Comments to Effective Heath Care Program Draft Documents

The Effective Health Care (EHC) Program encourages input on its projects. Comments may be submitted through this Web site, by letter, and by e-mail. Comments about draft reports and the response to the comments will be posted publicly on this Web site 3 months after the draft reports are finalized and published. Comments are not edited for spelling, grammar, or other content errors.

Registries for Evaluating Patient Outcomes: A User's Guide: 2nd Edition
Working White Papers: Emerging Issues

The 2007 handbook, Registries for Evaluating Patient Outcomes: A User's Guide, was developed by AHRQ as a handbook for establishing, maintaining, and evaluating the success of registries created to collect data about patient outcomes. Since the publication of the Guide, AHRQ has implemented a working white papers project to stimulate discussion and to build consensus on emerging issues related to the development and implementation of registries that cross technical, legal, and ethical disciplines. As broad consensus on the emerging issues develops, our goal is to incorporate the working white papers as new chapters into the updated version of the Guide, together with information on new methodological and/or technological advances, into existing chapters.

Four topics were identified as potential new chapters: "Use of Registries in Product Safety Assessment," "Linking Registry Data: Technical and Legal Considerations," "Interfacing Registries and EHRs," and "When To Stop a Registry." The white papers have been drafted and reviewed and were discussed at an AHRQ-sponsored meeting in April 2009. The papers were then posted for public comment on the EHC Program Web site in August and September 2009.

At the conclusion of the public comment period, the white papers were revised in response to the comments. Most of the content of these white papers was incorporated into the updated Guide. The "Use of Registries in Product Safety Assessment" paper became Chapter 5, the "Linking Registry Data" paper became Chapter 7, the "Interfacing Registries and EHRs" paper became Chapter 11, and the "When To Stop a Registry" paper became a sidebar discussion in Chapter 2.

Some issues raised within the public comment period are outside the scope of the new chapters, but may be potential topics for future white papers or a future version of the Guide. A summary of these issues is provided below.

- Patient identity-management strategies will become increasingly important as health-care data are linked across multiple systems. The white papers discuss only what is currently possible in terms of patient identity management, so a white paper that provides a more in-depth discussion of strategies and potential solutions (e.g., unique patient identifiers) may be needed.

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- An important issue to consider when linking data from multiple sources — and for registries in general — is the protection of data from litigation, which may expose providers, commercial participants, and institutions to legal and financial harm. The current Guide touches on this issue in Chapter 8, but a more detailed discussion (perhaps as an additional chapter or paper) may be needed.

- The new chapter on linking data does not extensively discuss the privacy, security, and data-protection concerns associated with health-care provider and industry sources of data. These issues are broad and may best be discussed in a new white paper.

- Public-private partnerships are an emerging model for developing registries and supporting data-linkage projects. Nonprofit entities that are developing and/or maintaining registries frequently link their data with government and other public data sources to expand the power of their data-analytic capability. Although the updated Guide discusses these partnerships briefly, a new white paper may be needed to fully explore the legal and technical issues involved in these partnerships.

- The new chapters provide an abundance of information about linking data from multiple sources, but they do not discuss in detail the supporting statistical tools (e.g., meta-analytical statistical techniques) for analyzing the combined data. A new white paper exploring the appropriate statistical techniques for analyzing data combined from multiple sources may be needed.

- The current Guide and new chapters briefly discuss the unique aspects of pregnancy registries in several places. However, the Guide does not specifically discuss some questions pertinent to pregnancy registries. For example, how do pregnancy registries address the problem of women not seeking prenatal care early in pregnancy? A more detailed discussion or a separate white paper addressing the unique challenges facing pregnancy registries may be needed.

- A challenge for some registries is the transition that occurs when a disease-based registry spans the market launch of a major new treatment. For example, a registry of rare diseases may be established when no treatment is available for a specific disease and then must be adapted once a treatment for the disease is released on the market. If the registry is industry sponsored, there may be new regulatory requirements in the post-launch period and associated potential risks and benefits. This issue is not currently addressed in the Guide or in the new chapters. A white paper may be needed to fully consider the regulatory, technical, and scientific issues that can occur in this situation.

The full disposition of comments, which addresses both public and peer review comments, is contained in the table below.

General Comments

Comment	Response
First, the AAOS believes that the government has a significant role to play in the development of health care registries. Federal agencies should financially support start-up funds for registries run by independent, nonprofit organizations with representation from a broad group of stakeholders including medical associations.	General comment - no changes to the text are needed.
Second, federal agencies should establish protections for the data from litigation, which may expose providers, commercial participants and institutions to legal and financial harm.	General comment - no changes to the text are needed.
Third, the AAOS appreciates that some of the contents of the white papers are forward looking. In some instances, the infrastructure has not been built; therefore, it is premature to forecast solutions to problems at this time.	General comment - no changes to the text are needed.
Lastly, the white papers should establish clear boundaries to differentiate between public and private efforts. The authors provide potential solutions for the government to impose penalties in order to compel private sector participation in government programs. This language is highly controversial and should be stricken from the next draft of the white papers, particularly in the registry of registries white paper.	The purpose of the registry of registries paper is to provide recommendations to AHRQ. This language is appropriate in that context.

