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Standards for Causal Inference Methods in Analyses of Data from Observational and Experimental Studies in Patient-Centered Outcomes Research

Final Technical Report

Prepared for: Patient-Centered Outcome Research Institute Methodology Committee

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March 15, 2012

I. INTRODUCTION

The demand for evidence to support a widening array of healthcare interventions continues to grow, and the Patient-Centered Outcome Research Institute (PCORI) is well positioned to guide this development of evidence. Recognizing that not all research results will be useful for comparing the effects of treatments, guidance on the proper conduct of research may improve the information that becomes available and is subsequently used to make comparisons and decide on appropriate healthcare interventions. The grand scale of this task can be made more tractable through the synthesis and application of existing standards and guidance documents, which have been promulgated by professional societies.

This report describes the development a set of minimum standards for causal inference methods for observational and experimental studies in patient-centered outcomes research (PCOR) and comparative effectiveness research (CER). A broad search was conducted to identify documents from which guidance could be drawn. From this search, eight minimum standards were developed that cover inter-related topics in causal inference. These minimum standards are intended to inform investigators, grant reviewers, and decision makers involved in generating, evaluating, or using PCOR/CER. The report also describes the rationale for identifying and selecting the standards, gives examples of their successful use, and identifies gaps where future work is needed.

II. SCOPE OF WORK

Causal inference is the primary objective of PCOR/CER when one seeks to understand whether and the extent to which a given therapy or intervention affects a particular outcome, or which among multiple interventions affects an outcome the most. There are many threats to causal inference in both randomized and observational studies.[1,2] Researchers must address these threats in order to produce the most valid results to inform patient decisions. Results of studies from which causality cannot be reasonably inferred can hamper decision-making and impede optimal treatment choices and outcomes.

While randomization is the most effective tool for reducing bias due to differences in outcome risk factors among compared groups, not all studies can or should employ randomization. Even when baseline randomization is effective, causal inference can be compromised when patients discontinue or

change therapies during follow-up.[3] Adhering to the standards proposed herein can enhance causal inference in both randomized and non-randomized PCOR/CER studies. However, these minimum standards do not guard against all forms of bias in PCOR/CER.

In identifying and developing our proposed standards, we considered many methods and general design and analytic strategies for promoting causal inference in PCOR/CER. Below, we list and briefly describe the topics that we considered. Items in **bold** represent those that are incorporated in the proposed minimum standards, with justification for those selections described in the Results section of this report.

- **Data source selection** (Standard 1): Data sources vary with respect to the availability, depth, quality, and accuracy of variables required for causal inference in specific PCOR studies.[1] A database that supports causal inference for one PCOR question may not contain the necessary information to support causal inference for another question.

- Design features: Many design features can be used to increase the validity of PCOR/CER study results. In particular, **new user designs** (Standard 4), follow patients beginning at the time of initiation of a particular intervention and therefore enable researchers to establish clear temporality among baseline confounders, exposures, and outcomes and they accurately characterize outcomes that occur shortly after initiation.[4] **Active comparators** (Standard 5), which are a form of negative controls,[5] can help establish a clear causal question, can facilitate appropriate comparisons, and can reduce biases due to confounding associated with initiating a treatment.[6] **Matching and restriction** (Standards 2 and 3) are commonly used approaches to reduce confounding bias by ensuring that patients are compared only to other patients with similar values for particular factors or combinations of factors. Other design options, such as the self-controlled case series[7] and the case-crossover design,[8] inherently control for confounding by patient factors that remain fixed over time because these approaches compare experiences within individuals.

- **Roles of intention-to-treat and per-protocol approaches to exposure definition** (Standard 2): Many approaches can be used to define to which exposure categories patients contribute information

during follow-up. In an intention-to-treat approach, patients are analyzed according to their randomized assignment or, in observational studies, to their initial exposure group, regardless of subsequent changes to their exposure status during follow-up.[9] In per-protocol analyses, only patients who adhere to the study protocol (e.g., those who adhere to a particular intervention) are analyzed.[10] Each approach may be associated with different biases.

- Analytic techniques for confounding control:

    - In addition to matching and restriction in the design stage, multiple approaches can be used to further address confounding in the analysis of PCOR/CER studies. Commonly used approaches include stratification (in which patients are grouped into and analyzed within categories based on cofounder values) and regression models (in which one evaluates the extent to which a particular outcome variable changes in relation to changes in values of an independent variable, while statistically holding constant other independent variables).

    - Confounder scores, such as **propensity scores**[11] (Standard 7) and disease risk scores,[12] can be used in combination with the abovementioned analytic approaches as dimension-reduction techniques to summarize multiple confounders into a single variable. Propensity scores reflect patients' probabilities of receiving a particular treatment in a given study, conditional on measured covariates. On average, patients exposed to different interventions (exposures) who have similar propensity scores will have similar distributions of variables that contributed to the propensity score. The disease risk score is the prognostic analogue of the propensity score, reflecting patients' likelihood of a particular outcome, and can be used in much the same way as the propensity score. A benefit of matching on confounder summary scores is that they enable researchers to readily **assess covariate balance** (Standard 7),[13] which can provide insight into the extent to which residual confounding by measured variables may impact the study.

- **Instrumental variable analysis** (Standard 8) is an alternative approach to causal inference that exploits variables that induce exposure variation but that are not associated with the outcome except through their associations with the exposure.[14] Instrumental variable analyses require assumptions that are not always well explicated in applications.[15]

- When researchers seek to adjust for confounding by factors that are affected by prior exposure and that affect subsequent exposure, traditional conditional methods (such as those described above – i.e., restriction, matching, stratification, and also regression analysis) can produce biased results.[16] However, methods exist to appropriately address such time varying confounding, including principal stratification analysis, and the more commonly used i**nverse probability weighted marginal structural models**[17] (Standard 6).

In the next section, we describe our approach to identifying and selecting guidance documents that address these topics, as well as primary methods papers and empirical examples that demonstrate successful implementation of the proposed standards.

III. METHODS

A. Search strategy

We employed a multipronged search strategy that involved both systematic and non-systematic processes to identify relevant guidance documents. We conducted a systematic search of three databases – MEDLINE, EMBASE, and Web of Science – through January 18, 2012, with no language limits. We developed separate search strings for each database (detailed in **Appendix A**) using terms related to guidelines or standards for research methods in both observational studies and randomized trials.

We augmented the systematic search with several non-systematic approaches. We located potentially relevant documents known to us, including unpublished draft guidelines, and we searched pertinent professional, governmental, and research organizations' websites, which are listed in **Appendix B**. We also conducted general Internet searches and hand-searched the reference lists of all identified documents.

B. Inclusion/exclusion criteria

We screened the titles and abstracts of publications identified in the systematic search to exclude those that were clearly not relevant to PCOR or CER (e.g., guidelines and studies related to non-human research) or to methods for causal inference (e.g., guidelines related to topics addressed by other contractors). Beyond these minimal criteria, we imposed few restrictions on our search in order to conduct a document identification process with high sensitivity. In particular, we did not limit documents on the basis of language or country of origin. We did exclude clinical practice standards, older versions of guidelines for which more recent guidelines had been developed, and non-English versions of guidelines for which English translations existed.

We obtained full text versions of all documents that passed our title and abstract screen. Three authors (JJG, JMP, JDS) reviewed the full text version of each document to further exclude those that did not address any of our topics of interest. Final included documents are catalogued in **Appendix C**.

