Standards in the Conduct of Registry Studies for Patient-Centered Outcomes Research

A Guidance Document for the Patient-Centered Outcomes Research Institute

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March 15, 2012

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Introduction

A patient registry is defined as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes."[1] Registries that enroll patients with a specific disease or who have received a particular treatment are an important source of data for patient-centered outcomes research (PCOR).[2,3] In addition to providing clinically relevant data that are meaningful to patients and providers, registries are known for their ability to provide data on populations not typically studied in clinical trials (e.g., children, elderly, minorities, pregnant women, those with multiple co-morbidities). Registries can offer adaptable designs and data collection strategies, making them particularly useful when treatments are rapidly changing. Because of their non-experimental design (i.e., no randomization), registries can be used to examine the impact of physician practice behaviors on quality of care, prescribing preference, and other important but difficult to quantify covariates. Good design and use of registries, however, requires strong understanding of both the potential for bias that threatens all observational studies and the methodological and operational tools that can be used to minimize the influence of such biases.[4,5]

As registries are increasingly used for PCOR, standards are needed to ensure that registry studies produce sufficiently valid and reliable evidence to support the mission of the Patient-Centered Outcomes Research Institute (PCORI). These standards must balance rigor with practicality and must incorporate the most important methodological advances from pharmacoepidemiology and outcomes research to ensure validity. Topics that should be addressed by the standards include: developing a protocol and data analysis plan, selecting and defining outcome measures and potential confounders and effect modifiers, determining the length of patient follow-up, using best practices to minimize the potential for selection bias, collecting data and ensuring data quality, minimizing information bias, reducing loss to follow-up, handling missing data, controlling confounding and evaluating effect modification, assessing the potential for bias, and evaluating external and internal validity. Data analysis standards should also inform standards for design and conduct of the registry.

The purpose of this project was to review existing guidelines and literature to develop methodological standards for the design and conduct of disease and treatment registries and the design and analysis of studies using registry data. This report summarizes the methods used to identify relevant guidelines and recommends minimum standards for registries designed to support PCOR.

Methods

The project team conducted a systematic review of existing methodology guidance publications and related documents using a formal search strategy. Relevant publications in the peer-

reviewed literature were identified through searches of PubMed. Searches used combinations of the following MeSH terms: registries; epidemiology; cohort studies; guidelines as topic; comparative effectiveness research; lost to follow-up; selection bias; propensity score; confounding factors (epidemiology); effect modifier, epidemiologic; bias (epidemiology). In addition, the terms "missing data," "instrumental variable," and "sensitivity analysis," which are not MeSH terms, were used in combination with MeSH terms. To identify guidance documents not published in the peer-reviewed literature, the project team reviewed websites of relevant organizations, including the Agency for Healthcare Research and Quality (AHRQ), Food and Drug Administration (FDA), International Society for Pharmacoepidemiology (ISPE), International Society For Pharmacoeconomics and Outcomes Research (ISPOR), Canadian Agency for Drugs and Technologies in Health (CADTH), National Institute for Health and Clinical Excellence (NICE), Institute for Quality and Efficiency in Healthcare (IQWIG), European Medicines Agency (EMA), and The Cochrane Collaboration. Finally, the project team reviewed the reference lists of included guidance publications to identify any additional, relevant documents.

Following the search phase, documents were reviewed for inclusion based on title and publication information. Publications describing the use of a method in a single study or the use of registries to support adherence to clinical guidelines were excluded, as were letters and commentaries published in response to these types of studies. Only documents published in English were included in the search results. In cases where multiple versions of a guidance document were identified, the most recent version was reviewed. Publication abstracts (or, in the case of some documents, executive summaries) were reviewed next. Again, publications describing the use of a method in a single study or the use of registries to support adherence to clinical guidelines were excluded, as were publications that did not discuss or apply to observational study methods. Lastly, the full text versions of the included documents were reviewed and abstracted using a standard abstraction tool (see Appendix 1).

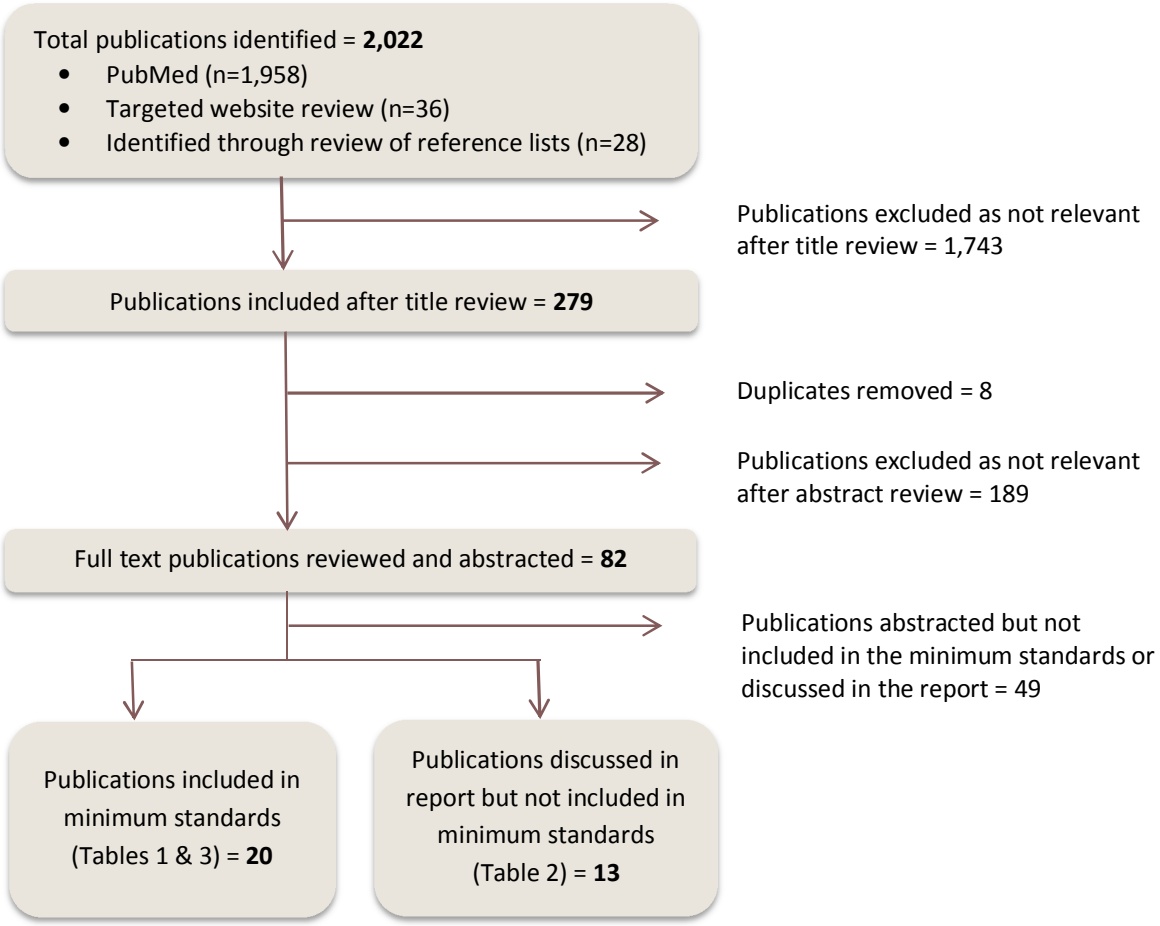
While reviewing the included documents, the project team extracted standards that are relevant to the use of registries for PCOR. Several criteria were used to identify relevant standards. First, the project team focused on identifying standards that balance the requirement for high quality, reliable, and valid data with the need for practical research designs that can be integrated into routine clinical practice and are not overly burdensome on participating patients and clinicians. The project team also focused on the unique needs of PCOR, such as generalizability, flexibility, incorporation of patient perspectives, and inclusion of long-term follow-up data on key outcomes. Lastly, the team focused on selecting the minimum standards necessary for the effective use of registries and registry data for PCOR. Standards that may help identify high quality studies and/or improve confidence in the validity or reliability of the results, but which are not strictly necessary for the use of registries for PCOR, are noted in the "Discussion" section.

Results

Search Results

The results of the systematic literature search are summarized in Figure 1.

Figure 1: Study Flow Diagram



The search identified 2,022 publications, 82 of which were abstracted. Review of the 82 publications resulted in the extraction of 96 relevant standards. During further discussion and review of the 96 standards, several standards were eliminated as applicable to clinical research generally and not specific to patient registries. Other standards were determined to be "best practice" rather than minimum standards and were eliminated. Lastly, many duplicative standards from different guidance documents were identified and combined.

Recommended Standards

The standards identification and development process resulted in the identification of 17 recommended minimum standards for the design and conduct of disease or treatment registries

and the design and analysis of studies using primarily or exclusively registry data for PCOR. These standards are summarized in Figure 2.

Figure 2: Recommended Minimum Standards for Registries Used for PCOR

1. **Develop a formal study protocol.** Develop a formal study protocol specifying: at least one purpose of the registry (e.g., effectiveness, safety, natural history of disease, quality improvement, or other) and research question(s); objectives; study design; target population, including subgroups of interest (if applicable); exposures of interest; primary and secondary endpoints; data sources and linkage plans, if any; measure(s) of effect; sample size and statistical power (if applicable); use of any standardized data dictionaries (nationally or internationally accepted); and likely sources of bias and plans to address them.
2. ***A priori*, specify plans for data analysis that correspond to major aims.** Describe the analytic approaches that will be used to address the major research aims. Provide definitions of key exposures, endpoints, and covariates. Identify patient subgroups of interest, plans (if any) for how new subgroups of interest will be identified, and/or how analysis plans may be adapted based on changing needs and scientific advances. Specify plans for how missing data will be handled.
3. **Choose outcomes that are clinically meaningful, patient-centered, and relevant to decision-makers.** Identify and select outcomes that are clinically meaningful, patient-centered, and relevant to decision-makers. Define outcomes clearly, especially for complex conditions or outcomes that may not have established clinical criteria. Provide information that supports the selection of outcomes as meeting the criteria of "clinically meaningful," "patient-centered," and "relevant to decision-makers," such as patient and decision-maker input from meetings or surveys or published literature relevant to the question of interest.
4. **Describe data linkage plans, if applicable.** For studies involving linkage of registry data to another data source, describe the other data source and its appropriateness and limitations for addressing specific hypotheses. Consider any additional requirements that may influence successful linkage, such as information needed to match patients, selection of data elements, and definitions used.
5. **Plan follow-up based on the registry objective(s).** The objective(s) of the registry should determine the type, extent, and length of patient follow-up. Ensure that the follow-up time planned is adequate to address the main objective and that patient retention efforts planned are suitable to the target population and anticipate challenges to retaining patients in the study. Expected loss to follow-up and potential impact on the results, including possible biases resulting from differential loss to follow-up, should be described.
6. **Use validated scales and tests.** Validated scales and tests should be used when such tools exist for the purpose needed.
7. **Address the potential for re-identification, if applicable, when using previously collected data.** Studies that use previously collected data (e.g., studies involving linkage of data or using repurposed data) that have the potential for re-identification must address this issue in accordance with local, national, and international regulations.
8. **When using previously collected data, address the impact of the legal and privacy conditions under which the data were collected initially.** Registries that re-use data must assess the legal and patient privacy conditions under which the data were originally collected and address the impact of those conditions on the new study.

Figure 2 (cont.)

9. **Take appropriate steps to ensure data quality.** Employ data checks using range and consistency checks where applicable. Create a quality assurance plan that addresses data review and verification. A risk-based approach to quality assurance is advisable.
10. **Document and explain any modifications to the protocol.** Modifications to a registry protocol may be necessary for a variety of reasons. When modifications are necessary, they should be clearly documented and justified.
11. **Collect data consistently.** Provide clear, operational definitions of data elements. Create and distribute standard instructions to data collectors. Use standardized data element definitions and/or data dictionaries whenever possible.
12. **Enroll and follow patients systematically.** Enroll patients systematically and follow them in as unbiased a manner as possible, using similar procedures at all participating sites. Describe how patients and providers were recruited into the study to allow the impact of selection bias to be clearly understood and any efforts employed to confirm the quality of adherence to agreed-on enrollment practices.
13. **Monitor and minimize loss to follow-up.** Monitor loss to follow-up to ensure that follow-up is sufficiently complete for the main objective. Devote reasonable efforts to minimizing loss to follow-up. Describe the impact of actual loss to follow-up on the study results, including possible biases resulting from differential loss to follow-up.
14. **Use appropriate statistical techniques to address confounding.** For registries that are intended to evaluate the effectiveness or safety of interventions, use appropriate statistical techniques to address confounding.
15. **Use sensitivity analyses to determine the impact of major decisions.** For registries that are intended to evaluate the effectiveness or safety of interventions, use sensitivity analyses to determine the impact of key assumptions, such as exposure and outcome definitions, on the research questions.
16. **Assess and report the extent of missing data.** For primary and secondary data collection, assess and report the extent of missing data at key points of follow-up for data elements that are critical to addressing the primary study questions.
17. **Provide sufficient information in reports of the registry findings to allow for assessments of the study's internal and external validity.** Describe the following elements in the registry report, if applicable: methods, including selection of study participants, data collection activities, settings where data were collected, analytic techniques, and approaches to handling missing data; data quality activities, including any issues that may have affected the quality or integrity of the data; comparability of the registry participants to the target population and any efforts to minimize selection bias; extent of missing data for key exposures, risk factors, and outcomes and impact of missing data on key study questions; length of follow-up period and impact of loss to follow-up on key study questions; and the role and impact of potential confounders.