When to Stop a Registry

Comment, by Section	Response

Stopping an Experiment	
I think the issue of stopping en experiment is out of scope, there are plenty of references and guidelines on that. The paper should restrict to non-experimental situations like the registries are.	The authors felt that the issue of stopping an experiment provides important context for the discussion of non-experimental studies. There are many references/guidelines for stopping experimental studies. It is important here to discuss why they are not particularly relevant to non-experimental studies, as the authors do in the text. We agreed with the authors, and no changes to the text were made in response to this comment.
Stopping a Fixed-Length Non-Experimental Study	
For stopping a fixed length non-experimental study: if reasons to stop the registry before the goal is met can be anticipated they should be written in the protocol. If they are not anticipated, the reasons for stopping should be in the final report and/or publications linked to the registry.	We added the following sentence to the "Stopping Decisions and Registry Goals" section: "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 registry include a clear discussion of the reasons for stopping."
Stopping an Open-Ended Study	
For stopping an open ended length non-experimental study: the reasons for stopping should be in the final report and/or publications linked to the registry.	We added the following sentence to the "Stopping Decisions and Registry Goals" section: "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 registry include a clear discussion of the reasons for stopping."
Conclusion	

On Page 2 of 10, final paragraph and page 3 of 10, key point, "Reasons for continuing a registry," bullet 1,we recommend that the term "grave safety concerns" be reworded using common regulatory language to refer to adverse events, specifically "serious and/or life threatening adverse events."	We removed the "Key Points" table from the text for consistency with the rest of the handbook.
General	
The AAOS acknowledges the importance of clearly defining the scope of a registry in its standard operating procedures. It is critical to establish policies that will protect patient confidentiality and provide for the maintenance and management of data when the useful life of the registry has been exhausted.	The importance of planning for the end of a registry is addressed in the Planning and Legal/Ethics chapters. No changes to the text of this white paper are needed.
The AAOS strongly encourages AHRQ to include additional information on the lifespan of long-running registries and recommendations for continuity planning should the registry experience changes in sponsorship or governance during its course. The paper relies heavily on clinical trials and other fixed length studies as examples that generally last a few years at most, whereas medical product and patient outcome registries tend to be operational for several decades. The AAOS suggests that the authors clearly differentiate between clinical trials and registries in the next iteration of the draft white paper.	The Planning chapter addresses continuity planning for sponsorship and governance changes and provides examples of registries that alter their purpose and continue to exist. The purpose of this paper is to address a specific issue of when a registry without a fixed end date should stop collecting data. No changes to the text of this white paper are needed.

Use of Registries in Product Safety Assessment

Comment, by Section	Response

Executive Summary	
Page 1, line 5 of "Use of Registries" section: the word "representativeness" is used, but it's not clear what it is representative of.	We removed the Executive Summary. In a similar sentence in the Introduction, we removed the word "representativeness." We changed the sentence to: "Trials conducted as part of clinical development are by necessity of limited duration and, size and generally focus on a narrowly defined population representativeness that represents only a narrow segment of the population characteristics of people with the disease or product use of interest. (e.g., people without any co-morbidities.)"
Page 2, first paragraph: the authors say the data from a registry created for a purpose other than safety assessment may be "insufficient for meaningful stand alone analysis and interpretation" but it's not clear why the data would be insufficient. Is this a general comment, or a specific comment on inadequate sample size? Inadequate outcome definition or outcome specification? Inadequate control of confounding?	We removed the Executive Summary. This sentence is also part of the Ad-Hoc Data Pooling section. In that section, we added the text in red to address this point: "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."
Page 2, paragraph 1 of conclusion: refer to "linkage and distributed network schemes and sentinel surveillance," but could not find definitions for these terms either in the Executive Summary or elsewhere in the document.	This paper is not an appropriate place for a detailed discussion of these topics. We added references for more information on "distributed network schemes" and "sentinel surveillance."

Page 3, bullet 3 of Key Points: Clarify who are these "stakeholders?"	We removed the Key Points for consistency with the other chapters. This phrase also appears later in the text, where it includes a parenthetical clarification: "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..."
In general, the Executive Summary section refers to "signals" without defining signals until much later (page 16) in the document. Key terms should be defined early in the document. A good place to define "signals" and other key terms may be at the beginning of the Introduction section.	The Executive Summary was removed from this document.
Page 1, line 5, "Use of Registries…" section: the term "representativeness" is used but it is not clear - representative of what? The term should be defined early in the document.	We removed the Executive Summary. In a similar sentence in the Introduction, we removed the word "representativeness." We changed the sentence to: "Trials conducted as part of clinical development are by necessity of limited duration and, size and generally focus on a narrowly defined population representativeness that represents only a narrow segment of the population characteristics of people with the disease or product use of interest. (e.g., people without any co-morbidities.)"

Page 2, paragraph 1, "Use of Registries…" section: The paper indicates data from a registry "collected for another purpose" (i.e., other than a safety assessment) may be "insufficient for meaningful stand-alone analysis and interpretation…" but it's not clear why the data would be insufficient. Is this a general comment, or a specific comment on inadequate sample size, inadequate outcome definition, inadequate outcome specification, or inadequate control of confounding variables? The inclusion of an example or two as to why such registries may be insufficient would be helpful.	We removed the Executive Summary. This sentence is also part of the Ad-Hoc Data Pooling section. In that section, we added the text in red to address this point: "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."
Page 2, paragraph 1, Conclusion section: The paper refers to "linkage and distributed network schemes and sentinel surveillance," but does not include definitions for these terms either in the Executive Summar or elsewhere in the document. Definitions for these terms should be included.	This paper is not an appropriate place for a detailed discussion of these topics. We added references for more information on "distributed network schemes" and "sentinel surveillance."
Introduction	
Page 4, paragraph 1 of Introduction: "signals" are referenece in the executive summary, but the reader has no definition for the term. This might be a good place to define signals	The Executive Summary was removed from this document.
Page 4, last paragraph: "It is widely acknowledged" Please provide a reference for this claim. (for someone who is hoping to do further reading or just to find the basis for the claim, it would be helpful to provide a reference.)	We added a reference to the 2007 NEJM article by Mark McClellan, where he states that AERs only captures a small percentage of events. McClellan M. "Drug safety reform at the FDA--pendulum swing or systematic improvement?" N Engl J Med. 2007 Apr 26;356(17):1700-2.