C. Abstraction

JJG, JMP, JDS abstracted data from each included document. We determined the topic(s) that each document addressed and indicated these in a grid (**Appendix D**). We liberally applied this criterion in the abstraction phase in order to maximize available information for identifying and selecting topics for potential standards. For example, we indicated that a document addressed a particular topic even if the document briefly mentioned the topic but did not provide guidance on how to use it.

D. Synthesis

Using the grid in Appendix D, we identified the most commonly mentioned topics, which tended to reflect the most commonly used methods in causal inference. We avoided focusing on topics that are extensively covered in standard textbooks, such as multivariable regression analysis. We also drew on our own methodological expertise in determining which topics cover broad principles of causal inference that constitute minimum standards. We sought to focus on methods and approaches that are commonly and increasingly used in CER but that might not be familiar to many stakeholders or methods that are

often inappropriately or unclearly applied. Finally, we conducted two meetings with approximately 12 researchers (clinicians, epidemiologists, and biostatisticians) working in PCOR/CER and causal inference methodology and solicited their feedback regarding our proposed standards to and identify additional topics within causal inference methods that would be particularly useful for investigators, grant reviewers, and decision-makers.

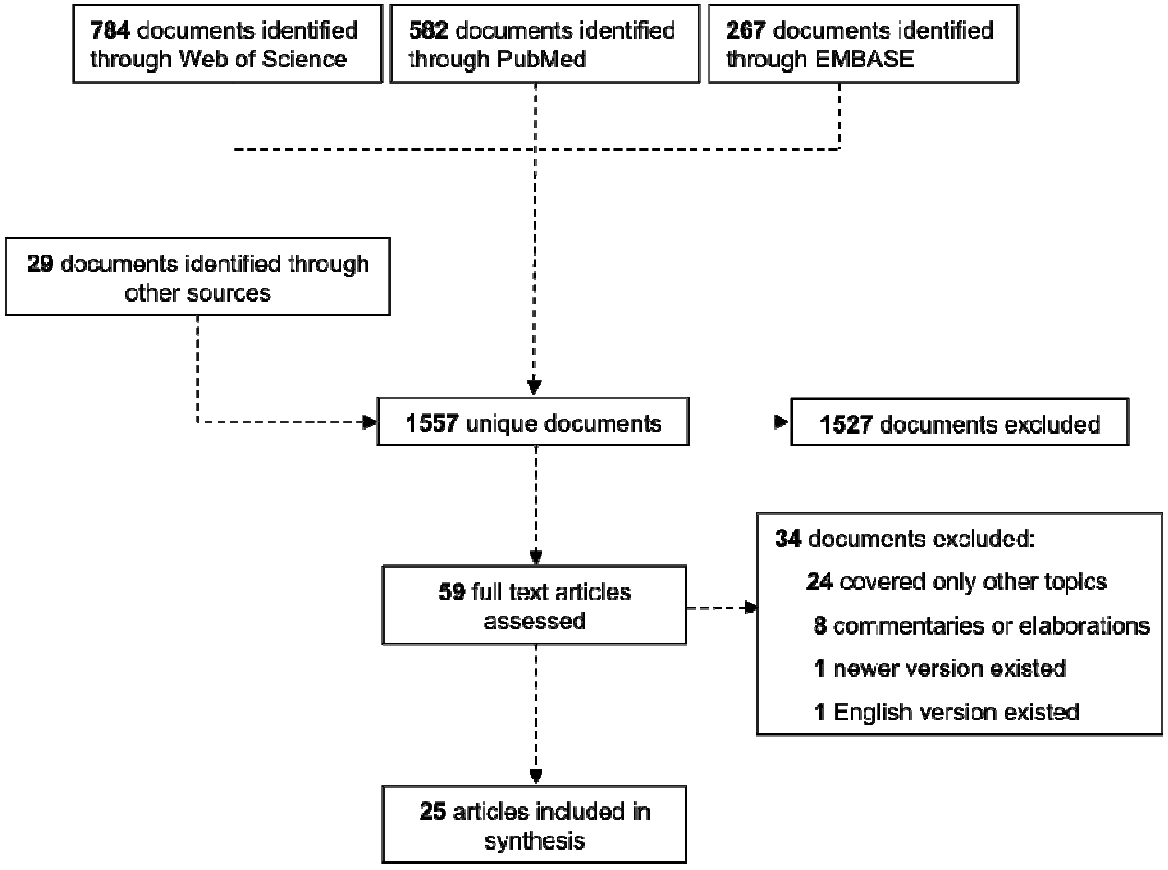
In addition to the guidance document search and selection process, we also identified primary methods research and examples of successful applications of these methods during the guidance document synthesis and standard development phases. Many of the methods and empirical application papers were derived from the references of the identified guidance documents. Others were identified based on our own knowledge of the literature and on *ad hoc* literature searches.

IV. RESULTS

A. Search results

Figure 1 below summarizes the results of the literature search and document selection process. We identified 1,557 unique documents in the systematic and non-systematic searches combined. After screening the titles and abstracts, we identified 59 potentially relevant documents for full text review. Upon full text review, we excluded 34 documents for reasons listed in Figure 1. The remaining 25 documents, which are described in Appendix C, mentioned one or more topics of interest. The grid in Appendix D indicates which topics in causal inference each document mentioned.

Figure 1. Flow diagram of guidance document identification and selection process



B. Main findings

While many existing guidance documents mention topics in causal inference, few provide clear guidance for using these methods. As one example, the US Food and Drug Administration's Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets recommends identifying and handling confounders, but states only that "There are multiple epidemiologic and statistical methods, some traditional (e.g., multiple regression) and some innovative (e.g., propensity scores), for identifying and handling confounding."

Several organizations have produced or are producing best practice guidelines, including the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Agency for Healthcare Research and Quality (AHRQ) through the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network. These largely address general principles of sound epidemiology and

biostatistics and provide state-of-the-art reviews of various methods and approaches to causal inference. Where multiple guidelines provided consistent recommendations, we sought to synthesize them into minimum standards (Standards 1, 2, 4, 5, and 8). Overall, however, few documents provide specific recommendations on minimum standards for causal inference methods. Therefore, we developed additional minimum standards largely *de novo*, based on primary methodological literature and on our own expertise in causal inference methods (Standards 3, 6, and 7).

In **Box 1**, we provide our eight recommended minimum standards. Before applying any of these standards, researchers must (1) *clearly articulate a specific causal hypothesis*; and (2) *precisely define relevant exposures and outcomes*. These are fundamental prerequisites for approaching the design and analysis of any PCOR/CER study in which researchers seek to establish causality.

Box 1. Recommended standards for causal inference methods in analyses of data from observational and experimental studies in patient-centered outcomes research

No.	Title	Description
1	Assess data source adequacy	In selecting variables for confounding adjustment, assess the suitability of the data source in terms of its capture of needed covariates.
2	Define analysis population using information available at study entry	Inclusion in an analysis should be based on information available at the time of study entry and not based on future information.
3	Describe population that gave rise to the effect estimate(s)	As many design and analytic strategies impose restrictions on the study population, the actual population that gave rise to the effect estimate(s) should be described.
4	Define effect period of interest	Precisely define the timing of the outcome assessment relative to the initiation and duration of therapy.
5	Select appropriate comparators	When evaluating an intervention, the comparator treatment(s) should be chosen to enable accurate evaluation of effectiveness or safety.
6	Measure confounders before start of exposure	In general, variables measured for use in adjusting for confounding should be ascertained prior to the first exposure to the therapy (or therapies) under study.
7	Assess propensity score balance	When propensity scores are used, assess the balance achieved across compared groups with respect to potential confounding variables.
8	Assess instrumental variable assumptions	If an instrumental variable approach is used, then empirical evidence should be presented describing how the variable chosen as an IV satisfies the three key properties of a valid instrument.