Discussion

The recommended standards in Figure 2 represent the minimum set of practices necessary to conduct a registry for PCOR that will produce evidence suitable to inform health care decisions. To produce evidence to inform decision-making, a registry must have sufficient internal and external validity, and the standards focus on these areas. To strengthen internal validity, the

standards include several practices that are essential for scientific rigor, such as developing a protocol and data analysis plan in advance and devoting efforts to data quality. The standards address external validity by focusing on enrolling a representative target population and minimizing selection bias and missing data. The themes of patient-centeredness and transparency appear in many of the standards as well, as these are critical components of PCOR. The rationale for the inclusion of each standard, the empirical evidence or theoretical base underlying the standard, and each standard's contribution to patient centeredness, scientific rigor, and transparency are presented in Appendix 2, along with information on current practice, examples, published guidance, implementation issues, and other considerations. The published guidance documents that are cited in the recommended minimum standards are summarized in Appendix 3 (Table 1) and described in more detail in Appendix 5 (Table 3).

In developing the minimum standards, the project team encountered two challenges. First, the minimum standards proposed here reflect topics that in many cases are not unique to patient registries. While these standards may be applicable to other types of observational research, they are considered to be of particular importance for patient registries. Only a few of the guidance documents identified for this project address patient registries exclusively or specifically. Standards that apply broadly to most or all clinical research are not included here. For example, several guidance documents address the ethical conduct of clinical research, but these rules apply to all research in some cases and all observational research in other cases.[6-13] These standards are not included here. However, the ethical issues around linking registry data to other data sources and reusing existing registry data sets for new purposes are included in the minimum standards because these issues are particularly important for and often unique to registry-based studies. Because of the broad nature of many of the guidance documents, only a relatively small set of the reviewed documents are cited in the minimum standards. Documents that were reviewed for this project and are discussed in this paper are described in Appendix 4.

A second challenged encountered by the project team was the number of areas where methodology is evolving, and recommending minimum standards is not yet possible. For example, an important strength of patient registries is their ability to collect long-term follow-up data on broad patient populations. However, loss to follow-up can reduce the value of the long-term data collection and limit the ability of the registry to achieve its objectives. Some publications identified in the literature review discuss potential strategies for improving follow-up rates,[14,15] but additional work is needed to test these strategies in different types of registries and among different patient populations. Strategies to reduce loss to follow-up that are based on empirical evidence would be a valuable tool for patient registries. A related topic where methods are continuing to evolve is missing data. Due to the observational nature of patient registries, registries are likely to have some missing data, as patients may miss visits, drop out of the registry, or decline to complete a patient-reported outcome questionnaire. Analytic techniques to handle missing data are described in the literature and may be synthesized into best practices or recommended approaches in the future; however, this type of guidance does not currently exist.

Analytic techniques for addressing measured and unmeasured confounding are another area of evolving methodology. The proposed minimum standards note the importance of considering potential confounding variables when developing analytic plans and using appropriate statistical techniques to address this issue during the analysis phase. However, techniques for addressing confounding are evolving rapidly, and each technique has strengths and limitations that must be considered in the context of a specific research question and the available data. For example, Arbogast et al suggest considering disease risk scores as an alternative to propensity scores in cases where there is a moderate association between covariates and exposure.[16] Curtis et al recommend inverse probability-weighted estimation as a useful approach in situations with time-dependent covariates or censored data.[17] Other publications recommend instrumental variable analyses for studies of intended effects in cases when an instrumental variable can be identified.[18-20] Currently, researchers must weigh the strengths and limitations of each approach and select the most appropriate option, given their research questions of interest and available data. Additional methods research in this area may lead to the development of more specific guidelines and standards for the appropriate use of these analytic techniques.

Lastly, as noted in the minimum standards, additional methodology work is needed to define a clear process for identifying and selecting outcomes that are patient-centered and relevant to patients and other decision-makers. Additional work is also needed to improve strategies for linking registry data and reducing the risk of re-identification. Currently, the selection of a specific strategy for a data linkage project must be guided by the available data, the type of linkage, and the potential for re-identification. Data linkage is an evolving field, though, and techniques to link datasets and manage patient identities across data sets are improving. The development of standards or recommended approaches may be possible in the future.

While not a challenge, a major factor that shaped the development of the recommended standards was the focus on minimum standards, rather than best practices. Registries are designed to fulfill many different purposes, and the standards proposed here represent minimum standards that can be applied to most, if not all, disease and treatment registries. The review of the literature did identify several best practices for patient registries. In particular, the AHRQ document, "Registries for Evaluating Patient Outcomes: A User's Guide" includes both basic good practices and potential enhancements for registries.[1] The potential enhancements represent a set of best practices that could be applied to most types of patient registries. In addition, several other guidance documents include best practices. For example, the proposed minimum standards emphasize using validated tools and measures when such tools exist. Potential best practices related to the use of validated tools and measures include using a combination of specific measures, generic profiles, and preference-base measures to measure health-related quality of life,[21] using measures that have been validated in the population most similar to that under study,[22] and collecting core components when capturing composite scores.[1,15] Many other best practices relate to data analysis. For example, registries designed to evaluate or compare treatment effectiveness may enhance the strength of their analyses by addressing issues of

adherence and compliance,[23] and they may improve confidence in their results by using a variety of statistical models and reporting a panel of results.[24] To support informed interpretation of the study results, registries may consider reporting confidence intervals in addition to p-values and including both absolute and relative risk estimates.[25] These types of best practices are not included in the proposed minimum standards. However, the development of best practices may be useful for PCOR in the future.

In conclusion, patient registries are a useful tool for PCOR, but they must be designed and conducted with sufficient rigor to produce evidence to inform decision-making. The goal of the minimum standards put forth here is to ensure that registries designed for PCOR meet a minimum level of rigor and produce reliable, valid evidence. Additional methodology work in several key areas, such as selection of the most suitable methods for addressing confounding, minimizing loss to follow-up, reducing missing data, identifying and selecting outcomes that are patient-centered, and linking data sets, will inform the development of future standards and will continue to support the use of high-quality registries for PCOR.

Appendices

Appendix 1: Abstraction Tool

The following data were abstracted in table format for each included publication:

1) Reference Source (PubMed, Google Scholar, Website Review, or Reference List Review)
2) Guideline Title
3) Organization or Authors
4) Year
5) Program (if applicable)
6) Country or Region where guideline originated
7) Country or Region to which guideline applies
8) Guideline subjected to independent external review? (Yes/No)
9) Research Design
10) Subtopic addressed by guideline (check all that apply)
    a) Design - Choosing the target population and comparator(s)
    b) Design - Sample size
    c) Design - Selection and definition of data on outcomes and potential confounders and effect modifiers
    d) Design - Length of follow-up
    e) Design - Using best practices to minimize the potential for selection bias
    f) Conduct - Enrollment
    g) Conduct - Data collection
    h) Conduct - Data quality assurance activities
    i) Conduct - Use of techniques to minimize information bias and reduce loss to follow-up
    j) Analysis - Handling missing data
    k) Analysis - Controlling confounding (measured and unmeasured) and effect modification through propensity scores (matching, trimming, modeling, etc.) and instrumental variables
    l) Analysis - Approaches for assessing the potential for bias (e.g., sensitivity analyses)
    m) Analysis - Procedures for evaluating data quality
11) Description
12) The purpose of the work is to define methodological standards for PCOR (Yes/No)
13) The applications of the standards to PCOR is clear (Yes/No)
14) The standards were developed by a professional group (Yes/No)
15) Patient's views and preferences were sought (Yes/No)
    a) If yes, describe how patient's views and preferences were obtained
16) Stakeholders were involved in the development of standards (Yes/No)
    a) If yes, describe how stakeholders were involved

17) A systematic process was used to generate recommendations (Yes/No)
18) Details of the systematic process used to generate recommendations are provided (Yes/No)
    a) If yes, describe the systematic process
19) There is an explicit link between the rationale for and the recommended standards (evidence) (Yes/No)
    a) If yes, describe the link
20) The recommendations are specific and unambiguous (Yes/No)
21) Key recommendations are clear (Yes/No)
22) The standards are editorially independent from the funding body (Yes/No)
23) Conflicts of interest have been recorded (Yes/No)
24) Reference citation

Appendix 2: Explanation and Examples for Minimum Standards

Standard 1

Name of Standard	**Develop a formal study protocol.**
Description of Standard	Develop a formal study protocol specifying: at least one purpose of the registry (e.g., effectiveness, safety, natural history of disease, quality improvement, or other) and research question(s); objectives; study design; target population, including subgroups of interest (if applicable); exposures of interest; primary and secondary endpoints; data sources and linkage plans, if any; measure(s) of effect; sample size and statistical power (if applicable); use of any standardized data dictionaries (nationally or internationally accepted); and likely sources of bias and plans to address them.
Current Practice and Examples	Development of a study plan, which may be less detailed than the formal study protocol described here, is considered basic good practice for patient registries.[1] Registries designed to study questions of effectiveness or safety are more likely to develop a formal study protocol, while registries intended to study the natural history of a disease or to support quality improvement activities may determine that a study plan is sufficient. <u>Example</u> • The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is designed to study outcomes of patients receiving left-ventricular assist device therapy, a specific type of mechanical circulatory support device therapy to treat advanced heart failure. The registry is a collaborative project, with support from the National Heart, Lung and Blood Institute, the Centers for Medicare and Medicaid Services, the Food and Drug Administration, clinicians, scientists, and industry representatives, and is managed by the University of Alabama at Birmingham. The registry protocol is not inserted here due to its length, but is included as a Supplemental Material 1 and is also available online.[26] The protocol describes the purpose of the registry (page 4), the objectives (page 4), the study design (page 6), target population (page 5); exposures of interest (page 5); primary and secondary endpoints (page 7); data sources and linkage plans (pages 6-7); and likely sources of bias and plans to address them (page 5).
Published Guidance	Guidance on observational study methods typically supports development of a formal study protocol.[1,10,21,25,27,28] Guidance documents vary on the level of detail that should be included in the study protocol.
Key Considerations for Methodology Committee (relevant points bolded) **Contribution to Patient**	This standard contributes to scientific rigor, transparency, and patient centeredness. Development of a formal protocol requires that the major aspects of the study (research questions, target population, data sources, etc.) have been considered and specified in advance. This step helps to avoid unanticipated issues during the conduct of the study. Specifying

Centeredness **Contribution to Scientific Rigor** **Contribution to Transparency** Empirical Evidence and **Theoretical Basis**	major aspects of the study in advance also helps to ensure that the proposed study is sufficient and appropriate to address the research question(s) of interest. The study protocol should provide enough detail for another investigator to potentially replicate the study to confirm the results, which improves transparency. Lastly, the study protocol must have objectives, target population, exposures, and endpoints of interest that are relevant to patients and other decision-makers in order to be patient-centered. A protocol provides more clarity to the investigator, including on the risks and burden to the patient, and enables the investigator to provide patients with more information to make educated decisions regarding their participation, thereby contributing to the patient-centeredness of the registry. The guidance documents that include this standard use a theoretical basis to support the standard. Empirical evidence is not cited.
Degree of Implementation Issues	Flexibility is a major strength of patient registries for patient-centered outcomes research. Planning for modifications to the protocol, with appropriate justification, during the course of the study is critical.
Other Considerations	Depending on the purpose of the registry, not all elements noted above may be applicable. For example, some registries may not use standardized dictionaries. Protocols for registries designed to study the natural history of a disease may not include formal sample size calculations. Registries that justify the sample size based on financial constraints or limits of available data on the target population should still describe the statistical power for a given study size.