Page 5 and 6, Introduction section: The paper indicates that "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." The paper should explicitly recognize that hospitals and other entitites are statutorily required to report adverse events, but that some user facilities fail to report as required. We recommend that the report explicitly recognize these challenges. It would also be helpful if the paper included information on how a registry might overcome this traditional challenge.	The pros and cons of using a registry for reporting adverse events are addressed in the "Adverse Event Detection, Processing, and Reporting" chapter and will not be addressed here. We revised the sentence in question here, with the addition of the text in red: "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."
Registries Specifically Designed for Safety Assessment	
General Comment: authors do not mention here the need to collect extremely detailed information about the exposure of interest. Without precise information about timing of exposure relative to timing of the onset of adverse event, as well as other exposure characteristics (i.e., dose, duration, route of administration,etc) , the ability to establish a cause and effect between the exposure and the adverse event is limited. (note this is discussed briefly later on page 10, in the section on Defining Exposure and risk Windows). Recommendation is to include in this section (design consideration) as well.	We added "defining the exposure and relevant risk window(s)," to the following sentence on page 7, "Consideration should be given during registry design to inclusion/exclusion criteria, appropriate comparator groups, and analysis planning."

Pg 7, paragraph 3: "Disease registries also can make a meaningful contribution to understanding adverse event rates in that they can provide large, systematic data collection for target populations of interest. The registry can be used to provide a background rate of the occurrence of these events in the affected population." Comment: Seems like an overstatement that registries in general can be used to compute meaningful rates of adverse events.. Often will NOT have a good enough understanding of denominator, ie.., characteristics of: (1) patients who get entered into registry vs. (2) universe of patients with condition of interest to provide an unbiased, generalizable adverse event rate associated with exposure of interest. (Exception may be extremely large , comprehensive , national disease registers). Also, exposure to medication of interest, if registry is a disease registry, may somehow be associated with other factors that increased probability that patient ended up in the registry (e.g., physician enrolling patients into the registry more likely to prescribe certain rx as treatment , and also has a unusual patient population in terms of demographics).	We modified this sentence and added an additional sentence to address this comment (the changes are in red text): "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."
Page 7, Design Considerations: This information is important both for designing registries (for study size calculations) and & It s not clear what they are suggesting. Some information on background rates is needed to do sample size calculations, but the information may not be available without the data collected by the registry. what the implication is of the comments?	We changed this sentence to: "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."

Page 7, same paragraph: What is meant by "managed by health care professionals?" please clarify.	We agree that this phrase is unclear and deleted it.
Same paragraph: What is meant by "unbiased" data? Presumably the data are collected accurately, in an "unbiased" manner. That doesn't necessarily mean that the measure of association between exposure and outcome will be unbiased. Please clarify.	We changed this sentence to: "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."
Page 7, next paragraph: It states that registries must be cognizant of possible bias , but what do those who establish registries do with this cognizance? Please clarify what the recommendation is. Once we recognize the potential for bias, what do we do? Do we decline to perform formal statistical comparisons between treatments, because of potential bias?	We added the following sentences to this paragraph: "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."
Page 9, first paragraph: It's not clear here what the authors mean by "validity." They may be mixing concepts of "applicability" (to what population do the results apply) and freedom from bias, adequate statistical precision, and others. Please be more specific.	We agreed with this comment and changed the word "validity" to "applicability."

Page 9, second paragraph: Authors may again be mixing concepts of completeness of ascertainment (and ascertainment of events without respect to exposure status) with adequate sample size. These are clearly very closely related concepts, as more complete ascertainment would be helpful with sample size issues, but it would seem helpful to keep the distinction clear.	The authors reviewed the text and believe that these concepts are being used appropriately here.
Page 10, paragraph 3: This is another place where the authors refer to the sample (the registry) being representative of the target population. Representative with respect to what? Demographics? Clinical characteristics? The only aspects of the registry that need to be representative are those related to the rate of adverse events and the association (if any) between exposures and adverse event rates.	The concept of "representative of the target population" is discussed in detail in both the design and analysis chapters of the handbook. We do not agree that a registry only need be representative in terms of the rate of AEs and association between exposures and AE rates. No change to the text will be made.

Page 12, Pregnancy Registries: How does a registry fix the problem of women not presenting early in pregnancy? If women don t present early enough, why would a registry fix that? Periodic monitoring of pregnancy status? Please clarify.	The authors acknowledge that this is a challenge for pregnancy registries. We added this statement: "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, to avoid selective recall of exposures by women experiencing bad pregnancy outcomes." However, pregnancy registries are unique in many ways. We address them in some detail in the handbook (and we included 3 pregnancy registry case examples, including one on enrollment strategies). We do not believe that this chapter is an appropriate place for a lengthy discussion of challenges unique to pregnancy registries. A more detailed section on pregnancy registries may be an appropriate topic for future papers.
Page 12, same paragraph: The authors make a good point about the exclusion of pregnant women from clinical trials of products for conditions that are not life threatening and not for pregnancy-related illnesses. However, if pregnant women are exposed post-approval, please explain why it is ethical not to randomize pregnant women so as to develop some understanding of causal relationships in that population.	By definition, pregnant women would not be 'randomly' exposed postapproval except in a clinical trial, and that is not the subject here.