The tables in **Appendix E** provide additional information related to reference source documents for each recommendation, rationale for choosing the recommended guidelines and the evidence behind the recommended guidelines, and examples of research that demonstrate selected minimum standards.

The proposed minimum standards represent guidelines that will help enhance the methodologic rigor of PCOR/CER studies that seek to infer causality about the effect of an intervention or interventions on an outcome. Despite the minimum nature of these standards, not all researchers currently adhere to them, likely owing in large part to a lack of familiarity with the biases associated with violating these principles. These standards are not intended to help researchers decide among methods, but rather to help researchers implement methods in a rigorous, transparent manner that facilitates causal interpretations of PCOR and promotes their transparent communication. Further, these standards are not intended to represent best practices, as many methods for causal inference are relatively novel and best practices for these methods have not been established in the primary methodological literature.

C. State of the art methods not included in the main findings

Challenges encountered and gaps

Few guidance documents provide clear recommendations for the use of causal inference methods, owing largely to the relative nascency of these methods and the lack of well-established best practices. However, as researchers continue to adopt innovative methods and the literature matures around them, future standards may be warranted for certain approaches.

Disease risk scores, which are summary scores similar to propensity scores but that balance confounders based on outcome prediction rather than exposure prediction, have been the focus of considerable recent methods work.[12,18] However, this approach has received little attention in existing guidance documents and could be a focus of future standards development.

Several recent methodologic papers have examined trimming, which is a form of restriction (See Standard 3), as a way to enhance the validity of propensity score analyses.[19,20] The results of these studies suggest that researchers should consider trimming in any propensity score application. However,

existing guidance documents do not discuss trimming. Thus, trimming might considered a best practice rather than a minimum standard.

Self-controlled designs are a useful approach for identifying triggers of outcomes.[7,8] These designs are widely used in environmental,[21] cardiovascular,[22] and medical product epidemiology research.[23] However, these approaches are most commonly used to assess causes of adverse events and are rarely used to compare the effectiveness of multiple interventions.

Variable selection is an important topic that is incompletely covered by existing guidance documents, but is central to any causal inference approach that relies on conditioning on measured variables (e.g., matching, restriction, stratification, model adjustment). However, several recent methodologic papers have explored variable selection and consistently recommend including outcome risk factors in the adjustment set, and recommend avoiding conditioning on instrumental variables.[24-26] However, as explained in Standard #8, whether a variable is an instrument can never be empirically verified.

Methodology gaps

Standards 2 and 6 allude to a general rule-of-thumb for causal inference that recommends avoiding conditioning on factors that occur after entry into the study or after the start of a treatment. Many novel methods have been developed to enable researchers to validly account for post-entry or post-treatment initiation variables, including g-methods,[27] targeted maximum likelihood estimation,[28] and principal stratification.[29]

Next steps

Comprehensive reviews of major classes of methods (e.g., methods to address baseline confounding, methods to address time-varying confounding) are needed to understand how these methods are being used in PCOR and CER and to establish best practices.

V. SUMMARY

Few existing guidelines provide specific recommendations on causal inference methods for observational and experimental studies. Combining what little guidance exists with recommendations from the primary methodologic literature, we developed eight minimum standards for using causal inference methods in PCOR and CER. These standards can help protect against many biases in studies that seek to determine causality and are consistently supported by theoretical and empirical evidence in the methodologic literature. While these standards are not currently universally adopted in applied literature, we identified examples of studies that successfully adhered to the standards and that can be used as templates.

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APPENDIX A: Systematic search strings

MEDLINE

(((((("Epidemiologic Research Design"[Majr] OR "Research Design/standards"[Majr]) OR "Information Dissemination/methods"[Majr]) OR ("Comparative Effectiveness Research/methods"[Majr] OR "Comparative Effectiveness Research/organization and administration"[Majr] OR "Comparative Effectiveness Research/standards"[Majr])) OR "Research Report/standards"[Majr]) OR ("Outcome Assessment (Health Care)"[Majr] OR ("Outcome Assessment (Health Care)/methods"[Majr] OR "Outcome Assessment (Health Care)/standards"[Majr]))) AND ("Checklist/methods"[Mesh] OR "Checklist/standards"[Mesh] OR "Publishing/standards"[Mesh] OR "Guideline"[Publication Type] OR "Guidelines as Topic/standards"[Mesh])

EMBASE

'pharmacoepidemiology'/exp OR 'clinical trial (topic)'/exp AND ('practice guideline'/exp/mj OR 'checklist'/exp/mj OR 'consensus'/exp/mj)

Web of Science

Topic = (research methods AND epidemiology) AND Topic = (guidelines OR guidance OR checklist OR standard)

APPENDIX B: Organizational websites included in non-systematic search

Acronym	Organization Name	Web address
ACE	American College of Epidemiology	http://www.acepidemiology.org/
AHA	American Heart Association	http://www.heart.org/
AHRQ	Agency for Healthcare Research and Quality	http://www.ahrq.gov/
ASA	American Statistical Association	http://www.amstat.org/
CADTH	Canadian Agency for Drugs and Technologies in Health	http://cadth.ca/
Cochrane	Cochrane Collaboration	http://www.cochrane.org/
CONSORT	Consolidated Standards of Reporting Trials Statement website	http://www.consort-statement.org/
DGEpi	German Society for Epidemiology (Deutsche Gesellschaft für Epidemiologie)	http://www.dgepi.org/
EMA	European Medicines Agency	http://www.ema.europa.eu/
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance	http://www.encepp.eu/
FDA	U.S. Food and Drug Administration	http://www.fda.gov/
GRACE	Good ReseArch for Comparative Effectiveness	http://www.graceprinciples.org/
IEA	International Epidemiological Association	http://www.ieaweb.org/
ISoP	International Society of Pharmacovigilance	http://www.isoponline.org/
ISPE	International Society for Pharmacoepidemiology	http://www.pharmacoepi.org/
ISPOR	International Society for Pharmacoeconomics and Outcomes Research	http://www.ispor.org/
IQWiQ	Institute for Quality and Efficiency in Health Care	http://www.iqwig.de/institute-for-quality-and-efficiency-in-health.2.en.html
NCI	National Cancer Institute	http://cancer.gov/
OMOP	Observational Medical Outcomes Partnership	http://omop.fnih.org/
PRISMA	Transparent Reporting of Systematic Reviews and Meta-Analyses	http://www.prisma-statement.org/
SER	Society for Epidemiologic Research	http://www.epiresearch.org/
STROBE	Strengthening the reporting of observational studies in epidemiology	http://www.strobe-statement.org/

APPENDIX C: Included guidance documents and process by which they were identified

