, Butler WE, et al. In-hospital mortality and morbidity after surgical treatment of unruptured intracranial aneurysms in the United States, 1996-2000: the effect of hospital and surgeon volume. Neurosurgery. 2003 May;52(5):995-1007; discussion 1007-9.
[17] Hannan EL, Racz M, Ryan TJ, et al. Coronary angioplasty volumeoutcome relationships for hospitals and cardiologists. JAMA. 1997;277: 892–898.
[18] Birkmeyer JD, Stukel TA, Siewers AE, et al. Surgeon volume and operative mortality in the United States. N Engl J Med. 2003;349:2117–2127.
[19] Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. Ann Intern Med. 2002;137:511–520.
[20] Kuntz RE, Normand SL. Measuring percutaneous coronary intervention quality by simple case volume. Circulation 2005;112:1088-91.
[21] Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Engl J Med. 2002 Apr 11;346(15):1128-37.
[22] National Cardiovascular Data Registry. Available at: http://www.ncdr.com. Accessed May 11, 2012.
[23] Tavris DR, Dey S, Albrecht-Gallauresi B, et al. Risk of local adverse events following cardiac catheterization by hemostasis device use - phase II. J Invasive Cardiol. 2005 Dec;17(12):644-50.
[24] STS/ACC TVT Registry. Available at: https://www.ncdr.com/TVT/Home/Default.aspx. Accessed May 11, 2012.
[25] Sedrakyan A, Paxton EW, Phillips C, et al. The International Consortium of Orthopaedic Registries: Overview and Summary. J Bone Joint Surg Am. 2011 Dec 21:93(Suppl 3): 1-12.
[26] Alings M, Vireca E, Bastian D, et al. AUTOMATICITY Study Investigators. Clinical use of automatic pacemaker algorithms: results of the AUTOMATICITY registry. Europace.2011 Jul;13(7):976-83.
[27] Alings M, Vorstenbosch JM, Reeve H. Automaticity: design of a registry to assess long-term acceptance and clinical impact of Automatic Algorithms in Insignia pacemakers. Europace. 2009 Mar;11(3):370-3.
[28] Andriulli J. Device monitoring of intrathoracic impedance: clinical observations from a patient registry. Am J Cardiol. 2007 May 21;99(10A):23G-8G.