Standard 2

Name of Standard	***A priori*, specify plans for data analysis that correspond to major aims.**
Description of Standard	Describe the analytic approaches that will be used to address the major research aims. Provide definitions of key exposures, endpoints, and covariates. Identify patient subgroups of interest, plans (if any) for how new subgroups of interest will be identified, and/or how analysis plans may be adapted based on changing needs and scientific advances. Specify plans for how missing data will be handled.
Current Practice and Examples	Registries designed to study questions of effectiveness or safety are more likely to develop analysis plans *a priori* than registries intended to study the natural history of a disease or to support quality improvement activities. <u>Example</u> • The National Oncologic PET Registry (NOPR) is designed to examine the impact of positron emission tomography with F-18 fluorodeoxyglucose (PET) on cancer patient management. The registry meets the Centers for Medicare & Medicaid Services data submission requirements under the coverage with evidence development program. The analysis plan (which is not inserted here due to its length) is included as Supplemental Material 2 and is also available online.[29] The analysis plan describes the approaches that will

	be used to address the major research aims (page 24), defines key exposures, endpoints, and covariates (page 20), identifies patient subgroups of interest (page 21), and discusses how analysis plans may be adapted (page 24); missing data is not addressed. • The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) is a registry designed to study treatment patterns and variations in care according to demographics, clinical factors, risk stratification, provider specialty, and geographic region for patients with incident and prevalent atrial fibrillation (AF). The registry published a report on its rationale and design, which describes the statistical analysis plan. The report describes: o Analytic approaches: "Univariate and multivariable approaches will be used to identify factors associated with primary and secondary outcomes. Propensity score techniques will be used to balance comparison groups according to baseline factors." o Subgroups of interest: "Characteristics of interest will include sex; race; age; prior stroke/transient ischemic attack (TIA); geographic region; socioeconomic status; CHADS2, CHA2DS2-VASc, and HAS-BLED scores; management strategies (eg, rate control vs rhythm control, catheter ablation vs medical management, and combination therapy with antiplatelet agents); and provider specialties." o Plans for handling missing data: "Variables with <15% missing will routinely be imputed, although missing data will be addressed on an analysis-specific basis." o Key exposures, endpoints, and covariates are also defined in the report.[30]
Published Guidance	Guidance on observational study methods for comparative effectiveness and safety typically supports development of a high-level plan for data analysis *a priori*.[1,25,27,28]
Key Considerations for Methodology Committee (relevant points bolded) **Contribution to Patient Centeredness** **Contribution to Scientific Rigor** **Contribution to Transparency** Empirical Evidence and **Theoretical Basis**	This standard contributes to scientific rigor and transparency. Developing the plan prior to beginning the study allows researchers to ensure that the proposed data collection will be sufficient to support the analyses (e.g., important covariates are collected in appropriate format for analysis). Following the plan during the analysis phase eliminates concerns that data mining-type analyses of the study may identify results that are statistically significant by chance, but not clinically or epidemiologically meaningful. In addition, the analysis plan contributes to patient-centeredness, in that the plan should reflect the major questions of interest to patients and other decision-makers. An *a priori* analysis plan also enables the registry to specify the required data elements and numbers of patients in a manner that will reduce unnecessary patient burden or enrollment, also contributing to patient centeredness. The guidance documents that include this standard use a theoretical basis to support the standard. Empirical evidence is not cited.

Degree of Implementation Issues	Overly prescriptive analysis plans and strict implementation of this practice could interfere with serendipitous discoveries that may not have been predicted in advance.
Other Considerations	The addition of new analyses may still be appropriate, if, for example, new questions emerge during the course of the study.

Standard 3

Name of Standard	**Choose outcomes that are clinically meaningful, patient-centered, and relevant to decision-makers.**
Description of Standard	Identify and select outcomes that are clinically meaningful, patient-centered, and relevant to decision-makers. Define outcomes clearly, especially for complex conditions or outcomes that may not have established clinical criteria. Provide information that supports the selection of outcomes as meeting the criteria of "clinically meaningful," "patient-centered," and "relevant to decision-makers," such as patient and decision-maker input from meetings or surveys or published literature relevant to the question of interest.
Current Practice and Examples	Registries typically aim to select outcomes that are clinically meaningful and relevant. <u>Example</u> • The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) is a registry designed to study treatment patterns and variations in care according to demographics, clinical factors, risk stratification, provider specialty, and geographic region for patients with incident and prevalent atrial fibrillation (AF). The registry published a report on its rationale and design, which describes the major aspects of the protocol. The report identifies and defines the outcomes of interest: ○ "The primary outcome event in ORBIT-AF is stroke or non–central nervous system (CNS; systemic) systemic embolism. Consistent with recent clinical trials, stroke will be defined as a new, sudden, focal neurologic deficit that persists beyond 24 hours and is not due to a readily identifiable, nonvascular cause (eg, seizure). Primary outcome events will be verified by single-source document submission (eg, hospital discharge report) and central review at the data coordinating center. The major safety outcome of interest will be major bleeding as defined by the International Society of Thrombosis and Haemostasis. Secondary outcomes will include major adverse cardiac events (MACE), defined as stroke or non-CNS systemic embolism, myocardial infarction, and cardiovascular death (online Appendix A). Additional secondary outcomes will include all-cause mortality, cardiovascular death, intracranial

	bleeding, myocardial infarction, sudden cardiac death, heart failure–related death, AF-related quality of life, and all-cause hospitalization (subcategorized as cardiovascular; bleeding related; and noncardiovascular, non–bleeding related)." ○ The authors also note the importance of quality of life and treatment satisfaction in treatment decisions for AF as part of their rationale for including quality of life as a secondary outcome, citing published literature. "Atrial fibrillation is associated with significantly impaired quality of life (Dorian et al J Am Coll Cardiol 2000). Accordingly, many treatment decisions in AF are predicated upon improving both short- and long-term quality of life (Fuster et al J Am Coll Cardiol 2006). Prior studies of quality of life have been informative but have suffered from several limitations, including relatively small sample size, restricted follow-up, and the lack of validated AF-specific qualify-of-life instruments (Thrall et al Am J Med 2006). The ORBIT-AF PRO cohort will allow for large-scale examination of AF related quality of life in a heterogeneous group of patients over long-term follow-up using a rigorously derived and validated quality-of-life instrument (Spertus et al Circ Arrhythm Electrophysiol 2011). … Taken together, the PRO data will provide much needed information regarding quality of life among patients with AF. … These data will inform comparative effectiveness, comparative safety, and future research to improve quality of life and outcomes in patients with AF."[30]
Published Guidance	Guidance on observational study methods typically supports the selection and definition of meaningful, relevant outcomes.[1,23,25,31,32]
Key Considerations for Methodology Committee (relevant points bolded) **Contribution to Patient Centeredness** **Contribution to Scientific Rigor** **Contribution to Transparency** Empirical Evidence and **Theoretical Basis**	This standard contributes to patient centeredness, scientific rigor, and transparency. To provide useful information for patients and other decision-makers, a registry must study outcomes that are clinically meaningful and relevant to these stakeholders. Outcomes must be clearly defined to ensure consistent interpretation and collection across registry participants. Consistent collection of key outcomes reduces the likelihood of misclassification or measurement bias and improves data quality, both of which are important for scientific rigor. Providing support for the selection of outcomes as "clinically meaningful," "patient-centered," and "relevant to decision-makers" improves transparency. The guidance documents that include this standard use a theoretical basis to support the standard. Empirical evidence is not cited.
Degree of Implementation Issues	There is no clear process for identifying, defining, and selecting outcomes that are patient-centered and relevant to patients and other decision-makers.

Other Considerations	None.

Standard 4

Name of Standard	**Describe data linkage plans, if applicable.**
Description of Standard	For studies involving linkage of registry data to another data source, describe the other data source and its appropriateness and limitations for addressing specific hypotheses. Consider any additional requirements that may influence successful linkage, such as information needed to match patients, selection of data elements, and definitions used.
Current Practice and Examples	Studies that link data from registries and other sources typically describe their data linkage plans. <u>Example</u> • The National Oncologic PET Registry (NOPR) is designed to examine the impact of positron emission tomography with F-18 fluorodeoxyglucose (PET) on cancer patient management. The registry describes data linkage plans in its operations manual (pages 21-22): "In addition, NOPR will link its data to the Medicare Claims Database to determine whether physicians' intended management plans match actual patient management. This validation of intended management and actual management will require defining a 'cross-talk' between CPT codes for the various clinical actions. Such cross talk definitions will be relatively easy to define for infusional chemotherapy, radiation therapy, and the most common alternative imaging methods (CT, MRI or ultrasonography of various organs (e.g., head, chest, abdomen, or pelvis). However, changes to and from oral chemotherapies will require an extensive potential list of alternatives that will need to be customized for each major cancer group in consultation with medical oncologists. The same challenge exists for the potential universe of biopsy and surgical procedures. The validation of intended vs. claims-based actual management will first be done for selected high-volume cancers: bladder, kidney, small cell lung and pancreas. An initial time frame of 30 days will be used for comparing the date of intended to actual management."[29]
Published Guidance	Guidance documents on observational study methods that describe data linkage activities support this standard.[1,25,31]
Key Considerations for Methodology Committee (relevant points bolded) Contribution to Patient Centeredness **Contribution to**	This standard contributes to scientific rigor and transparency. Carefully planning the data linkage at the start of the study helps to ensure that the linkage is feasible and that necessary data to support the linkage are collected, if relevant (e.g., if prospectively collected data are to be linked to another data source). The planning stage must include a review of the data elements, definitions, and subjects to identify any issues that may affect the study results (e.g., different definitions of a key outcome). In addition, plans for evaluating data quality should be described. Any issues identified in the

Scientific Rigor **Contribution to Transparency** Empirical Evidence and **Theoretical Basis**	planning or analysis stage should be documented so that they may be considered when interpreting the study findings. A clear data linkage plan also supports transparency, as it provides other investigators with the ability to recreate the study analyses and to understand the strengths and limitations of the study. The guidance documents that include this standard use a theoretical basis to support the standard. Empirical evidence is not cited.
Degree of Implementation Issues	Data linkage is an evolving field, and data linkage studies may need to refine their approach during the study to address unanticipated issues (e.g., changes in data definitions in one data source during the course of the study). Modifications to the data linkage plan should be justified and documented.
Other Considerations	At this time, it is not possible to recommend standards for data linkage methods. Additional methodological work is needed in this area.

Standard 5

Name of Standard	**Plan follow-up based on the registry objective(s).**
Description of Standard	The objective(s) of the registry should determine the type, extent, and length of patient follow-up. Ensure that the follow-up time planned is adequate to address the main objective and that patient retention efforts planned are suitable to the target population and anticipate challenges to retaining patients in the study. Expected loss to follow-up and potential impact on the results, including possible biases resulting from differential loss to follow-up, should be described.
Current Practice and Examples	The objectives of the registry generally drive follow-up plans; however, resource constraints also play a role in this decision. <u>Examples</u> • The Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) was designed to collect information on the health status outcomes of patients for one year after an acute myocardial infarction, with the goal of identifying determinants of outcomes to support improvements in myocardial infarction care. Because the registry sought to understand the transition from inpatient to outpatient care, follow-up information was collected at 1, 6, and 12 months.[33] • The Palivizumab Outcomes Registry was designed to collect data on infants receiving palivizumab injections, with the goals of characterizing the population of infants receiving prophylaxis for respiratory syncytial virus (RSV) disease and describing patterns of use for palivizumab, which is administered as a series of injections. Follow-up data were collected throughout the RSV season (November to March) to assess subsequent injections as well as hospitalizations for RSV. In this registry, the number of follow-up

	visits completed varied by patient, depending on the number of required of injections and whether the patient was hospitalized for RSV.[34]
Published Guidance	Guidance documents on observational study methods that describe follow-up activities support this standard.[1,10,35]
Key Considerations for Methodology Committee (relevant points bolded) Contribution to Patient Centeredness **Contribution to Scientific Rigor** Contribution to Transparency Empirical Evidence and **Theoretical Basis**	This standard contributes to scientific rigor. A major strength of registries is the ability to collect long-term follow-up data on broad groups of patients. The follow-up data should be sufficient to address the study objectives, in terms of the type and extent of data collected (patient-reported outcomes, physician visit information, etc.) and the length of the follow-up period. Some loss to follow-up should be anticipated in any registry, and the expected loss to follow-up should be described. The expected loss to follow-up should also be considered in planning the target enrollment for the study. The guidance documents that include this standard use a theoretical basis to support the standard. Empirical evidence is not cited.
Degree of Implementation Issues	Expected loss to follow-up can be difficult to estimate. Expected loss to follow-up rates vary widely by the type of registry and the length and nature of the follow-up data collection.
Other Considerations	Some registries may not collect follow-up data.

Standard 6

Name of Standard	**Use validated scales and tests.**
Description of Standard	Validated scales and tests should be used when such tools exist for the purpose needed.
Current Practice and Examples	There is widespread variation in how registries collect similar data. <u>Examples</u> • The Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD) is a registry designed to assess the prevalence and incidence of diabetes mellitus and cardiovascular disease, disease burden and progression, risk predictors, and knowledge, attitudes, and behaviors regarding health in the United States population. The registry uses several validated, patient-reported outcomes measures (PROs) to collect information on health status and behaviors: 1) the 12-item Short Form Health Survey and European Quality of Life (EuroQoL) EQ-5D instrument to assess health-related quality of life; 2) the Sheehan Disability Scale to assess the level of disruption in work, social life,

	and family/home life; 3) the 9-item Patient Health Questionnaire to assess depression; 4) the Work Productivity and Activity Impairment Questionnaire: General Health to assess work productivity and absenteeism; 5) the Diet and Health Knowledge Survey; 6) the Press-Ganey Satisfaction questionnaire; and 7) the International Physical Activity Questionnaire to assess health-related physical activity and sedentary behaviors. The goal of using validated measures in this registry is to allow the data from the registry to be compared to data from other studies.[36] • LUMINA is a registry designed to study outcomes in multiethnic population of patients with lupus. The registry uses validated scales to assess disease activity and damage: "Disease activity was assessed using the Systemic Lupus Activity Measure – Revised (SLAM-R) (Liang et al Arthritis Rheum 1989). The SLAM-R was examined at TD [Time of Diagnosis], T0 [Time of Enrollment] and all other visits; since the interval between visits tends to fluctuate with some intervals being longer than others, a weighted average SLAM-R was used for the TD–TL [Last Study Visit] interval. Damage was measured with the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). … Behavioural and psychological variables included social support, ascertained with the Interpersonal Support Evaluation List (ISEL) where higher scores indicate better social support (Cohen 1985); learned helplessness, ascertained with the Rheumatology Attitude Index (RAI) where higher scores indicate higher levels of helplessness (Engle Arthritis Rheum 1990) and abnormal illness-related behaviours, ascertained with the Illness Behaviour Questionnaire (IBQ) where higher scores indicate more abnormal illness-related behaviours (Pilowsky J Psycosom Res 1993). Finally, self-reported health-related quality of life physical and mental functioning was ascertained with the Short Form-36 (SF-36) physical and mental components summary measures (PCS and MCS, respectively) where higher scores indicate better function."[37] • The Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) was designed to collect information on the health status outcomes of patients for one year after an acute myocardial infarction, with the goal of identifying determinants of outcomes to support improvements in myocardial infarction care. The registry used four validated, patient-reported outcome measures: 1) Patient Health Questionnaire to assess depression; 2) ENRICHD Social Support Inventory to measure social support; 3) Short Form-12 to quantify overall mental and physical health; and 4) the Seattle Angina Questionnaire (SAQ) to understand the patients' perspective on how coronary disease affects their life.[33]
Published Guidance	The AHRQ Registries Guide and FDA Guidance for Industry support this standard.[1,38]
Key Considerations for Methodology Committee	This standard contributes to patient centeredness, scientific rigor, and transparency. Outcomes that are most important to patients may be