Ref. letter	Organization/ Author(s)	Full reference	Process of identification
A	ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance)	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Guide on Methodological Standards in Pharmacoepidemiology. 2011. Available at: http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE.pdf	Identified through investigators' prior knowledge
B	ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance)	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Checklist for Study Protocols. 2011. Available at: http://www.encepp.eu/standards_and_guidances/documents/ENCePPChecklistforStudyProtocols.doc	Found on ENCePP web site while looking for A
C	FDA (U.S. Food and Drug Administration)	US Food and Drug Administration. Guidance for Industry and FDA Staff: Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data sets. 2011. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf	Identified through investigators' prior knowledge
D	AGENS (Working Group for the Survey and Utilization of Secondary Data)	Working Group for the Survey and Utilization of Secondary Data (AGENS) with representatives from the German Society for Social Medicine and Prevention (DGSMP) and the German Society for Epidemiology (DGEpi) and Working Group for Epidemiological Methods with representatives from the German Society for Epidemiology (DGEpi), the German Society for Medical Informatics, Biometry and Epidemiology (GMDS) and the German Society for Social Medicine and Prevention (DGSMP). GPS – Good Practice in Secondary Data Analysis: Revision after Fundamental Reworking. 2008. Available at: http://dgepi.de/fileadmin/pdf/leitlinien/gps-version2-final_ENG.pdf	Identified through DGEpi (German Society for Epidemiology [Deutsche Gesellschaft für Epidemiologie]) website
E	DGEpi (German Society for Epidemiology [Deutsche Gesellschaft für Epidemiologie])	German Society for Epidemiology (DGEpi). Good Epidemiologic Practice. 2004. Available at: http://dgepi.de/fileadmin/pdf/GEP_LL_english_f.pdf	Identified through investigators' prior knowledge
F	ISPE (International Society for	Hall GC. Sauer B, Bourke A, Brown JS, Reynolds MW, Casale RL.	Identified through

	Pharmacoepidemiology)	Guidelines for good database selection and use in pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf* 2012;21:1-10. Available at: http://www.pharmacoepi.org/resources/Quality_Database_Conduct_2-28-11.pdf	investigators' prior knowledge
G	GRACE (Good ReseArch for Comparative Effectiveness)	Dreyer NA, Schneeweiss S, McNeil BJ, et al. GRACE Principles: Recognizing high-quality observational studies in comparative effectiveness. *Am J Manag Care* 2010;16:467-471. Available at: http://www.ajmc.com/issue/managed-care/2010/2010-06-vol16-n06/AJMC_10junDreyer_467to471	Identified through investigators' prior knowledge
H	FDA (U.S. Food and Drug Administration)	US Food and Drug Administration. Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. 2005. Available at: http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126834.pdf	Referred to in C
I	ISPOR (International Society for Pharmacoeconomics and Outcomes Research)	Motheral B, Brooks J, Clark MA, et al. A checklist for retroactive database studies--report of the ISPOR Task Force on Retrospective Databases. *Value Health* 2003;6:90-97. Available at: http://www.ispor.org/workpaper/research_practices/A_Checklist_for_Retroactive_Database_Studies-Retrospective_Database_Studies.pdf	Identified through investigators' prior knowledge
J	ISPOR (International Society for Pharmacoeconomics and Outcomes Research)	Berger ML, Mamdani M, Atikins D, Johnson ML. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: The International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Retrospective Database Analysis Task Force Report—Part I. *Value Health* 2009;12:1044-1052. Available at: http://www.ispor.org/TaskForces/documents/RDPartI.pdf	Identified through investigators' prior knowledge
K	ISPOR (International Society for Pharmacoeconomics and Outcomes Research)	Cox E, Martin BC, Van Staa T, Garbe E, Siebert U, Johnson ML. Good research practices for comparative effectiveness research: approaches to mitigate bias and confounding in the design of nonrandomized studies of treatment effects using secondary data sources: The International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Retrospective Database Analysis Task	Identified through investigators' prior knowledge

		Force Report—Part II. *Value Health* 2009;12:1053-1061. Available at: http://www.ispor.org/TaskForces/documents/RDPartII.pdf	
L	ISPOR (International Society for Pharmacoeconomics and Outcomes Research)	Johnson ML, Crown W, Martin BC, Dormuth CR, Siebert U. Good research practices for comparative effectiveness research: analytic methods to improve causal inference from nonrandomized studies of treatment effects using secondary data sources: The International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Retrospective Database Analysis Task Force Report—Part III. *Value Health* 2009;12:1062-1073. Available at: http://www.ispor.org/TaskForces/documents/RDPartIII.pdf	Identified through investigators' prior knowledge
M	ISPOR (International Society for Pharmacoeconomics and Outcomes Research)	The International Society for Pharmacoeconomics and Outcomes Research. Prospective observational studies to assess comparative effectiveness: ISPOR Good Research Practices Task Force Report (Draft). 2011. Available at: http://www.ispor.org/TaskForces/documents/ProspectiveObservationalStudiesGRPDraft.pdf	Identified through investigators' prior knowledge
N	AHRQ (Agency for Healthcare Research and Quality)	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. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/74/531/Registries%202nd%20ed%20final%20to%20Eisenberg%209-15-10.pdf	Referred to in A
O	AHRQ (Agency for Healthcare Research and Quality)	Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. August 2011. Chapters available at: www.effectivehealthcare.ahrq.gov	Referred to in G
P	ASRM (American Society for Reproductive Medicine)	The Practice Committee of the American Society for Reproductive Medicine. Interpretation of clinical trial results. *Fertil Steril* 2006;86(Suppl 1):S161-167. Available at: http://www.asrm.org/uploadedFiles/ASRM_Content/News_and_Publications/Practice_Guidelines/Educational_Bulletins/Interpretation_of_clinical(1).pdf	Identified in systematic search

Q	Gugiu and Gugiu	Gugiu PC, Gugiu MR. A critical appraisal of standard guidelines for grading levels of evidence. *Eval Health Prof* 2010;33:233-255. Available at: http://ehp.sagepub.com/content/33/3/233.abstract	Identified in systematic search
R	CONSORT (Consolidated Standards of Reporting Trials Statement)	Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement." *JAMA* 2006;295:1152-1160. Available at: www.consort-statement.org/index.aspx?o=1324	Identified in systematic search
S	Schneeweiss	Schneeweiss S. On Guidelines for Comparative Effectiveness Research Using Nonrandomized Studies in Secondary Data Sources. *Value Health* 2009;12:1041. Available at: http://www.ispor.org/publications/value/valueinhealth_volume12_issue8.pdf	Identified in systematic search
T	GRADE (Grading of Recommendations Assessment, Development and Evaluation)	Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol* 2011;64:407-415. Available at: http://www.ceb-institute.org/fileadmin/upload/refman/j_clin_epidemiol_2011_64_4_407_guyatt.pdf	Identified in systematic search
U	STROBE-ME	Gallo V, Egger M, McCormack V, et al. STrengthening the Reporting of OBservational studies in Epidemiolgy – Molecular Epidemiology (STROBE-ME): An Extension of the STROBE Statement. PLoS Med 2011;8:e1001117. Available at: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001117	Identified in systematic search
V	Lewis	Lewis JA. Statistical principles for clinical trials (ICH E9): an introductory note on an international guideline. *Stat Med* 1999;18:1903-1904.	Identified in systematic search
W	ISPE (International Society for Pharmacoepidemiology)	Andrews EA, Avorn J, Bortnichak EA, et al; ISPE. Guidelines for Good Epidemiology Practices for Drug, Device, and Vaccine Research in the United States. *Pharmacoepidemiol Drug Saf* 1996;5:333-338. Available at: http://www.pharmacoepi.org/resources/guidelines_08027.cfm	Identified in systematic search
X	Lu	Lu CY. Observational studies: a review of study designs, challenges and strategies to reduce confounding. *Int J Clin Pract* 2009;63:691-697.	Identified in systematic search
Y	AHRQ/DEcIDE	Johnson ES, Bartman BA, Briesacher BA, et al. The incident user design in comparative effectiveness research. Research from the Developing	Identified through investigators' prior

		Evidence to Inform Decisions about Effectiveness (DEcIDE) Network. AHRQ January 2012.	knowledge