Page 12: We share your concern about small populations, but am not sure that detailed information will always help "unravel the different parts of the puzzle" in the absence of randomization. We still may not know if it's the drug/device or the underlying condition causing a particular event (or some combination of both).	We agree that this is unclear. We removed the original sentence and replaced it with the following sentences: "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 follow-up obtained for orphan products."
Page 13, paragraph 2: Authors use the term adverse reactions on line 5 of the paragraph. This has a specific regulatory and clinical interpretation, with respect to causality. Do they mean adverse event?	We changed this term to adverse event.
Page 14: It would be helpful to add some discussion of the need to control for center or surgeon effects in trials of some (surgically implanted) devices, as these effects can lead to confounding and are particularly important in the setting of these devices.	We added a brief discussion of these challenges to this section: " 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."

Registries may be an appropriate choice for orphan populations or other populations in which it may be difficult to conduct clinical trials, such as pregnant women, or in populations where it may be difficult to accrue sufficient numbers of clinical trial participants over a reasonable timeframe and with a manageable number of investigational sites (e.g., in the area of pediatric device development). However, the paper does not adequately explain how registries may address safety issues in these populations.	Earlier chapters (Chapters 1, 2, and 3) in the handbook discuss why registries may be particularly valuable for these special populations. This chapter provides specific, detailed examples of how registries may be particularly useful for pregnant women and rare diseases. We do not believe more information needs to be provided on these points.
We also recommend that the pregnancy section be expanded to address confounding issues such as determining time of conception and the importance of capturing events outside of the medical system (e.g., non-drug exposures, termination of pregnancy not captured in medical care records).	The topic of pregnancy registry design is extensive and is not the focus of this paper. It is beyond the scope of this paper to address the many challenges of pregnancy registry design. See response to Comment 18.
In addition, the section titled "Special Conditions: Medical Devices" should be expanded to deal with unique device issues such as instances that require both surgeon and hospital data to fully understand and interpret patient outcomes.	We added a brief discussion of these challenges to this section: " 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."

Page 4, paragraph 1, "Design Considerations..." section: The draft paper states: "Disease registries also can make a meaningful contribution to understanding adverse event rates in that they can provide larege, systematic data collection for target populations of interest...the registry can be used to provide a background rate of the occurance of these events in the affected population..." Without appropriate qualifiers, it may be an overstatment to say that the registries in general can be used to compute meaningul adverse event rates. to calculate an unbiased, generalizable adverse event rate associated with the exposure of interest, one must first understand universe of the patients with the condition of interest. Then, if one is to rely on a particular registry to understand adverse event rates, you must then understant the characteristics of the patients that get entered into the registry. For example, exposure to the medication or device of interest may be associated with other factors that increased the probability that the patient ended up in the registry (e.g., a physician enrolling patients into the registry is more likely to perscribe a certain device or drug or has an unusual patient population in terms of demographics). the exception may be extremely large, comprehensive national disease registry.	We modified this sentence and added an additional sentence to address this comment (the changes are in red text): "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."

Additionally, although the "Defining exposure and risk windows" section discusses th eneed to collect information on the timing of events in relation to the initial diagnosis and in relation to timing of treatments, the "Design considerations…" section should also emphasize the need to collect extremely detailed information about the exposure of interest. Without precise information about the timing of exposure relative to timing of the onset of the adverse event(s), as well as other exposure characteristics (e.g., duration, route of administration, etc.), the ability to establish a cause and effect between the exposure and the adverse event is limited. The paper should make this point explicit.	We added "defining the exposure and relevant risk window(s)," to the following sentence on page 7, "Consideration should be given during registry design to inclusion/exclusion criteria, appropriate comparator groups, and analysis planning."
Page 7, paragraph 2, "Design considerations…" section: The paper states that registries "must be cognizant of possible bias…", but fails to provide any next steps once bias has been recognized. It would be helpful for the paper to clarify specific recommendations once bias has been recognized.	We added the following sentences to this paragraph: "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."

Page 12, Pregnancy Registries section: The draft paper seems to suggest that a registry would address the problem of women not presenting early in pregnancy but it is not clear how a registry addresses that concern. The paper should be expanded to clarify this point.	The authors acknowledge that this is a challenge for pregnancy registries. We added this statement: "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, to avoid selective recall of exposures by women experiencing bad pregnancy outcomes." However, pregnancy registries are unique in many ways. We address them in some detail in the handbook (and we included 3 pregnancy registry case examples, including one on enrollment strategies). We do not believe that this chapter is an appropriate place for a lengthy discussion of challenges unique to pregnancy registries. A more detailed section on pregnancy registries may be an appropriate topic for future papers.

Page 12, Orphan Drugs section: While we share your concern about small populations, the report should note that registries may not always help "to unravel the different parts of the puzzle" in the absence of randomization. For example, a registry may still not identify whether it is the device or drug or the underlying condition causing a particular event (or some combination of both).	We agree that this is unclear. We removed the original sentence and replaced it with the following sentences: "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 follow-up obtained for orphan products."
Page 13, paragraph 2: The draft paper uses the term "adverse reactions." This has a specific refulatory and clinical interpretation, with respect to causality. We recommend that the term "reactions" be changed to "events."	We changed this term to adverse event.
Page 14, Medical Devices section: As noted in our general comments, discussion of the need to control for "center" or surgeon effects in trials of surgically implanted devices should be added to the paper as these effects can lead to confounding and are particularly important with respect to devices.	We added a brief discussion of these challenges to this section: " 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."
Registries Designed for Purposed Other Than Safety	