(relevant points bolded) **Contribution to Patient Centeredness** **Contribution to Scientific Rigor** **Contribution to Transparency** Empirical Evidence and **Theoretical Basis**	studied through the use of patient-reported outcomes or quality of life instruments. Use of validated tools to collect data on these outcomes increases the validity of the data and the comparability of the results across studies. Use of validated instruments and tools also improves the ability of the data to be linked to other data sources, such as other registries, and makes it more feasible for another researcher to replicate the study procedures. The guidance documents that include this standard use a theoretical basis to support the standard. Empirical evidence is not cited.
Degree of Implementation Issues	Validated instruments and tools may not be available for some purposes. As registries become increasingly patient focused, validation in subgroups of interest or specific languages may not be available. Similarly, the mode of administration may not have been validated, even though the questions and scoring have been validated (e.g., paper-based scales may not have been validated for web-based use). Registries may also be used to validate new instruments or tools.
Other Considerations	Some degree of validation is desirable, even if the instrument has not been validated in the exact population or subgroup of interest. Also, modifying validated instruments should be avoided.

Standard 7

Name of Standard	**Address the potential for re-identification, if applicable, when using previously collected data.**
Description of Standard	Studies that use previously collected data (e.g., studies involving linkage of data or using repurposed data) that have the potential for re-identification must address this issue in accordance with local, national, and international regulations.
Current Practice and Examples	Holders of data sets that may be linked with other data sets are increasingly assessing the risk of re-identification as part of reviewing research proposals. <u>Example</u> • The Surveillance, Epidemiology and End Results (SEER) program of cancer registries includes demographic, clinical, and cause of death information for patients with cancer. The Medicare Health Outcomes Survey (MHOS) is a survey of Medicare beneficiaries in participating Medicare Advantage Organizations that collects information on self-reported socioeconomic, demographic, co-morbidity, and race/ethnicity. The SEER data were linked with the MHOS data to improve understanding of the health-related quality of life of cancer patients enrolled in Medicare health plans. The linked SEER-MHOS database is available for research, but some precautions have been

	taken to minimize the potential for re-identification: "The SEER-MHOS data are available to outside investigators for research purposes. Although personal identifiers for all patient and medical care providers have been removed from the SEER-MHOS data, there remains the remote risk of re-identification (given the large amount of data available). In light of the sensitive nature of the data, maintaining patient, hospital and health plan confidentiality is a primary concern of National Cancer Institute (NCI), SEER, and Centers for Medicare and Medicaid Services (CMS). Therefore, the SEER-MHOS data are not public use data files. Investigators are required to obtain approval in order to obtain the data. The purpose of the approval process is not to critique the methodology or merits of proposed projects, but to ensure the confidentiality of the patients and providers in SEER areas. NCI will work with investigators requesting data files to balance their research needs with those of the individuals and institutions included in the data. For reasons of confidentiality, selected variables are not routinely released on the SEER-MHOS files. These variables include the patient's Census tract identifier and ZIP code reported by SEER at the time of first cancer diagnosis, the ZIP code at the time of the MHOS survey, and the Managed Care Plan ID and Contract number. Selected 2000 Census data aggregated at the Census tract and ZIP code level are included in the file (see Data Dictionary documentation). However, the actual ZIP code and Census tract identifiers were removed. These aggregated variables have been slightly altered to prevent matching back to the Census data and identifying the actual Census tract or ZIP code."[39]
Published Guidance	The AHRQ Registries Guide supports this standard.[1]
Key Considerations for Methodology Committee (relevant points bolded) **Contribution to Patient Centeredness** Contribution to Scientific Rigor Contribution to Transparency **Empirical Evidence** and Theoretical Basis	This standard contributes to patient centeredness. Patient-centered research must respect the privacy of research participants. When de-identified data sets are linked, there exists the possibility for inadvertently combining sufficient information to re-identify patients in the new combined data set. This risk must be assessed in the project planning phase, and appropriate risk mitigation strategies should be employed if necessary. The guidance document that includes this standard cites empirical evidence in the form of statistical analyses that were done to show the potential for re-identification when linking different de-identified data sets.
Degree of Implementation Issues	The potential for re-identification is a complex statistical question and may require consultation with statisticians with subject matter expertise.

Other Considerations	At this time, it is not possible to recommend standards for assessing or mitigating the risk of re-identification. Additional methodological work is needed in this area.

Standard 8

Name of Standard	**When using previously collected data, address the impact of the legal and privacy conditions under which the data were collected initially.**
Description of Standard	Registries that re-use data must assess the legal and patient privacy conditions under which the data were originally collected and address the impact of those conditions on the new study.
Current Practice and Examples	The issue of data re-use is receiving increasing attention, particularly as the National Institutes of Health continue to develop data archives to support future research (e.g., Genome-wide association studies (GWAS) and related data re-use policies, National Database for Autism Research) <u>Examples</u> • The Society of Thoracic Surgeons National Database (STS NDB) collects in-hospital information on outcomes following adult cardiac, general thoracic, and congenital surgery. Linkage with national Medicare claims data was explored as an approach to providing information on long-term outcomes of cardiac surgery, such as survival, readmissions, and subsequent cardiac events. Before linking the datasets, researchers assessed the ethical and patient privacy considerations and determined that a waiver of authorization was required under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and a waiver of patient informed consent was required under the Common Rule.[40] • The CathPCI Registry studies inpatient and outpatient care for patients receiving diagnostic cardiac catheterizations and percutaneous coronary interventions. The registry does not collect long-term patient outcomes. To study long-term outcomes of these procedures, the registry explored linkage with Medicare claims data. Potential issues included the use of patient identifiers to perform the linkage and the potential need for informed consent. The registry determined that the data could be linked if a limited dataset were used instead of full identifiers and if an institutional review board granted a waiver of informed consent.[41]
Published Guidance	The AHRQ Registries Guide supports this standard.[1]
Key Considerations for Methodology Committee (relevant points bolded) **Contribution to Patient Centeredness**	This standard contributes to patient centeredness. Patient-centered research must be conducted with the full consent of research participants. The use of existing data sets for a new research purpose introduces the question of whether the participants in the original research consented to this new use of their data. For example, a patient may consent to participate in a study on cardiovascular disease conducted at a local

Contribution to Scientific Rigor Contribution to Transparency Empirical Evidence and **Theoretical Basis**	hospital, but may not wish to consent to have his or her data used in a new study on diabetes conducted by a different institution. The conditions under which the data were collected should be assessed during the planning phase to determine if the proposed re-use is appropriate and permitted. The guidance documents that include this standard use a theoretical basis to support the standard. Empirical evidence is not cited.
Degree of Implementation Issues	An Institutional Review Board or Ethics Committee generally will need to make the determination of whether the proposed data re-use is appropriate and permitted given the conditions under which the data were originally collected.
Other Considerations	This determination is particularly complex when the proposed data re-use involves data collected in more than one country or when the data includes genetic material.

Standard 9

Name of Standard	**Take appropriate steps to ensure data quality.**
Description of Standard	Employ data checks using range and consistency checks for key exposure and outcome variables and covariates. Create a quality assurance plan that addresses data review and verification. A risk-based approach to quality assurance is advisable.
Current Practice and Examples	Registries use a variety of approaches to address data quality, with different levels of rigor. <u>Examples</u> • The Fabry Outcome Survey (FOS) is a registry designed to improve understanding of the natural history of Fabry disease and to evaluate patients' response to enzyme replacement therapy with agalsidase alfa. The registry conducted a periodic review of a random sample of data and, based on the results, instituted new procedures to improve data quality. "Beginning in 2006, three measures were implemented to improve the collection and quality of data: development of a core data set to ensure evaluation of variables relevant to disease progression and the effect of treatment; increased concentration on centers that have enrolled 20 or more patients in FOS; and use of clinical project associates to monitor data capture and quality. … A random sample (25%) of all enrolled patients was taken before and after the introduction of the above measures to assess their effectiveness. This sample consisted of 197 out of 815 patients enrolled in 2005 and 404 out of 1616 patients enrolled in 2008. Increases in data capture were found for 9 of the 10 core variables, the only exception being

	patient weight which remained unchanged at 90% for both time points. Data capture increased from 66% to 83% for signs and symptoms, from 89% to 91% for serum creatinine, from 48% to 55% for left ventricular mass, and from 84% to 87% for NYHA (New York Heart Association) score. The proportion of females enrolled increased from 48% to 54%, which is more representative of the true Fabry population."[42]
Published Guidance	Guidance documents on observational study methods support this standard.[1,25]
Key Considerations for Methodology Committee (relevant points bolded) Contribution to Patient Centeredness **Contribution to Scientific Rigor** Contribution to Transparency Empirical Evidence and **Theoretical Basis**	This standard contributes to scientific rigor. The quality of the data collected for a study is an important factor in assessing the strength of the evidence resulting from the study. Poor data quality raises concerns about the validity of the study findings and may prevent the study from successfully completing the planned analyses. Range and consistency checks can help to ensure that inaccurate data are not entered into the study. A documented quality assurance plan is an important tool for consistent review and verification of the data across sites and over the life of the study. Because registries may collect large volumes of data over long timeframes, it is generally not feasible to audit or verify all fields for all patients from all sites. Instead, a risk-based quality assurance plan is recommended to focus resources on the key variables and outcomes of interest. The guidance documents that include this standard use a theoretical basis to support the standard. Empirical evidence is not cited.
Degree of Implementation Issues	Range and consistency checks and quality assurance plans may need to be adjusted over the life of the registry if the data being entered differ from what was anticipated.
Other Considerations	Data quality issues that may affect the study findings should be reported with the results of the study.

Standard 10

Name of Standard	**Document and explain any modifications to the protocol.**
Description of Standard	Modifications to a registry protocol may be necessary for a variety of reasons. When modifications are necessary, they should be clearly documented and justified.
Current Practice and Examples	Long-term registries, such as those designed to study the natural history of disease, and registries designed to fulfill multiple purposes may be more likely to modify the registry protocol during the life of the study. Similarly, protocols for registries intended to evaluate comparative effectiveness and safety may need to be modified over time to accommodate new comparators as new treatments are introduced into the marketplace. <u>Examples</u> • The Interagency Registry for Mechanically Assisted Circulatory

	Support (INTERMACS) is designed to study outcomes of patients receiving left-ventricular assist device therapy, a specific type of mechanical circulatory support device therapy to treat advanced heart failure. The registry protocol (which is not inserted here due to its length) is included as Supplemental Material 1 and is also available online.[26] The protocol was modified to clarify the inclusion criteria. The protocol modification is documented through an amendment to the protocol. The amendment (which is not inserted here due to its length) is included as Supplemental Material 3 and is available online.[43]
Published Guidance	Guidance documents on clinical research methods support this standard.[1,8,9,44]
Key Considerations for Methodology Committee (relevant points bolded) Contribution to Patient Centeredness **Contribution to Scientific Rigor** **Contribution to Transparency** Empirical Evidence and **Theoretical Basis**	This standard contributes to scientific rigor and transparency. A major strength of registries is their ability to be modified or adapted to meet changing needs. For example, a registry designed to study the natural history of a disease may be modified to include a newly launched product. Registries designed to study effectiveness may be expanded to recruit additional patients from a subgroup of interest. When these modifications occur, they should be clearly documented and justified in a revised study protocol, so that a complete, accurate protocol exists for the study. The protocol should provide enough detail that another investigator could potentially replicate the study to confirm the results. The guidance documents that include this standard use a theoretical basis to support the standard. Empirical evidence is not cited.
Degree of Implementation Issues	There is broad support for this standard, and few barriers to implementation exist.
Other Considerations	While this is considered a good practice for clinical research generally, it is particularly important for patient registries because of the likelihood of protocol modifications. Patient registries, particularly those that are designed to follow patients for many years, may modify their protocol multiple times, making clear documentation essential.