APPENDIX D. Abstraction tool and summary of topics covered by each guidance documents (guidance document letters correspond to references in Appendix C)

Guidance document	A	B	C	D	E	F	G	H	I	J	K	L	M
Topic													
Data source selection	X	X	X			X	X	X	X	X			
• Strengths and limitations of data sources with respect to the depth, quality, and accuracy of measured variables to control confounding						X	X		X	X			
Design features	X												
• New user designs	X										X		X
• Active comparators/negative controls			X				X		X		X		X
• Matching				X	X								
• Restriction					X						X		
• Self-controlled designs			X							X		X	X
Roles of intention to treat, as treated, and per protocol approaches to exposure definition		X					X						X
Analytic techniques for confounding control		X	X										
• Standardization													
• Stratification							X		X			X	
• Regression			X						X			X	
• Confounder summary scores			X										
○ Propensity scores	X		X				X					X	
▪ Development (e.g. high-dimensional propensity scores)													
▪ Application (e.g. matching, stratification, weighting)												X	
○ Disease risk scores	X												
▪ Development (e.g. most appropriate population in which to estimate)													
▪ Application (e.g. matching, stratification, weighting)													
○ Trimming confounder summary scores													
○ Approaches to assess covariate balance													
• Variable selection												X	
• Instrumental variable analyses	X						X		X			X	
• Approaches to handling post-treatment variables												X	
○ Principal stratification analysis													
○ Inverse probability weighting												X	
○ Marginal structural models/g-estimation	X											X	
• Structural equation modeling												X	
Sensitivity analyses	X		X									X	
• Internal adjustment (e.g. medical record to obtain additional confounder data)												X	

Guidance document	N	O	P	Q	R	S	T	U	V	W	X	Y
• External adjustment (e.g. propensity score calibration)												X
Topic										X		
Data source selection							X	X	X			
• Strengths and limitations of data sources with respect to the depth, quality, and accuracy of measured variables to control confounding												
Design features						X		X				
• New user designs		X				X						X
• Active comparators/negative controls						X	X	X	X			
• Matching				X							X	
• Restriction									X		X	
• Self-controlled designs									X		X	
Roles of intention to treat, as treated, and per protocol approaches to exposure definition			X		X				X			
Analytic techniques for confounding control												
• Standardization												
• Stratification									X		X	
• Regression							X		X		X	
• Confounder summary scores												
○ Propensity scores	X			X							X	
▪ Development (e.g. high-dimensional propensity scores)												
▪ Application (e.g. matching, stratification, weighting)												
○ Disease risk scores												
▪ Development (e.g. most appropriate population in which to estimate)												
▪ Application (e.g. matching, stratification, weighting)												
○ Trimming confounder summary scores												
○ Approaches to assess covariate balance												
• Variable selection												
• Instrumental variable analyses											X	
• Approaches to handling post-treatment variables												
○ Principal stratification analysis												
○ Inverse probability weighting												
○ Marginal structural models/g-estimation												
• Structural equation modeling												
Sensitivity analyses	X											
• Internal adjustment (e.g. medical record to obtain additional												

confounder data)

- External adjustment (e.g. propensity score calibration)

APPENDIX E

Standard 1: Assess data source adequacy		
Identification and background of the proposed standard	1. Description of standard	If information on important confounding variables is not available in a given data source, results produced by most methods for causal inference may be biased (see "Other Considerations" for exceptions). In selecting variables for confounding adjustment, researchers should **assess the suitability of the data source in terms of its capture of needed covariates.** Even sophisticated methods such as propensity scores, disease risk scores, and marginal structural models, cannot account for bias resulting from confounders that are not measured in the dataset.
	2. Current Practice and Examples	The most commonly used methods for causal inference in observational studies rely on conditioning on measured variables to address confounding. Even the most advanced of these will produce biased results if important confounders are not measured. <u>Examples:</u> • Rubin DB. On the limits of comparative effectiveness research. *Stat Med* 2010;29:1991-1995. • Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol* 2005;58:323-337. • Tooth L, Ware R, Bain C, Purdie DM, Dobson A. Quality of reporting of observational longitudinal research. *Am J Epidemiol* 2005;161:280-288. Many observational studies seek to augment unmeasured confounding in many ways (see "Other Considerations").
	3. Published Guidance	Ensuring that the data source to be used for an observational study includes all necessary confounding variables has broad support in many existing guidelines: • European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Checklist for Study Protocols. [B; letter corresponds to references in Appendix C] • US Food and Drug Administration. Guidance for Industry and FDA Staff: Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data sets. 2011. [C] • Hall GC. Sauer B, Bourke A, Brown JS, Reynolds MW, Casale RL. Guidelines for good database selection and use in pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf* 2012;21:1-10. [F] • Dreyer NA, Schneeweiss S, McNeil BJ, et al. GRACE Principles: Recognizing high-quality observational studies in comparative effectiveness. *Am J Manag Care* 2010;16:467-471. [G]

		• US Food and Drug Administration. Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. 2005. [H] • Motheral B, Brooks J, Clark MA, et al. A checklist for retroactive database studies--report of the ISPOR Task Force on Retrospective Databases. *Value Health* 2003;6:90-97. [I] • Berger ML, Mamdani M, Atikins D, Johnson ML. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: The International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Retrospective Database Analysis Task Force Report—Part I. *Value Health* 2009;12:1044-1052. [J] • Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol* 2011;64:407-415. [T] • Andrews EA, Avorn J, Bortnichak EA, et al; ISPE. Guidelines for Good Epidemiology Practices for Drug, Device, and Vaccine Research in the United States. *Pharmacoepidemiol Drug Saf* 1996;5:333-338 [W]
MC Key Criteria: Rationale for and against adoption of the proposed standard	4. Contribution to Patient Centeredness	Patients require valid study results to make informed treatment decisions. Some data sources simply do not support causal inference for some PCOR/CER questions.
	5. Contribution to Scientific Rigor	Valid treatment effect estimation in observational research depends on being able to account for systematic differences between compared groups. Absence of a confounding variable in a data source limits the ability of most methods to account for confounding due to that variable.
	6. Contribution to Transparency	Preferentially selecting data sources that include information on important confounders improves the transparent handling of the confounders in analyses.
	7. Empirical Evidence and Theoretical Basis	Practical examples, theoretical analyses, and simulation studies clearly illustrate the occurrence of bias from omission of confounding variables. • Bross IDJ. Spurious effects from an extraneous variable. *J Chronic Dis* 1966;19:637-647. • Psaty BM, Kepsell TD, Lin D, et al. Assessment and control for confounding by indication in observational studies. *J Am Geriatr Soc* 1999;47:749-754. • Schlesselman JJ. Assessing effects of confounding variables. *Am J Epidemiol* 1978;108:3-8.
Additional considerations	8. Degree of Implementation Issues	Despite the resounding support for this standard in existing guidance documents, observational studies are often conducted in data sources that lack important variables, and/or use analytic approaches that fail to account for important confounding by unmeasured factors.