Page 15, Ad Hoc pooling section: The Ad Hoc pooling section should be expanded to include reference to other sources of data that could contribute to understanding such as automated data, patient-reported data or physician-capture data. This section should also reference the potential use of meta-analysis.	We added the following text to the first paragraph under Ad Hoc Data Pooling: "An alternative to pooling data is to conduct meta-analyses of various studies using appropriate statistical and epidemiologic methods."
Signal Detection in Registries and Observational Studies	
Page 16, bottom: It would be helpful if the draft paper commented on the possibility of adapting existing data collection mechanisms (e.g., electronic medical records data) to perform specific studies. For example, a "pop-up" screen could be added to collect specific information on a specific adverse event in the course of routine medical care, even though that information might not be part of the usual data collection for that electronic medical records (EMR) system.	The ASTER case example is actually exactly this. We added a reference to the ASTER case example in this section of the paper.
Page 16, bottom: It might be worth commenting on the possibility of adapting existing data collection mechanisms (e.g., electronic medical records data) to perform specific studies. Could we, for example, add a pop-up screen to collect specific information on a specific adverse event in the course of routine clinical care, even though that information might not be part of the usual data collection for that EMR system?	The ASTER case example is actually exactly this. We added a reference to the ASTER case example in this section of the paper.

Page 18: A number of questions around stents have been addressed by a number of meta-analyses of randomized (and sometimes other) studies. It would be appropriate to mention these other approaches to the problem, in addition to the SCAAR analyses.	The point of this paragraph is to provide an example of a registry being used to further investigate an identified signal. While it is interesting that meta-analyses were also used, it is not relevant to the point being made here.
General	
The use of registries for product safety assessment should augment all of the other safety programs employed by the FDA and international safety agencies. In the U.S., adverse events are submitted through the FDA's MedWatch program. Further, the FDA uses the MedSun program, post-market surveillance studies, and post-approval studies to capture safety data, and is currently developing the Sentinel Initiative. Additionally, the AHRQ may fund a short term orthopaedic device registry. Therefore, with recently appropriated additional resources, several HHS agencies are improving the networks for product safety assessments.	General statement that does not request specific change. No response needed.

This white paper notably fails to mention manufacturer or hospital reported product safety and adverse event data. Physician reporting is of course voluntary and occasional. As we have stated previously, physicians and surgeons in the U.S. continue to have significant concerns about medical liability and the lack of protection afforded to their data. As a result, reporting on off-label use would be an unusual occurrence. The time constraints of physicians and surgeons further inhibit adverse event reporting. Therefore, physician reporting on product safety will likely continue to constitute a very low percentage of cases.	The paper makes this point clearly in the last paragraph on Page 4: "It is widely acknowledged , however, that spontaneous reporting captures an extremely small percentage of the actual events…" The paragraph goes on to explain the barriers to spontaneous reporting. No changes to the text are necessary to address this comment.
The AAOS has some concerns about the ad hoc pooling of data referenced in this white paper. Sources of the data may have different elements and lack interoperability.	The first paragraph on Page 15 addresses this concern. It states, "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." The paragraph goes on to note other challenges to ad-hoc data pooling. No changes to the text are necessary to address this comment.
International populations have disparate health systems and may not reflect the American population's health characteristics and yield results that cannot be generalized to the U.S. population	The paper does not state that non-U.S. registries would be generalizable to the U.S. population. No changes to the text are necessary to address this comment.

AAOS offers that registries that collect product safety information in this country must adhere to all of the pertinent U.S. regulations and laws. It would be helpful if this white paper discussed the relevant U.S. regulations and laws covering product and patient safety assessments.	A complete review of relevant U.S. regulations is beyond the scope of this paper. However, we added a clarifying statement in the Introduction to acknowledge the regulatory requirements are not addressed here and to point readers to other sections of the handbook: "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 9, respectively. Chapter 12 discusses practical and operational issues with reporting adverse event data from registries."
This white paper provides a useful theoretical framework for consideration of the development and utility of registries and the potential value of data derived from various registry schemes. The paper provides important points of consideration as medical device sponsors develop their own registries in response to FDA regulatory requirements, or as they consider the support of and participation in registry efforts by others. For example, the authors point out that observational data of all kinds are only as strong as their ability to measure and to control for potential biases, including confounding and misclassification. We do, however, have a number of concerns and recommendations to improve the draft white paper described below.	General statement that does not request specific change. No response needed.

Include Conflict of Interest Statements from Authors and In-Depth Comparisons of Registry Approach Vs	Financial disclosure forms from authors were collected, per AHRQ procedures, and the authors' affiliations are clearly stated in the paper.
Although, we understand this paper will eventually be included in a second edition of the AHRQ handbook titled "Registries for Evaluating Patinet Outcomes: A User's Guide," there is a clear bias in favor of registries that appears throughout the paper. For example, the paper seems to "retrofit" a registry as a solution to each problem requiring the identification and evaluation of a potential safety issue. Much text is spent explaining a given safety problem followed by one or two concluding paragraphs that indicate a registry could solve the problem. A substantive, in-depth discussion about why a registry uniquely responds to the particular safety issue(s) identified would greatly improve the paper. For example, a comparison of the value of a registry contrasted with a large simple safety study in terms of time, cost and other resources would be a valuable addition to the paper.	The purpose of the paper is not to discuss IF a registry should be used (that is discussed in Chapter 2 - Planning), but rather how a registry could be used. The pros and cons of registries vs. other study types are covered elsewhere in the handbook.

In-depth comparisons of the pros and cons of a registry approach versus other study approaches would also be beneficial given the recent emphasis on registries by policy makers and others - an emphasis that sometimes appears to lack a comprehensive understanding of the costs and challenges associated with registries.	The purpose of the paper is not to discuss IF a registry should be used (that is discussed in Chapter 2 - Planning), but rather how a registry could be used. The pros and cons of registries vs. other study types are covered elsewhere in the handbook.
Registry Definition Again, although we understand this white paper will be incorporated into a second edition of the AHRQ handbook titled "Registries for Evaluating Patient Outcomes: A User's Guide," that document is quite lengthy and it would be helpful to specifically define in this paper what is meant by the term registry, including its application as a prospective or retrospective design, and how it is or is not different from a cohort design.	The definition of a "registry" is provided in Chapter 1. We do not repeat it in each chapter. No change will be made to address this comment.
Inclusion of Comparator Group This is a critical component of most safety assessments that is poorly discussed in t	We refer readers to Chapter 3 (Design), which includes an in-depth discussion of comparator groups.