Standard 11

Name of Standard	**Collect data consistently.**
Description of Standard	Provide clear, operational definitions of data elements. Create and distribute standard instructions to data collectors. Use standardized data element definitions and/or data dictionaries whenever possible.
Current Practice and Examples	Registries that collect data at multiple sites, rather than at a single center, are more likely to develop data element definitions and standards instructions for data collectors. Registries in similar disease areas often collect similar data differently, which makes comparing and combining data

	more difficult. Examples • The British Society for Rheumatology Biologics Register (BSRBR) was designed to monitor the long-term safety of new biologic treatments for severe rheumatoid arthritis and other rheumatic conditions. The registry collaborates with similar registries in other European countries. To facilitate collaboration, the registries have agreed on several fundamental data collection issues, including: "the definition of time windows for the attribution of serious adverse events to specific drugs; 'events of interest' which require additional and event specific queries; and The Medical Dictionary for Regulatory Activities (MedDRA) as preferred dictionary for the coding of adverse events."[45] • The Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) was designed to collect information on the health status outcomes of patients for one year after an acute myocardial infarction, with the goal of identifying determinants of outcomes to support improvements in myocardial infarction care. When developing the registry, researchers used standard definitions whenever possible to allow the data to be compared to other studies. In particular, the registry "used the American College of Cardiology Data Standards for Acute Coronary Syndromes for data definitions of any overlapping fields."[33]
Published Guidance	The AHRQ Registries Guide supports this standard.[1]
Key Considerations for Methodology Committee (relevant points bolded) Contribution to Patient Centeredness **Contribution to Scientific Rigor** **Contribution to Transparency** Empirical Evidence and **Theoretical Basis**	This standard contributes to scientific rigor and transparency. Data elements must be clearly defined in operational terms and data collectors must follow the same instructions in order for data to be collected consistently across participating sites over the life of the registry. Consistent collection of data reduces the likelihood of misclassification or measurement bias and improves data quality, both of which are important for scientific rigor. Clear documentation of data definitions and instructions for data collectors support transparency. The use of standardized data dictionaries, when possible, makes it more likely that the registry data can be linked to or compared with other data sources. The guidance documents that include this standard use a theoretical basis to support the standard. Empirical evidence is not cited.
Degree of Implementation Issues	Standardized data dictionaries are not available for all purposes. When creating a new registry, researchers should review published literature to identify existing, widely used definitions before drafting new definitions.
Other Considerations	None.

Standard 12

Name of Standard	**Enroll and follow patients systematically.**
Description of Standard	Enroll patients systematically and follow them in as unbiased a manner as possible, using similar procedures at all participating sites. Describe how patients and providers were recruited into the study to allow the impact of selection bias to be clearly understood and any efforts employed to confirm the quality of adherence to agreed-on enrollment practices
Current Practice and Examples	Registries use a variety of approaches to patient enrollment, ranging from enrollment of all eligible patients to enrollment of consecutive eligible patients up to a target number to the use of sampling frameworks. Registries may document enrollment procedures in training materials, through recruitment logs, and in publications of study methods and/or findings. <u>Example</u> • The Vascular Study Group of Northern New England (VSGNNE) registry is designed to collect data to support improvements in the quality, safety, effectiveness, and cost of caring for patients with vascular disease. The registry collects data at the time of hospitalization and during a follow-up visit at the surgeon's office. "All patients receiving one of the procedures of interest at a participating hospital are eligible for enrollment in the registry. In considering the areas of greatest risk in evaluating the quality of this registry, the registry developers determined that incomplete enrollment of eligible patients was one major potential area for bias. It was determined that an audit of included versus eligible patients could reasonably address whether this was a significant issue. … The audit found that approximately 7 percent of eligible patients had not been enrolled in the registry. Because of concerns that the missing patients may have had different outcomes than the patients who had been enrolled in the registry, the registry team asked participating hospitals to complete registry forms for all missing patients. This effort increased the percentage of eligible patients enrolled in the registry to over 99 percent. The team also compared the discharge status of the missing patients to the enrolled patients and found no significant differences in outcomes; the team concluded that the patients had been missed at random and that there were no systematic enrollment issues. Discussions with the hospitals identified the reasons for not enrolling patients as confusion around eligibility requirements, training issues, and questions about informed consent requirements."[46]
Published Guidance	Guidance documents on observational study methods that describe enrollment and follow-up activities support this standard.[1,47,48]
Key Considerations for Methodology Committee	This standard contributes to patient centeredness, scientific rigor, and transparency. Two major strengths of registries for patient-centered

(relevant points bolded) **Contribution to Patient Centeredness** **Contribution to Scientific Rigor** **Contribution to Transparency** Empirical Evidence and **Theoretical Basis**	outcomes research are their ability to collect data on a broad, representative patient population and their ability to collect long-term follow-up data on these patients. To obtain a representative patient population, which is critical for patient centeredness, patients must be enrolled systematically, using similar procedures at all participating sites. 'Systematically' can refer to any consistent approach, such as enrolling all eligible patients or using a sampling frame. Patients also should be followed in a consistent way. Using systematic procedures for enrollment and follow-up improves scientific rigor by reducing the likelihood of meaningful differences between those who are eligible and enrolled and those who are eligible but not enrolled, and between those who complete the study and those who are lost to follow-up. Documentation of enrollment and follow-up procedures improves transparency by allowing the potential for selection bias, which may influence interpretation of the study results, to be assessed. The guidance documents that include this standard use a theoretical basis to support the standard. Empirical evidence is not cited.
Degree of Implementation Issues	Registries may need to adapt enrollment or follow-up strategies if recruitment goals or follow-up goals are not being met. Changes to the enrollment or follow-up procedures should be clearly documented and justified. Verifying compliance with agreed-upon enrollment strategies can be difficult.
Other Considerations	The issue of selection bias is particularly important for registries intended to study effectiveness or support quality improvement activities.

Standard 13

Name of Standard	**Monitor and minimize loss to follow-up.**
Description of Standard	Monitor loss to follow-up to ensure that follow-up is sufficiently complete for the main objective. Devote reasonable efforts to minimizing loss to follow-up. Describe the impact of actual loss to follow-up on the study results, including possible biases resulting from differential loss to follow-up.
Current Practice and Examples	The extent of monitoring loss to follow-up and the efforts devoted to minimizing loss to follow-up vary depending on the type and extent of follow-up data being collected by the registry. Registries differ widely in the type and extent of follow-up data that they collect. Some registries may only collect follow-up data at a single point (e.g., three months after a procedure), while others collect data at multiple points over several years (e.g., twice per year for five years). <u>Example</u> • The Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) was designed to collect information on the health status outcomes of patients for one year after an acute myocardial infarction, with the goal of identifying determinants of

	outcomes to support improvements in myocardial infarction care. Follow-up information was collected at 1, 6, and 12 months. The registry devoted substantial efforts to engaging participating physicians and patients in the registry to minimize loss to follow-up, and the registry met its follow-up goals. Only 9 percent of patients were lost to follow-up after 1 month,[49] and over 85 percent of participants completed the 12 month follow-up forms.[33]
Published Guidance	The AHRQ Registries Guide supports this standard.[1]
Key Considerations for Methodology Committee (relevant points bolded) Contribution to Patient Centeredness **Contribution to Scientific Rigor** Contribution to Transparency Empirical Evidence and **Theoretical Basis**	This standard contributes to scientific rigor. A major strength of a patient registry is its ability to collect long-term follow-up data on a broad, representative patient population. Monitoring loss to follow-up is important to ensure that the registry collects sufficient follow-up data to meet its objective(s). When monitoring detects an issue with follow-up rates, the registry should devote reasonable efforts to reducing loss to follow-up. In particular, it is critical for the registry to address issues that affect the representativeness of the patient population (e.g., loss to follow-up that appears to be disproportionately high in a specific patient subgroup). The guidance documents that include this standard use a theoretical basis to support the standard. Empirical evidence is not cited.
Degree of Implementation Issues	Actual loss to follow-up should be compared to the expected loss to follow-up described at the start of the study. Expected loss to follow-up rates vary widely by the type of registry and the length and nature of the follow-up data collection. It is not possible to recommend a single standard for expected follow-up rates.
Other Considerations	Unexpectedly high loss to follow-up may require changes to the study protocol or to study procedures.

Standard 14

Name of Standard	**Use appropriate statistical techniques to address confounding.**
Description of Standard	For registries that are intended to evaluate the effectiveness or safety of interventions, use appropriate statistical techniques to address confounding.
Current Practice and Examples	Registries use a variety of statistical techniques, including propensity scores and instrumental variables, to address confounding. <u>Example</u> • The British Society for Rheumatology Biologics Register (BSRBR) was designed to monitor the long-term safety of new biologic treatments for severe rheumatoid arthritis and other rheumatic conditions. In discussing the analysis plans, the researchers noted:

	"The greatest challenge lies in the adequate statistical analysis of the observational data. Several methods controlling for confounding by indication have been applied during the past decade. Propensity score risk adjustment and propensity-based matching are the most widely used methods. The propensity score reflects the probability of receiving a specific treatment based on prognostically relevant baseline data. Patients treated with biologicals and controls are stratified according to their propensity score value. Within propensity score strata, the covariates in biologicals and control patients are equally distributed. Propensity-based matching means that the propensity score is used to select patients from the control group who are similar with respect to their propensity scores to the biological patients. The problem here is that atypical patients are chosen from the biologicals and the control group due to the unequal distributions among cases and controls. These patients may therefore no longer represent the patients in each respective group."[45] • The OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry was designed to improve quality of care and promote evidence-based therapies in heart failure. The registry published results describing the characteristics, treatments, and outcomes of patients with preserved and reduced systolic function heart failure. In describing the analyses, the authors note: "Propensity score analysis was used to account for medication selection bias when looking at the association between the medication and outcome. The variables selected for the score were applied to a logistic regression model with the probability of receiving the medication generated as the score."[50] • The Avian/Pandemic Flu Registry was designed to study the diagnosis, treatment, and outcomes of human cases of the highly pathogenic avian influenza (HPAI) H5N1 virus. The registry published a report on the effectiveness of antiviral treatment for human influenza A(H5N1) infections. In the report, the authors describe the use of a propensity score to address potential confounding: "A propensity score model was developed as a summary measure of factors associated with oseltamivir treatment, as described above in the section on statistical analysis. Variables retained in the final propensity score model included age, country (Vietnam), direct exposure to live poultry, indirect exposure to poultry, exposure to a case of avian influenza in the home, a history of respiratory compromise, symptoms of unexplained respiratory disease, rhinorrhea, sore throat, fatigue, and myalgia at onset, presentation at an emergency room for treatment, and presentation at a rural health center for treatment. The *c* statistic for the final propensity score model was 0.85, indicating that the model is highly predictive of treatment with oseltamivir. The

	estimated propensity score was then used as a covariate in a multivariate analysis to adjust for potential confounding by factors associated with treatment."[51]
Published Guidance	Guidance documents on observational study methods support this standard.[1,23,25,28,31,32]
Key Considerations for Methodology Committee (relevant points bolded) Contribution to Patient Centeredness **Contribution to Scientific Rigor** **Contribution to Transparency** Empirical Evidence and **Theoretical Basis**	This standard contributes to scientific rigor and transparency. Confounding is a major concern for observational studies intended to evaluate the effectiveness or safety of interventions. Appropriate techniques to address confounding should be used. Some statistical techniques, such as propensity scores, are only capable of addressing measured confounding. Registries should identify potential confounders during the planning phase and collect sufficient data on these potential confounders to facilitate the use of appropriate statistical techniques during the analysis phase. Other techniques, such as instrumental variable approaches, may address unmeasured confounding; however, the large sample sizes required for these techniques may not be achievable in some registry-based studies, and it may not be possible to identify a suitable instrument for some studies. The rationale for using selected techniques, any assumptions made, and the strengths and limitations of the techniques should be described in reports of the study findings to allow for informed interpretation of the results. The guidance documents that include this standard use a theoretical basis to support the standard. Empirical evidence is not cited.
Degree of Implementation Issues	Statistical techniques to address confounding are evolving rapidly, and it is not possible to recommend specific approaches at this time. Additional methodological work is needed in this area.
Other Considerations	None.