		Optimal data sources may not exist to answer some PCOR/CER questions for which an observational study is required. When designing studies involving primary data collection, important potential confounders should be identified prior to study inception and data collection. Existing data sources can also be augmented with prospectively collected data on otherwise missing confounder variables. When this is impracticable, researchers should consider alternative databases or alternative methodologic approaches, as described below in "Other Considerations."
	9. Other Considerations	If a data source is missing a potentially relevant confounder, researchers can conduct sensitivity analyses to assess the impact of that confounder on the study results. See: Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf* 2006;15:291-303. Researchers might also consider other approaches to augment data sources, such as external adjustment. See: Stürmer T, Glynn RJ, Rothman KJ, Avorn J, Schneeweiss S. Adjustments for unmeasured confounders in pharmacoepidemiologic database studies using external information. *Med Care* 2007;45(10 Supl 2):S158-165. If data are partially missing for a particular covariate in a data source, analytic options, such as multiple imputation and weighting approaches, can be used. Newer applications of confounder summary scores might also be able to account for unmeasured confounding variables to the extent that other measured variables represent proxies for them. For example, high-dimensional propensity scores seek to do this through the inclusion of large numbers of variables, thereby improving the potential for proxy representation of unmeasured confounders. See: Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology* 2009;20:512-522. While most methods for causal inference in observational studies produce biased results when important confounders are not measured, instrumental variable analysis (see Standard 8 for more on instrumental variables) and, to some extent, self-controlled designs may be exceptions. In particular, self-controlled designs can produce valid results when unmeasured confounding factors do not vary over time. See: Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol* 1991;133:144-153.

Standard 2: Define analysis population using information available at study entry		
Identification and background of the proposed standard	1. Description of standard	In clinical trials and in clinical practice, patients often change exposure status over time. For example, patients assigned to a particular therapy in a randomized trial might switch to a different therapy or discontinue therapy altogether. However, **decisions about whether patients are included in an analysis should be based on information available at each patient's time of study entry** and not based on future information, such as future changes in exposure. Excluding patients on the basis of exposure changes that occur during follow-up can severely distort results of PCOR studies by selectively removing patients who do particularly well or poorly with a given therapy.
	2. Current Practice and Examples	Most researchers agree that primary analysis of randomized trial data should include all patients who entered the study, regardless of exposure changes that occur during follow-up. The recommendation is implicit in the commonly used intention-to-treat (ITT) principle. See: • Fergusson D, Aaron SD, Guyatt G, Hébert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002;325:652. • Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomized controlled trials. *BMJ* 1999;319:670. Whether following an IT or an "as treated" paradigm, in which patients are analyzed according to the therapy that they actually received, observational studies should be analyzed similarly to randomized trials insomuch as patients who are eligible for the study based on information available at the time of entry (i.e., the start of follow-up) are not excluded based on subsequent changes in exposure: • Hernán MA, Alonso A, Logan R, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology 2008;19:766-779. • Suissa S. Effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease: immortal time bias in observational studies. *Am J Respir Crit Care Med* 2003;168:49-53.
	3. Published Guidance	The standard is reflected in the guidelines developed by the International Conference on Harmonisation Expert Working Group, describing statistical principles for clinical trials and is consistent with other general recommendations for the analysis of clinical trials: • Lewis JA. Statistical principles for clinical trials (ICH E9): an introductory note on an international guideline. *Stat Med* 1999;18:1903-1942. [V] • Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ; CONSORT

		Group. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 2006;295:1152-1160. [R] For observational studies, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards In Pharmacoepidemiology cautions against excluding person-time between the start of follow-up and subsequent exposure change: • European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Guide on Methodological Standards in Pharmacoepidemiology. 2011. [A]
MC Key Criteria: Rationale for and against adoption of the proposed standard	4. Contribution to Patient Centeredness	Patients require valid study results to make informed treatment decisions. Studies that inappropriately favor or disfavor a given therapy because patients are incorrectly censored from analysis can produce biased results.
	5. Contribution to Scientific Rigor	Excluding patients from the analysis based on future changes in exposure status can introduce non-conservative bias (i.e., bias in either direction that may be unpredictable) in both randomized trials and observational studies. One such manifestation is the introduction of immortal time, which is person-time that is event free by definition. Immortal time can severely bias treatment effect estimates. See: Suissa S. Effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease: immortal time bias in observational studies. *Am J Respir Crit Care Med* 2003;168:49-53. In addition, covariate balance is not guaranteed in the per-protocol analysis set of a randomized trial. Further, restricting analyses to patients who comply with a given treatment regimen can also introduce bias known as the "healthy adherer bias," where tendency to adhere is associated with other health-seeking behaviors that may affect the outcome. This not only restricts the analysis population to a specific subgroup of the population, but can also be associated with large biases. See: Shrank WH, Patrick AR, Brookhart MA. Health user and related biases in observational studies of preventive interventions: a primer for physicians. *J Gen Intern Med* 2011;26:546-550.
	6. Contribution to Transparency	Excluding patients based on changes in exposure that occur during follow-up generally ignores the associated biases. Surveys have found that even when researchers state that they conducted certain analyses that avoid this problem, these approaches are not always adequately applied. Clearly stating *and describing* the analytic approach used can enhance transparency of the study methods and results. See: Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomized controlled trials. *BMJ* 1999;319:670.
	7. Empirical	There is strong theoretical support for defining analysis-eligible

	Evidence and Theoretical Basis	patients using only information available at baseline. Completely excluding from the analysis those patients whose exposure changes during follow-up can differentially exclude person-time from the denominator of a rate or incidence measure, which can distort study results. Post-randomization (or post-cohort entry) exclusions can disrupt baseline balance in outcome risk factors, and also restricts the analysis population to patient who a specific subset of the original population. Suissa has demonstrated the potential bias related to immortal time that can occur when conditioning the analysis population on exposure changes that occur during follow-up: • Suissa S. Effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease: immortal time bias in observational studies. *Am J Respir Crit Care Med* 2003;168:49-53. • Suissa S. Immortal time bias in observational studies of drug effects. *Pharmacoepidemiol Drug Saf* 2007;16:241-249.
Additional considerations	8. Degree of Implementation Issues	The standard has broad support in the clinical trials setting, where the ITT principle is used as the primary analysis standard for superiority studies involving beneficial outcomes. However, randomized trials sometime use per-protocol analyses. When conducting analyses on the per-protocol set, the precise reasons for excluding patients from the analysis on the basis of exposure status after time zero should be fully defined and documented, and potential biases resulting from such exclusions should be explained. Researchers should also report the results of per-protocol analyses alongside results from analyses that include all patients (See: McAlister FA, Sackett DL. Active-control equivalence trials and antihypertensive agents. Am J Med 2011;111:553-558), as done in the following examples: • Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with long-acting calcium-channel blocker or diuretic in the Internal Nifedipine GITS study: intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000;356:366-372. • Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999;353:611-616. In addition to ITT, as-treated analyses also avoid exclusions based on future events. Analogous to per protocol analyses of RCTs, observational studies sometimes exclude patients who change exposure status during the

		observation window. This can result in differential exclusion of immortal person-time (i.e., person-time that is event free by definition) from the different exposure groups, which can differentially distort the outcome event rates in each group, as described above.
	9. Other Considerations	While the ITT approach ensures consistency with this standard, it is not the only strategy that can be used to analyze data from all study participants. Researchers can also conduct what are sometimes call "on treatment" or "as treated analyses" (though these terms are not consistently defined), in which patients are censored after they discontinue or switch therapies. This allows patients to contribute person-time to the analysis prior to the censoring event. Alternatively, researchers can allow participants to contribute to multiple exposure categories during follow-up, allowing participants to contribute person-time to their current exposure group. However, these approaches can introduce other biases if subjects preferentially switch or discontinue treatment just before an event.