Complexity of Patients If this issue is addressed in the draft paper, it is done in a fragmented way. There is a strong interplay between representativeness, patient recruitment, sample size and power, and patient complexity. The paper would be greatly improved if it not only identified the problem of patient complexity but also gave credible reasons and examples as to why a registry approach is advantageous for managing patient complexity.	We added a statement specifically referring to patient complexity: "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." Other chapters of the handbook (Chapters 2 and 3, in particular) discuss the value of registries for managing patient complexity.
The retention of subjects is mentioned in the draft paper but it is not clear why and how a registry would be more successful than other approaches at patient retention. A thorough discussion of this issue would be helpful.	Issues of retention are important for registries generally, not just in the context of safety. We discuss retention in Chapter 9 (Recruitment and Retention) and again in Chapter 13 (Analysis). We don't believe that a detailed discussion of retention would be useful in this chapter.
The white paper addresses representativeness in a cursory way but fails to discuss how a registry approach can assure representativeness, especially in light of other study designs. For example, there is no assurance that a registry will be representative. It may be overrepresented in some areas and under-representative in others.	The second paragraph of the Challenges section discusses representativeness in detail and explains issues/approaches to consider when enrolling patients. We also added a reference to Chapters 3 and 13 (which discuss representativeness in detail) to this paragraph.

The paper is well written and covers the breadth of the topic in the description of the many different types of registries encountered in drug utilisation and pharmacovigilance. The paper goes some way in pointing out shortfalls in many registries considering the detection of adverse drug events and inherent design weaknesses with regards to both internal and external validity for the interpretation of causality (e.g. on page 7: "… in collecting unbiased, interpretable long-term safety data as they may allow objective comparisons across generations of drugs, devices or other interventions"). For the purpose of a handbook, the paper would possibly have a greater impact if it resulted in a set of specific recommendations for how registries could be designed to fulfil safety as well as efficacy, effectiveness and other objectives. Alternatively, this could be achieved by examples of best-practice, for example by describing some particularly well-designed registries. The examples should preferably cover the areas, where registries are one of the few, if not sole, means of obtaining data to improve therapies, e.g. orphan indications and drug use in pregnancy and other special populations.	This will be addressed by the inclusion of case examples highlighting how registries can be designed for safety assessments. Case examples include a national registry that provided data to support a safety assessment of a biologic; a registry used to monitor safety in a pediatric population; and a large, procedure-based registry used to examine safety for medical devices.

While I believe the current draft of this report contains some useful guidance, I would very much like to see the draft expanded to include some guidance on transitional issues to consider when a disease state registry spans the market launch of a major new treatment. If the registry is sponsored by industry, there are new regulatory requirements which come into play in the post-launch period and associated potential risks and benefits -- I'd love to see this guidance address those and outline the considerations to address in these instances.	This is an important point. This chapter focuses specifically on design issues, with regulatory issues addressed elsewhere in the handbook. This specific regulatory issue hasn't been addressed in other chapters. However, this may be a useful topic to consider for future papers/updates.

Linking Registry Data

Comment, by Section	Response
Executive Summary	
Other than understanding the importance of data linkage and privacy and confidentiality from a legal view point I have little to offer as far as input.	No response needed.
General	

Legal and technical considerations are clearly issues of great importance to the AAOS given its current focus on the development of the American Joint Replacement Registry (AJRR). However, this white paper omits a number of critical issues that raise significant concerns for the AAOS and the AJRR. The first omission is the failure to address the protection of data from litigation, which may expose providers, commercial participants and institutions to legal and financial harm. ** additional details in AAOS letter, page 7	This is an important issue, but it is quite large in scope and may require its own chapter/section of the handbook. As the letter from AAOS notes, this issue applies to registries generally, and not just data linkage projects. We referenced the Legal chapter of the handbook (where there is some mention of this) as an immediate solution, but this topic should be considered for future papers.
While the white paper does extensively cover the legal protections for identifiable patient health information, it does not adequately address legal issues associated with provider and industry sources of data. Registry data linkages should be structured to maximize the widest array of participation from different sectors to develop the most comprehensive data set. The final draft of the white paper should comprehensively address the privacy, security, and data protection concerns for all sectors and participants to achieve that result. ** additional details in AAOS letter, page 8	The authors of the white paper recognized the issue of provider identification and chose not to address it extensively, only because it would have expanded the length and scope of the paper beyond the original vision of a 10- to 20-page paper. As AAOS points out, this topic is illustrated in the appendix case example, and they would like to see it discussed as an important issue in the paper. However, the authors felt that it was impossible to address this topic sufficiently in the context of this white paper. We added the following sentence to page 6 as an acknowledgment of this point: "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." This topic should be considered for future papers.