Standard 15

Name of Standard	**Use sensitivity analyses to determine the impact of key assumptions.**
Description of Standard	For registries that are intended to evaluate the effectiveness or safety of interventions, use sensitivity analyses to determine the impact of key assumptions, such as exposure and outcome definitions, on the research questions.
Current Practice and Examples	Sensitivity analyses are commonly used to assess the impact of various factors, such as variations in definition of exposure or outcomes, impact of missing data, or unmeasured confounding, on the key research aims. <u>Examples</u> • A study compared the effectiveness of angiotensin receptor II blockers (ARBs) with that of angiotensin-converting enzyme inhibitors (ACEIs) in elderly hypertensive patients in whom ACEI/ARB therapy had been initiated after hospitalization for coronary artery disease (CAD), heart failure (HF), or stroke. The

	study used administrative data linked to registry data. In discussing their analyses, the authors noted, "Because the guidelines for treatment of HF recommend ACEI as the first-line treatment for symptomatic or asymptomatic systolic dysfunction, patients in the ARB group may be less likely to have systolic dysfunction as compared to those in the ACEI group. It is also likely that ARBs are more frequently used for patients with HF in which ejection fraction (EF) is preserved; there were a few trials that tested the efficacy of an ARB in patients with preserved EF and found a trend toward reduction in the rates of hospitalization for HF and CV [cardiovascular]-related death. It is also suggested that the risk of SCD [sudden cardiac death] is higher in patients who have HF along with low EF. Altogether, these factors could potentially have contributed to the apparent protective effect of ARBs on the SCD outcome. We therefore conducted sensitivity analyses to assess the impact of unmeasured EF on SCD. We estimated that low EF (<45%) in patients with HF was associated with a ~2.5 times higher risk for SCD as compared to a higher EF (≥45%). Given that the overall prevalence of low EF in HF patients was ~50%, we assumed that the prevalence of low EF in the ACEI group would be ~60%. We then varied the estimated prevalence levels of low EF in the ACEI and ARB groups to arrive at a quantitative estimation of the corrected association between SCD and ARBs vs. ACEIs."[52] • The Avian/Pandemic Flu Registry was designed to study the diagnosis, treatment, and outcomes of human cases of the highly pathogenic avian influenza (HPAI) H5N1 virus. The registry published a report on the effectiveness of antiviral treatment for human influenza A(H5N1) infections. In the report, the authors describe the use of a sensitivity analysis: "We examined the sensitivity of the findings to variations in country-specific mortality and to secular trends. Comparing the countries with high and low mortality rates, ≥ 50 cases, and sustained outbreaks lasting for 13 years, the relative risk of survival from oseltamivir treatment within 6 days of symptom onset was 1.75 (95% CI, 1.13–2.72) in the country with low mortality rate and 3.45 (95% CI, 1.2–10.1) in the country with high mortality rate."[51]
Published Guidance	Guidance documents on observational study methods support this standard.[1,22,23,25,28,31]
Key Considerations for Methodology Committee (relevant points bolded) Contribution to Patient Centeredness **Contribution to Scientific Rigor**	This standard contributes to scientific rigor and transparency. Sensitivity analyses may be used to assess the sensitivity of study findings to changes in exposure and outcome definitions and to other key assumptions made in implementing the study. Confounding is a major concern for observational studies intended to evaluate the effectiveness or safety of interventions. Sensitivity analyses may also use informed assumptions to quantify the effect of a potential unmeasured confounder on the study results. While sensitivity analyses do not adjust for confounders, they do provide information that can be used to assess the sensitivity of the study results to potential unmeasured confounding. The results of sensitivity analyses

Contribution to Transparency Empirical Evidence and **Theoretical Basis**	should be reported with the study findings to allow for informed interpretation of the results. The guidance documents that include this standard use a theoretical basis to support the standard. Empirical evidence is not cited.
Degree of Implementation Issues	Multiple techniques for sensitivity analyses exist, each with their own strengths and limitations. Researchers should understand the assumptions of each approach and select the most appropriate technique for the specific study. The rationale for the selected approach should be documented.
Other Considerations	None.

Standard 16

Name of Standard	**Assess and report the extent of missing data.**
Description of Standard	For primary and secondary data collection, assess and report the extent of missing data at key points of follow-up for data elements that are critical to addressing the primary study questions.
Current Practice and Examples	The extent and type of missing data varies widely among different registries. <u>Examples</u> • The National LymphoCare Study is a registry designed to study treatment regimens and long-term outcomes for patients with follicular lymphoma. The registry published the results of analyses describing the patient population and treatment patterns. When describing the data, the authors note, "As shown in Figure 2, 2,234 (82%) of 2,728 patients had calculable Follicular Lymphoma International Prognostic Index (FLIPI) scores based on initial investigator work-up. Two thousand fifty one of 2,728 had data for all FLIPI components. FLIPI was calculable for an additional 183 patients because missing data would not change the FLIPI category." Figure 2 used a flow chart to depict the missing elements in FLIPI scores for the entire cohort.[53] • The Avian/Pandemic Flu Registry was designed to study the diagnosis, treatment, and outcomes of human cases of the highly pathogenic avian influenza (HPAI) H5N1 virus. The registry published a report on the effectiveness of antiviral treatment for human influenza A(H5N1) infections. In the report, the authors describe the handling of missing data: "Because missing data are not a rarity in observational studies derived from existing records, we chose to impute missing dates for Cox proportional hazards analyses, blinded to treatment status of patients. Patients reported as alive at last contact were assumed to have lived ≥30 days after presentation for medical care. Two of 150 patients reported as deceased did not have a recorded date of death; for these 2

	patients the mean time to death of 8 days was imputed. For 148 patients with information about date of symptom onset but not date of presentation for treatment, the date of presentation for treatment was imputed as 2 days after symptom onset for all patients, on the basis of the overall mean observed time from symptom onset to presentation for treatment. For one patient who survived <1 day, the survival time was estimated to be 0.5 days for analysis. No other missing data were imputed." The authors present a flow chart describing the availability of data on medication and dates of presentation for medical care.[51]
Published Guidance	Guidance documents on observational study methods support this standard.[1,23,31]
Key Considerations for Methodology Committee (relevant points bolded) Contribution to Patient Centeredness Contribution to Scientific Rigor **Contribution to Transparency** Empirical Evidence and **Theoretical Basis**	This standard contributes to transparency. Patient registries are by definition observational studies. Missing data may occur for several reasons, such as patients missing a scheduled visit or not completing a patient-reported outcome measure at a visit. Patients may also drop out of the study. Missing data may reduce the number of patients eligible to be included in the analysis, which may in turn reduce the statistical power of the study. In addition, missing data can introduce bias into the study if the data are not missing at random (e.g., patients with poor outcomes are more likely to drop out than those with positive outcomes). Therefore, it is important to assess and report on the extent of missing data, particularly at key points of follow-up for data elements that are critical to addressing the primary study questions. Reporting on missing data improves transparency by allowing reviewers of the study results to consider the missing data when interpreting the study results. The guidance documents that include this standard use a theoretical basis to support the standard. Empirical evidence is not cited.
Degree of Implementation Issues	The amount of missing data that is acceptable and expected within a registry varies widely among different types of registries. A registry designed to study effectiveness with short-term follow-up may expect far less missing data than an open-ended registry designed to study the natural history of a disease. It is not possible to recommend a single standard for expected rates of missing data.
Other Considerations	Approaches to handling missing data are evolving, and it is not possible to make recommendations for specific analytic approaches at this time. Additional methodological work is needed in this area.

Standard 17

Name of Standard	**Provide sufficient information in reports of the registry findings to allow for assessments of the study's internal and external validity.**
Description of Standard	Describe the following elements in the registry report, if applicable: methods, including selection of study participants, data collection activities, settings where data were collected, analytic techniques, and approaches to handling missing data; data quality activities, including any issues that may

	have affected the quality or integrity of the data; comparability of the registry participants to the target population and any efforts to minimize selection bias; extent of missing data for key exposures, risk factors, and outcomes and impact of missing data on key study questions; length of follow-up period and impact of loss to follow-up on key study questions; and the role and impact of potential confounders.
Current Practice and Examples	Registries that publish their findings in the peer-reviewed literature often report sufficient information to assess the internal and external validity of the study. <u>Examples</u> • The National LymphoCare Study is a registry designed to study treatment regimens and long-term outcomes for patients with follicular lymphoma. The registry published the results of analyses describing the patient population and treatment patterns. The report describes the study participants, data collection activities, settings where data were collected, analytic techniques, missing data and its impact on key study questions, comparability of study participants to the target population, efforts to minimize selection bias, length of follow-up data, and the role and impact of potential confounders.[52] • The Avian/Pandemic Flu Registry was designed to study the diagnosis, treatment, and outcomes of human cases of the highly pathogenic avian influenza (HPAI) H5N1 virus. The registry published a report on the effectiveness of antiviral treatment for human influenza A(H5N1) infections. The report describes the study participants, data collection activities, settings where data were collected, analytic techniques, missing data and its impact on key study questions, data quality activities, length of follow-up, and the role and impact of potential confounders. Comparability of study participants to the target population and efforts to minimize selection bias were not relevant for this study.[51]
Published Guidance	Guidance documents on reporting observational studies support this standard.[1,25,54-56]
Key Considerations for Methodology Committee (relevant points bolded) Contribution to Patient Centeredness Contribution to Scientific Rigor **Contribution to Transparency**	This standard contributes to transparency. Reviewers of findings from registry studies need sufficient information to assess the internal and external validity of the study. Understanding the internal and external validity of the study supports an informed interpretation of the study findings. It is particularly important for reviewers of patient-centered outcomes research to understand the generalizability of the registry population and the robustness of the long-term follow-up data. The guidance documents that include this standard use a theoretical basis to support the standard. Empirical evidence is not cited.

Empirical Evidence and **Theoretical Basis**	
Degree of Implementation Issues	Registries are designed to fill many purposes, and it may not be meaningful for all registries to report on all elements noted in this standard. For example, a registry designed to study the natural history of a rare disease may seek to enroll all known patients with the disease. It may not be possible to describe the comparability of the target population with the actual population in this case. Further, restrictions on length of journal articles and preferences of individual journal editors may influence the extent of information included in a specific article.
Other Considerations	Reporting standards for observational studies (e.g., STROBE) focus on many factors that may be relevant for observational studies. However, when registries are used for patient-centered outcomes research, generalizability and long-term follow-up data are critical factors. The standard included here focuses on the factors most important for reporting the results of registries designed for patient-centered outcomes research.

Appendix 3: Description of Guidance Documents Included in Main Findings

Table 1: Description of Guidance Documents Included in Main Findings

Guideline	Organization or Authors	Year	Program	Country or Region	Guideline subjected to independent external review?	Research Design	Description
Comparative Effectiveness Research: Challenges for Medical Journals	Sox HC, Helfand M, Grimshaw J, et al	2010	None	International	No	Comparative effectiveness research (CER)	Guidance for the conduct of CER.
The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials	Moher D, Schulz KF, Altman D for the CONSORT group	2010	None	International	Yes	Parallel group randomized trials	Provides a checklist for the reporting of parallel group randomized trials.
Draft Guidance for Industry and FDA Staff: Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data sets	U.S. Food and Drug Administration (FDA)	2011	None	USA	Yes	Pharmaco-epidemiologic safety studies using electronic healthcare data sets	Guidance for industry when submitting pharmacoepidemiologic safety study protocols and final reports to FDA. Also provides guidance for FDA to use when conducting these studies.

Guideline	Organization or Authors	Year	Program	Country or Region	Guideline subjected to independent external review?	Research Design	Description
Good research practices for comparative effectiveness research: approaches to mitigate bias and confounding in the design of nonrandomized studies of treatment effects using secondary sources	International Society for Pharmaco-economics and Outcomes Research (ISPOR)	2009	The ISPOR Good Research Practices for Retrospective Database Analysis Task Force	International	Not stated	CER; nonrandomized retrospective database analysis	Guidance for minimizing bias and confounding the design of retrospective database analyses for CER.
Good Research Practices for Comparative Effectiveness Research: Defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources	International Society for Pharmaco-economics and Outcomes Research (ISPOR)	2009	The ISPOR Good Research Practices for Retrospective Database Analysis Task Force	International	Not stated	CER; nonrandomized retrospective database analysis	Guidance for the design and reporting of retrospective database analyses for CER.
GRACE Principles: Recognizing high-quality observational studies of comparative effectiveness	Dreyer N, Schneeweiss S, McNeil B, et al	2010	Good Research for Comparative Effectiveness (GRACE) Initiative	USA	Yes	Nonrandomized, observational CER studies	Provides three questions or principles to consider when evaluating nonrandomized CER studies.
Guidance for Industry: E6 Good Clinical Practice: consolidated guidance	U.S. Food and Drug Administration (FDA)	1996	Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research	International	Not stated	Clinical trials	Guidance for industry generating clinical trial data that are intended to be submitted to regulatory authorities.

Guideline	Organization or Authors	Year	Program	Country or Region	Guideline subjected to independent external review?	Research Design	Description
Guidance for Industry: Establishing pregnancy exposure registries	U.S. Food and Drug Administration (FDA)	2002	Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research	USA	Not stated	Registries measuring outcomes in pregnant women exposed to medical products	Guidance for industry on the design, conduct, and regulatory reporting requirements for registries measuring outcomes in pregnant women exposed to specific medical products.
Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims	U.S. Food and Drug Administration (FDA)	2009	Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH)	USA	Not stated	Medical product clinical trials that use patient-reported outcome (PRO) tools to collect data to measure treatment benefit or risk.	Describes how the FDA evaluates PRO instruments used in clinical trials to support labeling claims and provides guidance on the design of clinical trials that plan to use PROs for this purpose.
Guide on Methodological Standards in Pharmaco-epidemiology	European Network of Centres for Pharmaco-epidemiology and Pharmaco-vigilance (ENCePP)	2011	None	Europe	Yes	Pharmaco-epidemiologic and pharmacovigilance studies.	Reviews existing methodological guidance for pharmacoepidemiologic research.

Guideline	Organization or Authors	Year	Program	Country or Region	Guideline subjected to independent external review?	Research Design	Description
Guideline for Good Clinical Practice	European Medicines Agency	2002	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	International	Not stated	Clinical trials	Guidance for the design and conduct of clinical trials that involve human subjects.
Guidelines for Economic Evaluation of Pharmaceuticals: Canada	Canadian Coordinating Office for Health Technology Assessment	1997	None	Canada	Not stated	Pharmacoeconomic studies	Guidance on the design, conduct, analysis, and reporting of pharmacoeconomic studies.
Guidelines for Good Pharmacoepidemiology Practice	International Society for Pharmaco-epidemiology (ISPE)	2008	None	International	Not stated	Pharmaco-epidemiologic studies, including feasibility studies, validation studies, descriptive studies, and etiologic investigations	Guidance on protocol development, study conduct, responsibilities, personnel, facilities, resource commitment, contractors, adverse event reporting, archiving and communication.