Standard 3: Describe population that gave rise to the effect estimate(s)		
Identification and background of the proposed standard	1. Description of standard	Many approaches to causal inference impose some form of restriction on the original study population in order to mitigate confounding. This can be done explicitly by restricting to patients with a certain confounder value (e.g., age restriction) or implicitly as with matching that excludes patients for whom reasonable matches cannot be found. **When conducting analyses that in some way exclude patients from the original study population, researchers should describe the final analysis population that gave rise to the effect estimate(s).** If patients excluded from the original study population differ from included subjects on factors that modify the effect of the therapy or therapies, then the resulting effect estimate may not accurately apply to the whole study population.
	2. Current Practice and Examples	Restriction, matching, and stratification are common approaches to address confounding by measured factors in observational studies. Restriction explicitly excludes patients from an analysis to increase the similarity of compared patients on one or more potential confounding factors. Matching and stratification can also result in exclusions of patients if researchers are unable to find suitable matches for some patients or if some strata contain patients from only one treatment group. Note that as per Standard 2, any exclusions should be based on patients' information at study entry. While excluding patients from the analysis can increase the validity of results, the analysis population (1) may not represent the original study population (i.e., loss of generalizability) and; (2) may be too small to allow for adequate precision of the derived estimates (i.e., loss of power). Restricting, stratifying, or matching on individual confounders (e.g., age) can make it very clear who resides in the analysis population. However, when using confounder scores (e.g., propensity scores), which summarize multiple covariates into single variables, the characteristics of excluded and included patients become less transparent. Studies that employ propensity score matching present characteristics of the population in terms of a "Table 1." These tables illustrate the characteristics of patients before matching and after matching (forming the subset of the population from which the effect estimate is derived). Propensity score stratified analyses may include tables of characteristics that illustrate balance within strata of the propensity score and directly characterize the population involved in analyses that include specific strata. <u>Examples</u>: • Connors AF, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *JAMA* 1996;276:889-897.

		• Seeger JD, Walker AM, Williams PL, Saperia GM, Sacks FM. A propensity score-matched cohort study of the effect of statins, mainly fluvastatin, on the occurrence of acute myocardial infarction. *Am J Cardiol* 2003;92:1447-1451.
	3. Published Guidance	While many guidance documents mention the benefits of restriction, matching, and stratification, none address the potential limitation that these approaches may exclude patients from the analysis and that the results may therefore not apply to the original study population. However, this has been described in the methodologic literature: • Lunt M, Solomon D, Rothman K, et al. Different methods of balancing covariates leading to different effect estimates in the presence of effect modification. *Am J Epidemiol* 2009;169:909-917. • Kurth T, Walker AM, Glynn RJ, Chan KA, Gaziano JM, Berger K, Robins JM. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. *Am J Epidemiol* 2006;163:262-270. • Schneeweiss S, Patrick AR, Stürmer T. Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. *Med Care* 2007;45(10 Supl 2):S131-142. • Stürmer T, Rothman KJ, Glynn RJ. Insights into different results from different causal contrasts in the presence of effect-measure modification. *Pharmacoepidemiol Drug Saf* 2006;15:698-709. • Stürmer T, Rothman KJ, Avorn J, Glynn RJ. Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution--a simulation study. *Am J Epidemiol* 2010;172:843-854.
MC Key Criteria: Rationale for and against adoption of the proposed standard	4. Contribution to Patient Centeredness	Patients should be able to assess if a study's results are applicable to them based on their respective clinical and demographic profiles. Researchers who describe their analytic population and clarify to whom their results apply make their research more relevant to patients.
	5. Contribution to Scientific Rigor	Treatment effect estimates may vary across subgroups of a population (effect measure modification or treatment effect heterogeneity). The effect estimate provided by a study most directly applies to the population from which the estimate arose. However, because of methods that exclude patients, the population from which the estimate arose may not reflect the original study population. The attribution of an effect estimate to a different population (generalization) requires assumptions about the homogeneity of the effect across the characteristics of the population that defines the subgroup. Being explicit about these assumptions improves the scientific rigor of the research.

	6. Contribution to Transparency	By explicitly defining the population in which estimates are derived, researchers improve transparency of the result, and also the transparency of any subsequent generalization of the result.
	7. Empirical Evidence and Theoretical Basis	The articles referenced above in "Published Guidance" represent a sample of the work that forms the empirical and theoretical basis for this standard.
Additional considerations	8. Degree of Implementation Issues	Written reports of studies that restrict, match, or stratify on the propensity score are sometimes not explicit about the final population included in the analysis. This omission can result in the attribution of subgroup effects to broader populations and might represent inappropriate extrapolation of findings to the extent that effect measure modifiers exist.
	9. Other Considerations	Weighting by the propensity score does not exclude patients from the analysis *per se*, but can produce different results that apply to different populations when different weights are used and when effect modification exists. When using weighting, researchers should be explicit about the population to which the results apply.

Standard 4: Define effect period of interest		
Identification and background of the proposed standard	1. Description of standard	The effects of many interventions vary with duration of use. To ensure that an effect estimate corresponds to the question that researchers seek to answer, the researchers must **precisely define the timing of the outcome assessment relative to the initiation and duration of therapy**. The new user design, which focuses on patients who initiate the therapy being studied for the first time, helps make explicit when outcomes are assessed with respect to treatment initiation and duration. This makes it possible to quantify the incidence rate of a given outcome in the period shortly after therapy initiation, which cannot be done accurately when prevalent users are studied. Prevalent users are more likely to "survive" the early period of use, when side effects, adverse outcomes, treatment discontinuation due to no effect, and treatment non-adherence may be more likely to occur.
	2. Current Practice and Examples	New user designs restrict the eligible study population to patients who initiate treatment for the first time, or after a defined period of non-use. In contrast, prevalent user designs include all patients who are currently using a treatment. This approach excludes patients who are non-compliant with treatment over time, have early adverse events that result in treatment discontinuation, or who discontinue treatment due to lack of effect. Most randomized controlled trials routinely implement a new-user design, randomizing patients to treatment, sometimes after a "washout period" of non-use. Observational studies have increasingly used a new user design. <u>Examples</u>: • Cadarette and colleagues compared the relative effectiveness of osteoporosis drugs in a new user design. See: Cadarette SM, Katz JM, Brookhart MA, Stürmer T, Stedman MR, Solomon DH. Relative effectiveness of osteoporosis drugs for prevention nonvertebral fracture. *Ann Intern Med* 2008;148:637-646. • Ray provides examples of new user and prevalent user designs and describes the potential biases associated with prevalent user designs. See: Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003;158:915-20. • Suissa and colleagues discuss how treatment duration may have biased results in prevalent user studies of oral contraceptives and venous thromboembolism. See: Suissa S, Spitzer WO, Rainville B, Cusson J, Lewis M, Heinemann L. Recurrent use of newer oral contraceptives and the risk of venous thromboembolism. *Hum Reprod* 2000;15:817-821.
	3. Published Guidance	The new user design is recommended as the main design for studies assessing treatment effects in guidance documents from numerous