The white paper should address public-private partnerships with respect to data linkages. The white paper acknowledges that it does not analyze potential partnerships between public and private sectors with respect to data linkages. The Academy recommends that the AHRQ address this issue in the final draft because the Academy and other nonprofit entities that are developing and/or maintaining registries frequently link their data with the government and other public data sources to expand the power of their data analysis capability. A discussion of the legal issues and technical issues involved in these partnerships would help facilitate these relationships.	The topic of partnerships, and public-private partnerships in particular, is an important topic, but, again, one related to registries in general and a good candidate for a future paper/chapter. While data-linkage projects might often lend themselves to the formation of "partnership" arrangements, not all data linkage projects would require a complex partnership agreement (e.g., just purchasing a data file from a government agency, does not necessarily imply a partnership). IOM is also interested in this topic. Multi-stakeholder partnerships, and public-private partnerships in particular, are discussed in some detail in Chapter 2 (Planning) and in a related case example (INTERMACS). Again this topic, while not addressed in detail here, should be considered for future papers.
The white paper should discuss and clarify the applicability or non-applicability of the Common Rule to registry data and data linkages. ** additional details in AAOS letter, page 10	As AAOS notes in the letter, the applicability or non-applicability of the Common Rule to registry data and data linkage projects depends on both the nature of the project and whether the research is supported or otherwise subject to regulation by any federal department or agency. The authors removed the sentence that AAOS highlighted as being confusing ("If research is one purpose of the project, then the Common Rule (regulations for human subjects protection) is likely to apply to the project."). However, a detailed discussion of the Common Rule already exists in the Legal chapter (now Chapter 8) and does not need to be duplicated here. We added a reference to the legal chapter to address this comment.

Interfacing Registries and Electronic Health Records

Comment, by Section	Response
Executive Summary	
There are many definitions of interoperability. The seminal piece on this is a working paper developed by the HL7 EHR Workgroup which you can find at http://www.hln.com/assets/pdf/Coming-to-Terms-February-2007.pdf (the HL7 website is still impossible to navigate). I suggest these consensus definitions be used.	A standard definition was utilized.
There is an insufficient amount of treatment given in this paper to the importance of standards in interoperability. There is VERY brief treatment given to HL7, IHE, and HITSP. One or two HITSP artifacts are mentioned in an almost arbitrary way, with no mention at all of the Interoperability Specifications (ISs) which make up the core of HITSP's documentation.	The purpose of the paper is to describe how EHRs interface with registries currently. The paper discusses relevant standards in sufficient detail to explain how they fit into these interfaces. The paper also frequently emphasizes the importance of standards in general. It is beyond the scope of this paper to describe standards in more detail. The appendix provides information on standards organizations and includes websites in the references.
The last sentence of the Introduction sentence is confusing. Most disease registries and clinical trials are patient focused as well as certain public health registries. It seems to conflict with the previous statement. I would prefer to see the examples I give placed with the preceding example and change the last sentence to include something like "where patient identifiable information is not required/collected".	We disagree with this statement. Registries are focused on population results. Identifiability is not the distinguishing element.
A very interesting white paper and well thought out, Landon has an excellent undrestanding of what has to be accomplished. This chapter nicely describes the task.	General comment - no changes to the text are needed.

Introduction	
In the opening paragraph, it says "registries are population focused". This is a confusing definition and is not consistent across the set of 5 papers being offered for public comment. The definition continues on p. 7 and is not an inclusive enough definition.	The definition of a patient registry included in Chapter 1 of the handbook is utilized here. However, the statement that registries are population-focused is consistent with the handbook definition, which states that registries are defined by a population.
On p. 6 the abbreviation "ONCHIT" should be replaced by "ONC" as is the current convention.	ONC is the new preferred abbreviation, but the sentence is describing ARRA, which specifically refers to ONCHIT. We added a parenthetical note, "(now commonly referred to as the ONC)" to this sentence.
EHR functionality continues to grow in the area of population management and clinical decision support. Specifically in the form of preventative alerts and reminders, care plans, and population reports. In addition, vendors are partnering with EHR vendors to provide data mining tools to identify gaps in care for various chronic conditions. The current Meaningful Use debate will likely push vendors farther down the path of population management and clinical decision support. As this functionality evolves within the EHR, so does the overlap with patient registries.	General comment - no changes to the text are needed.
Background	

Bi-directional interfaces between EHR systems and patient registries are very important going forward, but given the evolution of EHR functionality, perhaps more emphasis should be placed on semantic interoperability (common vocabularies) in the building block approach. This allows clinical decision support and population management functionality to continue to grow within the EHR while prioritizing the development work on common data terminology.	The text describes the importance of semantic interoperability. The building block approach really focuses on connectivity at this point.
Even though ARRA will stimulate EHR deployment, there will be many individual physicians and small group practices that choose not to implement an EHR. This will heighten the significant role for patient registries, especially for practices without an EHR. Focusing on semantic interoperability will allow for data aggregation and broad analysis through clinical data repositories, which will improve quality patient care and CER research.	The reviewer makes a prediction that is speculative.
The Vision of EHR-Registry Interoperability	
Syntactic interoperability, moving uniform data sets bi-directionally to and from EHR's and patient registries are very much needed and very complex. Moving from EHR presentation layers (alerts) through middleware with selective input to registry and EHR databases, and then back to safety and quality reporting modules seems very aggressive given the status of standards and number of CCHIT certified EHR vendors.	We are describing what is possible today. With ARRA leading to much greater standardization, we do not think this is an aggressive view.
Interoperability Challenges	