Guideline	Organization or Authors	Year	Program	Country or Region	Guideline subjected to independent external review?	Research Design	Description
Observational studies of cause-effect relationships: an analysis of methodologic problems as illustrated by the conflicting data for the role of oral contraceptives in the etiology of rheumatoid arthritis	Esdaile JM, Horwitz RI	1986	None	International	Not stated	Case-control and prospective cohort studies	Provides six criteria for evaluating the validity of the study design of case-control and prospective cohort studies.
Outcomes Research in the Development and Evaluation of Practice Guidelines	Pilote L, Tager IB	2002	None	International	Not stated	Outcomes research to evaluate practice guidelines	Proposes methodological model for outcomes research designed to evaluate clinical practice guidelines.
Patient Registries of Acute Coronary Syndrome : Assessing or biasing the clinical real world data?	Ferreira-González I, Marsal JR, Mitjavila F, et al	2009	None	Spain	Not stated	Systematic review	Assesses selection bias in acute coronary syndrome registry and explores ways of conducting and reporting patient registries of acute coronary syndrome to minimize this bias.
Randomized Clinical Trials and Observational Studies: Guidelines for assessing respective strengths and limitations	Hannan EL	2008	None	USA	Not stated	Randomized clinical trials and observational studies	Proposes criteria for evaluating whether an RCT or observational study is appropriate for a given problem, and how to assess the validity of RCTs and observational studies that yield different conclusions.

Guideline	Organization or Authors	Year	Program	Country or Region	Guideline subjected to independent external review?	Research Design	Description
Registries for Evaluating Patient Outcomes: A User's Guide: 2nd edition	Agency for Healthcare Research and Quality (AHRQ)	2010	Developing Evidence to Inform Decisions about Effectiveness (DEcIDE)	USA	Yes	Registries for evaluating patient outcomes	Addresses practical issues in creating, operating, and evaluating patient registries.
The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement	von Elm E, Altman DG, Egger M, et al.	2007	STROBE Initiative	International	Yes	Case-control, cohort, and cross sectional studies	Provides a checklist to be used when reporting case-control, cohort, or cross sectional study results.
"Ten Commandments" for Conducting Comparative Effectiveness Research Using "Real-World Data"	Willke RJ, Mullins CD	2011	None	USA	No	CER	Proposed rules for the conduct of CER using 'real-world data.'

Appendix 4: Description of Guidance Documents Not Included in Main Findings

Table 2: Description of Guidance Documents Not Included in Main Findings

Guideline	Organization or Authors	Year	Program	Country or Region	Guideline subjected to independent external review?	Research Design	Description
American College of Epidemiology Ethics Guidelines	American College of Epidemiology	2000	None	USA	Not stated	Epidemiologic studies	The guidelines include four parts: Part 1 describes core values, duties, and virtues in epidemiology and provides concise definitions of these concepts. Part 2 provides general statements of the obligations that epidemiologists have to various parties. Part 3 provides more detailed discussion of these guidelines. Part 4 provides a summary, outlines some remaining issues, and draws some conclusions. Overall, the guidelines identify ethical rules and professional norms in the field that should therefore be viewed as normative.
Analysis of Observational Studies in the Presence of Treatment Selection Bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods	Stukel TA, Fisher ES, Wennberg DE, et al	2007	None	USA/ Canada	Yes	Observational studies	The article compares four different analytic methods for removing the effects of selection bias in observational studies.

Guideline	Organization or Authors	Year	Program	Country or Region	Guideline subjected to independent external review?	Research Design	Description
Comparative Effectiveness of Prostate Cancer Treatments: evaluating statistical adjustments for confounding in observational data	Hadley J, Yabroff KR, Barrett MJ, et al	2010	None	N/A	Not stated	Using observational data for comparative effectiveness research	The focus of this article is methods to address confounding in treatment and survival of patients with early-stage prostate cancer in observational data, and comparing the study's findings with those from a benchmark randomized clinical trial.
Confounding Control in Healthcare Database Research: challenges and potential approaches	Brookhart MA, Sturmer T, Glynn RJ, et al	2010	None	USA	No	Studies of medication use and outcomes; epidemiological studies that use healthcare databases as their data sources	This article describes potential sources of confounding and issues with confounding control in two study designs. It also reviews current theoretical and practical approaches to controlling confounding.
Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health	Andrews EB	1999	International Society for Pharmaco-epidemiology Ad Hoc Committee on Data Privacy in the US and Canada; Ad Hoc Committee on Data Privacy in the European Union; Public Policy and Ethics Committee	International	Not stated	Record-linkage studies, case-control studies, and prospective cohort studies	The article provides a review of pharmacoepidemiology, the three major methods of conducting pharmacoepidemiologic research (record linkage, case-control, and prospective cohort studies), and specific recommendations to protect data privacy and confidentiality for these types of studies.
EULAR points to consider when establishing, analysing and reporting safety data of biologics	Dixon WG, Carmona L, Finckh A, et al	2010	European League Against Rheumatism (EULAR)	Europe	Yes	Patient registers	The emphasis in this article is on expanding on generic guidelines to provide recommendations that are specific to biologics registries.

Guideline	Organization or Authors	Year	Program	Country or Region	Guideline subjected to independent external review?	Research Design	Description
registers in rheumatology							
Good Research Practice	Medical Research Council	2005	None	UK	Not stated	All research, clinical and non-clinical	This document provides guidelines for conducting research funded by the MRC. It covers the topics of planning and conducting the research, recording data, and reporting and disseminating results.
Instrumental Variable Methods in Comparative Safety and Effectiveness Research	Brookhart MA, Rassen JA, Schneeweiss S	2010	None	USA	Not stated	Comparative safety and effectiveness research	The article provides a summary of the use of instrumental variable (IV) methods for controlling confounding in comparative safety and effectiveness research. The authors then provide seven proposed standards for reporting on studies that use IV methods.
International Guidelines for Ethical Review of Epidemiological Studies	Council for International Organizations of Medical Sciences	1991	Council for International Organizations of Medical Sciences	Internati onal	Not stated	Epidemiological studies (observational and experimental)	The guidelines go into moderate detail about general ethical principles such as informed consent, maximizing benefit and minimizing harm, confidentiality, conflict of interest, and ethical review procedures.
Methods to Increase Response to Postal and Electronic Questionnaires (Review)	Edwards PJ, Roberts I, Clarke MJ, et al	2009	Cochrane Methodology Review Group	Internati onal	Not stated	Health research that uses postal or electronic questionnaires to elicit responses from research participants	This article describes a systematic review of methods that researchers can use to increase response to postal and electronic questionnaires.
Performance of Disease	Arbogast PG,	2011	None	Not	Not stated	Cohort studies	This paper is not a guideline, but

Guideline	Organization or Authors	Year	Program	Country or Region	Guideline subjected to independent external review?	Research Design	Description
Risk Scores, Propensity Scores, and Traditional Multivariable Outcome Regression in the Presence of Multiple Confounders	Ray WA			stated			presents simulation studies comparing the unexposed-only disease risk score (DRS), full-cohort DRS, and propensity score analyses with traditional regression models that include all of the individual covariates used to construct these summary scores.
Updated Guidelines for Evaluating Public Health Surveillance Systems: recommendations from the Guidelines Working Group	Centers for Disease Control and Prevention	2001	Guidelines Working Group	USA	No	Public health surveillance systems	This report presents guidelines for evaluating whether a public health surveillance system is accomplishing its purpose in terms of providing needed information to measure a public health problem or evaluate the effectiveness of an intervention.
Using Inverse Probability-Weighted Estimators in Comparative Effectiveness Analyses with Observational Databases	Curtis LH, Hammill BG, Eisenstein EL, et al	2007	None	USA	Not stated	Comparative effectiveness analyses on observational databases	This article describes the use of inverse probability-weighted estimators to adjust for confounding when conducting comparative effectiveness research with observational databases.

Appendix 5: Selected Additional Characteristics of Guidance Statements

Table 3: Selected Additional Characteristics of Guidance Statements

Guideline	The purpose of the work is to define methodological standards for PCOR	The applications of the standards to PCOR is clear	The standards were developed by a professional group	Patient's views and preferences were sought	Stakeholders were involved in the development of standards	A systematic process was used to generate recommendations	Details of the systematic process used to generate recommendations are provided	There is an explicit link between the rationale for and the recommended standards (evidence)	Guideline subjected to independent external review?	The recommendations are specific and unambiguous	Key recommendations are clear	The standards are editorially independent from the funding body	Conflicts of interest have been recorded
Comparative Effectiveness Research: Challenges for Medical Journals	Yes	Yes	No	No	No	No	N/A	No	No	Yes	Yes	Yes	Yes (conflicts reported)
The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials	No	Yes	Yes	Not stated	Yes	No	N/A	Yes	Yes	Yes	Yes	Yes	Not recorded
Draft Guidance for Industry and FDA Staff: Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data sets	No	Yes	Yes	No	Yes	Not stated	N/A	Yes	Not stated	Yes	Yes	Not stated	Not recorded

Guideline	The purpose of the work is to define methodological standards for PCOR	The applications of the standards to PCOR is clear	The standards were developed by a professional group	Patient's views and preferences were sought	Stakeholders were involved in the development of standards	A systematic process was used to generate recommendations	Details of the systematic process used to generate recommendations are provided	There is an explicit link between the rationale for and the recommended standards (evidence)	Guideline subjected to independent external review?	The recommendations are specific and unambiguous	Key recommendations are clear	The standards are editorially independent from the funding body	Conflicts of interest have been recorded
Good Research Practices for Comparative Effectiveness Research: Approaches to mitigate bias and confounding in the design of nonrandomized studies of treatment effects using secondary sources	Yes	Yes	Yes	No	Yes	Not stated	N/A	Yes	Yes	Yes	Yes	Yes	Not recorded
Good Research Practices for Comparative Effectiveness Research: Defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources	Yes	Yes	Yes	No	Yes	Not stated	N/A	Yes	Yes	Yes	Yes	Yes	Not recorded
GRACE Principles: Recognizing high-quality observational studies of comparative effectiveness	Yes	Yes	Yes	Not stated	Yes	Not stated	N/A	Some (Article cites relevant methodology papers supporting rationale for the latter two principles, but not for the first.)	Yes	Yes	Yes	Yes	Yes (conflicts reported)

Guideline	The purpose of the work is to define methodological standards for PCOR	The applications of the standards to PCOR is clear	The standards were developed by a professional group	Patient's views and preferences were sought	Stakeholders were involved in the development of standards	A systematic process was used to generate recommendations	Details of the systematic process used to generate recommendations are provided	There is an explicit link between the rationale for and the recommended standards (evidence)	Guideline subjected to independent external review?	The recommendations are specific and unambiguous	Key recommendations are clear	The standards are editorially independent from the funding body	Conflicts of interest have been recorded
Guidance for Industry: E6 Good Clinical Practice: consolidated guidance	No	Yes	Yes	Not stated	Yes	Yes	No	No	Not stated	Yes	Yes	Not stated	Not recorded
Guidance for Industry: Establishing pregnancy exposure registries	No	Yes	Yes	Not stated	Not stated	Not stated	N/A	No	Not stated	No	No	Not stated	Not recorded
Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims	No	Yes	Yes	Not stated	Not stated	Not stated	N/A	No	Not stated	No	No	Not stated	Not recorded
Guide on Methodological Standards in Pharmacoepidemiology	No	Yes	Yes	Not stated	Yes	Not stated	N/A	Yes	Yes	Yes	Yes	Not stated	Not recorded
Guideline for Good Clinical Practice	No	Yes	Yes	Not stated	Yes	Not stated	N/A	No	Not stated	Yes	Yes	Not stated	Not recorded
Guidelines for Economic Evaluation of Pharmaceuticals: Canada	No	No	Yes	Not stated	Yes	Yes	Yes	Yes	Not stated	Yes	Yes	Not stated	Not recorded

Guideline	The purpose of the work is to define methodological standards for PCOR	The applications of the standards to PCOR is clear	The standards were developed by a professional group	Patient's views and preferences were sought	Stakeholders were involved in the development of standards	A systematic process was used to generate recommendations	Details of the systematic process used to generate recommendations are provided	There is an explicit link between the rationale for and the recommended standards (evidence)	Guideline subjected to independent external review?	The recommendations are specific and unambiguous	Key recommendations are clear	The standards are editorially independent from the funding body	Conflicts of interest have been recorded
Guidelines for Good Pharmacoepidemiology Practice	No	Yes	Yes	No	Not stated	Not stated	N/A	No	Not stated	No	Yes	Not stated	Yes (none reported)
Observational studies of cause-effect relationships: an analysis of methodologic problems as illustrated by the conflicting data for the role of oral contraceptives in the etiology of rheumatoid arthritis	No	No	No	No	Not stated	Not stated	N/A	No	Not stated	Yes	Yes	Not stated	Not recorded
Outcomes Research in the Development and Evaluation of Practice Guidelines	No	Yes	No	Not stated	Not stated	Not stated	N/A	No	Not stated	Yes	No	Not stated	Yes (none reported)
Patient Registries of Acute Coronary Syndrome: Assessing or biasing the clinical real world data?	No	Yes	No	No	No	Yes	Yes	Yes	Not stated	Yes	Yes	Not stated	Yes (none reported)
Randomized Clinical Trials and Observational Studies: Guidelines for assessing respective strengths and limitations	No	Yes	No	No	No	Yes	No	Yes (Document cites relevant methodology papers.)	Not stated	Yes	Yes	Not stated	Not recorded

Guideline	The purpose of the work is to define methodological standards for PCOR	The applications of the standards to PCOR is clear	The standards were developed by a professional group	Patient's views and preferences were sought	Stakeholders were involved in the development of standards	A systematic process was used to generate recommendations	Details of the systematic process used to generate recommendations are provided	There is an explicit link between the rationale for and the recommended standards (evidence)	Guideline subjected to independent external review?	The recommendations are specific and unambiguous	Key recommendations are clear	The standards are editorially independent from the funding body	Conflicts of interest have been recorded
Registries for Evaluating Patient Outcomes: A User's Guide: 2nd edition	Yes	Yes	No	Not stated	Yes	Yes	Yes	No	Yes	Yes	No	Not stated	Not recorded
The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement	No	Yes	Yes	No	Yes	No	N/A	Yes	Yes	Yes	Yes	Yes	Yes (none reported)
"Ten Commandments" for Conducting Comparative Effectiveness Research Using "Real-World Data"	Yes	Yes	No	No	No	No	N/A	No	No	No	Yes	Not stated	Yes (conflicts reported)

References

[1] Gliklich RE, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. (Prepared by Outcome DEcIDE Center [Outcome Sciences, Inc. d/b/a Outcome] under Contract No. HHSA29020050035I TO3.) AHRQ Publication No.10-EHC049. Rockville, MD: Agency for Healthcare Research and Quality. September 2010.