Once again, the treatment of HITSP and standards development and harmonization is much too light. CCD is mentioned, but the current vendor push towards CCD, it's prominence in the HIMSS/IHE Interoperability Showcase, and in HITSP is understated.	See response to Comment 2.This paper is not intended to be a recitation of standards. We provide a glossary of standard setting entities in the appendix, and the reader can refer to those authoritative sources.
On p. 12 in the middle there is a description of a process by which vendors pay for specifications and for conformance testing. While we certainly have examples of that (IHE, CCHIT) it is not the only model for achieving this end.	We added the following sentence to the end of this section: "These examples describe two models for using EHRs to populate registry databases; other models exist."
Page 8, second paragraph " ....no current EHRs are fully interoperable in the core functions....". Please cite source that proves no ehrs.	We changed this to "Most EHRs…"
page 9 last sentence on the page: spell out SOAP, useful to provide citation for readers to obtain more information?	We spelled out SOAP (Simple Object Access Protocol) and refer to the W3C recommendations (http://www.w3.org/TR/soap/).
Page 11: Beyond individual organizations having patient identification issues, registries receiving information from multiple sources see this as one of the bigges challenges they have. Even if you back it into a central resource such as PIX, someone has to do a review of the greyzone matches (records that fall between a no match and a positive match). See next section to include a potential solution.	A detailed discussion of potential solutions for patient identify management is beyond the scope of this paper. The current section only covers what is currently available. This topic could be considered for future papers/chapters.
Another challenge, and I'm not sure where to include it in this paper (if at all), but open standard does not mean the same as freely available standard. We're rellying on HL7 for many of the "open standards" but companies need to pay for the standard.	We clarified what is meant by 'open standard' in a footnote in the Introduction.

To fully implement interoperability additional priorities relative to semantic and syntactic interoperability should be established. Having EHR's and patient registries talking the same language (semantic interoperability) will dramatically enhance data aggregation and CER research. This would produce aggregated clinical data more quickly while allowing EHR vendors to further develop their own population management/clinical decision support functionality. More clinical data analysis and more population management tools will be a win-win for patients, providers, and payers.	General comment - no changes to the text are needed.
In addition to interoperabilty challenges when combining information from mutliple sources, visualiazation of the data and usabilty of the information is equally critical.	We agree with the reviewer but believe that this is implied in how we have described interoperability,.i.e., that its useful.
The aggregated data must be converted into relevant information and further into actionable knowledge for the user depending on their role and the context in which the information is used	This paper only covers the actual interface of the registry and the EHR; analysis and interpretation of data are covered elsewhere in the handbook. No changes to the text will be made to address this comment.
Partial and Potential Solutions	
The section "What Has Been Done" might benefit from another mature example: Immunization Registries which support interoperability with EHR systems and which are explicitly mentioned in the definition of "meaningful use" under ARRA when it comes to interoperability.	We searched for and did not find a publicly available example of an immunization registry that is linked with an EHR.

Related to the missing issue of resources and risks for matching patients across organizations, a suggestion for a unique patient identifier should be mentioned as an option. It isn't an attractive option for the federal government and some public advocacy groups, but I think it should at leas be mentioned. Alternately freely available software should be developed to make the greyzone as small as possible.	A detailed discussion of potential solutions for patient identify management is beyond the scope of this paper. The current section only covers what is currently available. This topic could be considered for future papers/chapters.
Conclusions	
Suggest that key point 4, "Care must be taken to ensure that integration efforts comply with legal and regulatory requirements for the protection of patient privacy" be added to the conclusion section.	We added this sentence to the Conclusion section.
Page 6 of 23, last paragraph. Suggest the addition of a specific reference to the section of ARRA relevant to electronic health record standards.	We added the requested reference.
The authors point out that interoperability is critical to useful large-scale healthcare information infrastructure, but we are not there yet in the U.S., so much of what is discussed is about their "vision" and various possible solutions. The authors do talk about importance of standards, which we would agree are critical.	General comment - no changes to the text are needed.

The GAO technical comittee discussions clearly outline the need for 1. EMRs to capture the metrics automatically which are needed for reporting as the clinciian is using the EMR for taking care of the patient 2. the abilty of filters to act on multiple EMRs to aggregate the reporting metrics for both a single patient and patient populations That would be the only way meaningful use can be attained and at the same time allow for the inftrastructure for registries to be created efficiently	General statement of a particular view point. No specific change needed.
The linkage of registires with HIEs (Health information exchanges) is as critical as linkage of EHRs with Registries.	We added, "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." We referenced the Sept 15 Quality Working Group report from the HIT Committee.
The abilty of quality reporting to be tightly integrated with registries and the HIE and the EHRs are all needed in the ecosystem	See response to Comment 27. Quality reporting may not be appropriate for all registries.

General Comments

The white paper references “indicate a small minority of U.S. physicians have implemented partial or complete electronic health record (EHR) systems in their practice.” Many factors may contribute to increased adoption of these systems in the next ten years, but what will be implemented, how they will be connected, and when this will happen is still undetermined. It is unreasonable to expect the private sector to shoulder the burden of technology adoption and standardization when the federal government has not harmonized data within its programs. The AHRQ’s substantial funding from the American Reinvestment and Recovery Act of 2009 (ARRA) (Pub. L. 111-5) was an important step in providing physician practices with some initial financial support for EHR systems. The AAOS recognizes the importance of standardizing these systems to facilitate communication within healthcare on multiple levels. A more practical approach would include the creation of standards based on existing data collection, such as the UB-04 form, the FDA MedWatch forms, and other mandated reporting systems. The Academy also encourages AHRQ to take cues from the efforts of existing registries, such as the European Federation of National Association of Orthopaedics and Traumatology, whose European Arthroplasty Registry has developed minimum data sets for use by member registries. AHRQ should carefully evaluate the progress of EHR system deployment prior to including this paper in a registry handbook. The Academy learned from a registry pilot project the considerable expense of linking up disparate health information systems from different hospitals. We believe the best recommendation is to defer commitment to a specific standard until such time that the market or the government identifies the default standard.	The comment is essentially stating the simpler forms of linkage, such as standards based on existing data collection such as the UB-04, Medwatch, etc., would provide some incremental benefit in a pre-interoperability environment. We added the following (in red) to the sentence on page 8: "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."