[2] Dreyer NA, Garner S: Registries for robust evidence. JAMA 2009; 302(7):790-791.

[3] Dreyer NA. Tunis SR, Berger M, et al. Why observational studies should be among the tools used in comparative effectiveness research. Health Affairs 2010; 29(10): 1818-1825.

[4] Dreyer NA. Making observational studies count: shaping the future of comparative effectiveness research. Epidemiology 22(3):295-297, May 2011.

[5] Schneeweiss S, Gagne JJ, Glynn RJ, Ruhl M, Rassen JA: Assessing the comparative effectiveness of newly marketed medications: methodological challenges and implications for drug development. Clin Pharmacol & Ther 2011:90:777-790.

[6] American College of Epidemiology Ethics Guidelines. Ann Epidemiol 2000; 10(8): 487-497.

[7] Andrews EB. Data privacy, medical record confidentiality, and research in the interest of public health. Pharmacoepidemiol Drug Saf. 1999 Jul;8(4):247-60.

[8] European Medicines Agency. ICH Topic E 6 (R1) Guideline for Good Clinical Practice. Accessed November 18, 2011. http://www.emea.europa.eu/pdfs/human/ich/013595en.

[9] U.S. Food and Drug Administration. Guidance for Industry: Good Clinical Practice. 1996.

[10] U.S. Food and Drug Administration. Guidance for Industry: Establishing Pregnancy Exposure Registries. 2002. Available at: http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133332.pdf. Last accessed on 6 March 2012.

[11] Council for International Organizations of Medical Sciences. Accessed November 18, 2011. http://www.cioms.ch/publications/guidelines/1991_texts_of_guidelines.htm.

[12] Medical Research Council. Good Research Practice. 2005. Available at: http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002415. Last accessed on 7 March 2012.

[13] German RR, Lee LM, Horan JM, Milstein RL, Pertowski CA, Waller MN. Updated guidelines for evaluating public health surveillance systems: recommendations from the Guidelines Working Group. MMWR Recomm Rep. 2001 Jul 27;50(RR-13):1-35.

[14] Edwards PJ, Roberts I, Clarke MJ, Diguiseppi C, Wentz R, Kwan I, et al. Methods to increase response to postal and electronic questionnaires. Cochrane Database Syst Rev. 2009(3):MR000008.

[15] Dixon WG, Carmona L, Finckh A, et al. EULAR points to consider when establishing, analyzing and reporting safety data of biologics registers in rheumatology. Ann Rheum Dis 2010 Jun 4 [Epub].

[16] Arbogast PG, Ray WA. Performance of disease risk scores, propensity scores, and traditional multivariable outcome regression in the presence of multiple confounders. Am J Epidemiol. 2011 Sep 1;174(5):613-20.

[17] Curtis LH, Hammill BG, Eisenstein EL, Kramer JM, Anstrom KJ. Using inverse probability-weighted estimators in comparative effectiveness analyses with observational databases. Med Care. 2007 Oct;45(10 Supl 2):S103-7.

[18] Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. Pharmacoepidemiol Drug Saf. 2010 Jun;19(6):537-54.

[19] Hadley J, Yabroff KR, Barrett MJ, Penson DF, Saigal CS, Potosky AL. Comparative effectiveness of prostate cancer treatments: evaluating statistical adjustments for confounding in observational data. J Natl Cancer Inst. 2010 Dec 1;102(23):1780-93.

[20] Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias. JAMA 2007; 297:278-285.

[21] Guidelines for the economic evaluation of health technologies: Canada [3rd Edition]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.

[22] Cox E, Martin BC, Van Staa T, Garbe E, Siebert U, Johnson ML. Good research practices for comparative effectiveness research: approached to mitigate bias and confounding in the design of nonrandomized studies of treatment effects using secondary sources: The International Society for Pharmacoeconomics and Outcome Research Good Research Practices for Retrospective Analysis Task Force Report—Part II. Value Health. 2009;12:1053–1061.

[23] Dreyer NA, Schneeweiss S, McNeil BJ, Berger ML, Walker AM, Ollendorf DA, et al. GRACE principles: recognizing high-quality observational studies of comparative effectiveness. Am J Manag Care. 2010 Jun;16(6):467-71.

[24] Brookhart MA, Sturmer T, Glynn RJ, Rassen J, Schneeweiss S. Confounding control in healthcare database research: challenges and potential approaches. Med Care. 2010 Jun;48(6 Suppl):S114-20.

[25] Food and Drug Administration. Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data sets. In: US Department of Health and Human Services FaDA, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). 2011.

[26] University of Alabama at Birmingham. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). Protocol 2.3. Accessed March 13, 2012. http://www.uab.edu/ctsresearch/intermacs/Document%20Library/Protocol%20V2.3%20FINAL,%2010-30-08.doc.

[27] Guidelines for Good Pharmacoepidemiology Practice. Pharmacoepidemiol Drug Safety 2008; 17:200-8.

[28] ENCePP. Guide on Methodological Standards in Pharmacoepidemiology. 13 May 2011. Doc. Ref. EMA/95098/2010 (amended). Accessed March 13, 2012. http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE.pdf.

[29] The National Oncologic PET Registry (NOPR). Development, Design and Methods of Data Collection and Analysis. Accessed March 13, 2012. http://www.cancerpetregistry.org/pdf/NOPR%20Operations%20Manual%20Combined_02-01-11_Final.pdf.

[30] Piccini JP, Fraulo ES, Ansell JE, Fonarow GC, Gersh BJ, Go AS, Hylek EM, Kowey PR, Mahaffey KW, Thomas LE, Kong MH, Lopes RD, Mills RM, Peterson ED. Outcomes registry for better informed treatment of atrial fibrillation: rationale and design of ORBIT-AF. Am Heart J. 2011 Oct;162(4):606-612.e1.

[31] Willke RJ, Mullins CD. "Ten commandments" for conducting comparative effectiveness research using "real-world data". J Manag Care Pharm. 2011 Nov-Dec;17(9 Suppl A):S10-5.

[32] Hannan EL. Randomized clinical trials and observational studies: guidelines for assessing respective strengths and limitations. JACC Cardiovasc Interv. 2008 Jun;1(3):211-7.

[33] Leavy MB, Spertus J. Case Example 17: Understanding the needs and goals of the registry participants. In: Gliklich RE, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. (Prepared by Outcome DEcIDE Center [Outcome Sciences, Inc. d/b/a Outcome] under Contract No. HHSA29020050035I TO3.) AHRQ Publication No.10-EHC049. Rockville, MD: Agency for Healthcare Research and Quality. September 2010. 122-124.

[34] Leavy MB, Boron M. Case Example 38: Using registry data to study patterns of use and outcomes. In: Gliklich RE, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. (Prepared by Outcome DEcIDE Center [Outcome Sciences, Inc. d/b/a Outcome] under Contract No. HHSA29020050035I TO3.) AHRQ Publication No.10-EHC049. Rockville, MD: Agency for Healthcare Research and Quality. September 2010. 303-304.

[35] Esdaile JM, Horwitz RI. Observational studies of cause-effect relationships: an analysis of methodologic problems as illustrated by the conflicting data for the role of oral contraceptives in the etiology of rheumatoid arthritis. J Chronic Dis. 1986;39(10):841-52.

[36] Fox KM, Leavy MB. Case Example 18: Using validated measures to collect patient reported outcomes. In: Gliklich RE, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. (Prepared by Outcome DEcIDE Center [Outcome Sciences, Inc. d/b/a Outcome] under Contract No. HHSA29020050035I TO3.) AHRQ Publication No.10-EHC049. Rockville, MD: Agency for Healthcare Research and Quality. September 2010. 124-125.

[37] Bertoli AM, Vilá LM, Reveille JD, Alarcón GS; LUMINA study group. Systemic lupus erythaematosus in a multiethnic US cohort (LUMINA) LIII: disease expression and outcome in acute onset lupus. Ann Rheum Dis. 2008 Apr;67(4):500-4. Epub 2007 Aug 24.

[38] U.S. Food and Drug Administration. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2009. Available at: http://www.ispor.org/workpaper/FDA%20PRO%20Guidance.pdf. Last accessed on March 5 2012.

[39] National Cancer Institute. Overview of the Process for Obtaining SEER-MHOS Data. http://www.outcomes.cancer.gov/surveys/seer-mhos/obtain/. Accessed March 15, 2012.

[40] Dokholyan, RS, Muhlbaier L, et al. Regulatory and ethical considerations for linking clinical and administrative databases. Am Heart J 2009; 157(6): 971-982.

[41] Fox MJ, Leavy MB. Case Example 21: Linking a procedure-based registry with claims data to study long-term outcomes. In: Gliklich RE, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. (Prepared by Outcome DEcIDE Center [Outcome Sciences, Inc. d/b/a Outcome] under Contract No. HHSA29020050035I TO3.) AHRQ Publication No.10-EHC049. Rockville, MD: Agency for Healthcare Research and Quality. September 2010. 164-165.

[42] Clarke JT, Leavy MB. Case Example 29: Data collection challenges in rare disease registries. In: Gliklich RE, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. (Prepared by Outcome DEcIDE Center [Outcome Sciences, Inc. d/b/a Outcome] under Contract No. HHSA29020050035I TO3.) AHRQ Publication No.10-EHC049. Rockville, MD: Agency for Healthcare Research and Quality. September 2010. 247-248.

[43] University of Alabama at Birmingham. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). Protocol 2.3 Amendment 1. Accessed March 13, 2012. http://www.uab.edu/ctsresearch/intermacs/Document%20Library/Protocol%202%203%20Amendment%201%209-15-2010.pdf .

[44] Sox HC, Helfand M, Grimshaw J, Dickersin K; PLoS Medicine Editors, Tovey D, Knottnerus JA, Tugwell P. Comparative effectiveness research: challenges for medical journals. Am J Manag Care. 2010 May 1;16(5):e131-3.

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

[46] Cronewett J, Leavy MB. Case Example 32: Using audits to monitor data quality. In: Gliklich RE, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. (Prepared by Outcome DEcIDE Center [Outcome Sciences, Inc. d/b/a Outcome] under Contract No. HHSA29020050035I TO3.) AHRQ Publication No.10-EHC049. Rockville, MD: Agency for Healthcare Research and Quality. September 2010. 251-252.

[47] Ferreira-Gonzalez I, Marsal JR, Mitjavila F, Parada A, Ribera A, Cascant P, et al. Patient registries of acute coronary syndrome: assessing or biasing the clinical real world data? Circ Cardiovasc Qual Outcomes. 2009 Nov;2(6):540-7.

[48] Pilote L, Tager IB. Outcomes research in the development and evaluation of practice guidelines. BMC Health Serv Res. 2002 Mar 25;2(1):7.

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

[50] Fonarow, G. C., W. G. Stough, et al. (2007). "Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry." J Am Coll Cardiol 50(8): 768-777.

[51] Adisasmito, W., P. K. Chan, et al. (2010). "Effectiveness of antiviral treatment in human influenza A(H5N1) infections: analysis of a Global Patient Registry." J Infect Dis 202(8): 1154-1160.

[52] Setoguchi, S., W. H. Shrank, et al. (2011). "Angiotensin receptor blockers and Angiotensin-converting enzyme inhibitors: challenges in comparative effectiveness using medicare data." Clin Pharmacol Ther 89(5): 674-682.

[53] Friedberg JW, Taylor MD, Cerhan JR, et al. Follicular Lymphoma in the United States: First Report of the National LymphoCare Study. J Clin Oncol 2009;27:1202-1208.

[54] von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Ann Intern Med 2007;147(8):573-7.

[55] Berger ML, Mamdani M, Atkins D, Johnson ML. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: The ISPOR good research practices for retrospective database analysis task force report – Part 1. Value in Health 2009; 12:1044-52.

[56] Moher D, Schulz KF, Altman D for the CONSORT group. The CONSORT Statement: revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001;285:1987-91.