		organizations including: • European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Guide on Methodological Standards in Pharmacoepidemiology. 2011. [A] • Motheral B, Brooks J, Clark MA, et al. A checklist for retroactive database studies--report of the ISPOR Task Force on Retrospective Databases. *Value Health* 2003;6:90-97. [I] • Cox E, Martin BC, Van Staa T, Garbe E, Siebert U, Johnson ML. Good research practices for comparative effectiveness research: approaches to mitigate bias and confounding in the design of nonrandomized studies of treatment effects using secondary data sources: The International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Retrospective Database Analysis Task Force Report—Part II. *Value Health* 2009;12:1053-1061. [K] • Johnson ES, Bartman BA, Briesacher BA, et al. The incident user design in comparative effectiveness research. Research from the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network. AHRQ January 2012. [Y]
MC Key Criteria: Rationale for and against adoption of the proposed standard	4. Contribution to Patient Centeredness	The new user design captures the clinical consequences of the entire therapeutic strategy over time, including early events that may cause patients to discontinue use or co-interventions that might mediate therapeutic effectiveness. The new user design can also provide information about the induction period to experience an outcome.
	5. Contribution to Scientific Rigor	New users may differ from prevalent users in their response to treatment. The new user design follows patients from the initiation of treatment, preventing bias associated with treatment duration by evaluating the complete course of treatment. The new user design also supports Standard 2 by including patients who experience adverse events early in treatment, preventing under-ascertainment of these events, and includes patients who become non-compliant with treatment who may have different clinical profiles than those who remain adherent. Secondly, the new user design supports Standard 6 by enabling covariate measurement in the period prior to treatment initiation. This allows for appropriate measurement of and adjustment for these covariates before they are affected by treatment. In contrast, in studies with prevalent users, covariates may be measured after they are impacted by treatment exposure. Adjustment for these covariates might underestimate (adjust away) the treatment effect if they are intermediates on the causal pathway, or they might create bias in either direction if they share common causes with the outcome.
	6. Contribution to Transparency	Restricting the study population to new initiators of a treatment prevents biases associated with treatment duration and clarifies the study question. Studies of new users and studies of prevalent users

		provide answers to different questions.
	7. Empirical Evidence and Theoretical Basis	Much empirical evidence describes the biases associated with prevalent user designs: • Danaei G, Tavakkoli M, Hernán MA. Bias in observational studies of prevalent users: lessons for comparative effectiveness research from a meta-analysis of statins. *Am J Epidemiol* 2012;175:250-262. • Feinstein AR. Clinical biostatistics. XI. Sources of 'chronology bias' in cohort statistics. *Clin Pharmacol Ther* 1971;12:864-879. • Hernán MA, Alonso A, Logan R, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. *Epidemioligy* 2008;19:766-779. • McMahon AD, MacDonald TM. Design issues for drug epidemiology. *Br J Clin Pharmacol* 2000;50:419-425. • Schneeweiss S, Patrick AR, Stürmer T, et al. Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. *Med Care 2*007;45:S131–S142. • Suissa S, Spitzer WO, Rainville B, Cusson J, Lewis M, Heinemann L. Recurrent use of newer oral contraceptives and the risk of venous thromboembolism. *Hum Reprod* 2000;15:817-821. The theoretical rationale for the new user design is well grounded in the principles of epidemiology: • Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003;158:915-20.
Additional considerations	8. Degree of Implementation Issues	While the new user design has strong support in the comparative effectiveness research community in both observational and experimental settings, there are several considerations that merit scrutiny when such a design is implemented: • Applicability: In some exposure settings (e.g., smoking, nutrient exposure), true new users may be difficult to find or identify and randomization to new use of a treatment may be unethical. • Applicability: Even when a year or more of "pre-exposure" time is available to indicate that a treatment is new, a patient may have been exposed to the regimen under study years before the period covered in the dataset available for analysis. • Generalizability: New users can be difficult to find when disease is severe or has already progressed beyond an early stage, when treatment does not follow guidelines or when treatment has progressed over time. This restricted patient sample may limit the generalizability of results. • Generalizability: The length of the period of non-use prior to treatment initiation can affect the likelihood of outcomes, as true

		new users may be at an earlier point in the natural history of their illness or have milder severity of illness and therefore are at lower absolute risk of clinical events. The longer the "washout period" of non-use, the more likely it is that fewer adverse outcomes will occur. • Precision: Because finding new users can be difficult, study size and thus the number of observed events may be reduced. Wide confidence intervals due to lack of power will limit the statistical inferences that can be made about benefits or harms.
	9. Other Considerations	If the study goal is to capture the totality of benefits and harms across episodic treatment use, structural models that account for time-varying exposures and confounding must be used, even if first use is restricted to new initiators of treatment (see Standard 6). If the new user definition is based on meeting a certain therapy definition, i.e., filling 3 prescriptions, but the date of follow-up starts prior to the date at which patients meet the new user criterion, then the study design incorporates immortal time and bias may result if this time is differential across exposure groups. Owing to the implementation issues described above, new user designs cannot be categorically required of all patient-centered outcomes research studies. If prevalent users (i.e., patients currently using treatment, regardless of duration) are included in the study population, a clear description of how duration of therapy might impact the causal relationship should be given, including the effects of under-ascertainment of events early in treatment, whether risk of events is thought to vary with time, whether barriers to treatment initiation and factors associated with treatment adherence may result in a selected population, and how covariates associated with treatment initiation but also affected by treatment use are handled.

Standard 5: Select appropriate comparators		
Identification and background of the proposed standard	1. Description of standard	The causal interpretation of a PCOR/CER study depends on the choice of comparator(s). A treatment found to be effective relative to one comparator might not be effective in another study if a different comparator is used. Moreover, in observational studies, use of different comparator groups can be associated with different degrees of bias. **When evaluating an intervention, the comparator treatment(s) must be chosen to enable accurate evaluation of effectiveness or safety**. Researchers should make explicit what the comparators are and how they were selected, focusing on clearly describing how the chosen comparator(s) define the causal question and impact the potential for biases. Generally, non-use (or no treatment) comparator groups should be avoided.
	2. Current Practice and Examples	An ideal study, whether randomized or observational, controls all sources of outcome variation except those caused by the intervention(s) under study. Active comparators enhance the causal interpretation of randomized trials by controlling sources of bias when using non-use comparator groups. Examples: • In a randomized controlled trial, Lieberman et al. compared the effectiveness of newer atypical versus older conventional antipsychotic medications in the treatment of schizophrenia by randomizing patients to one of three active comparison exposures: perphenazine, olanzapine, or ziprasidone. See: Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia *N Engl J Med* 2005;353:1209-1223. • Chokshi and colleagues describe the importance of appropriate comparator selection and its impact on the causal question. See: Chokshi DA, Avorn J, Kesselheim AS. *Health Affairs* 2010;29:1842-1848. In an observational study, the most valid evaluation of a treatment's effect can be achieved by choosing one or more active comparator treatments that have similar indication for use among a patient population with similar disease status in terms of presence, severity, and duration. Active comparators can also reduce information bias in situations where treated patients are more likely to have important confounders measured than non-treated patients. Examples: • Mauri and colleagues compared mortality rates among patients with acute myocardial infarction who received either a drug-eluting or a bare metal stent during PCI. See: Mauri L, Silbaugh TS, Garg P et al. Drug-eluting or bare-metal stents for acute myocardial

		infarction. *N Engl J Med* 2008;359:1330-1342. • Schneweiss and colleagues investigated mortality risk among patients undergoing CABG who received either aprotinin or aminocaproic acid. See: Schneeweiss S, Seeger JD, Landon J, Walker AM. Aprotinin during coronary-artery bypass grafting and risk of death. *N Engl J Med* 2008;358:771-783. • Solomon and colleagues conducted an observational comparative safety study among opioids used for nonmalignant pain in older adults. See: Solomon DH, Rassen JA, Glynn RJ, et al. The comparative safety of opioids for nonmalignant pain in older adults. *Arch Intern Med* 2010;170:1979-86.
	3. Published Guidance	Multiple guidance documents recommend active comparator groups for conducting CER: • US Food and Drug Administration. Guidance for Industry and FDA Staff: Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data sets. 2011. [C] • Dreyer NA, Schneeweiss S, McNeil BJ, et al. GRACE Principles: Recognizing high-quality observational studies in comparative effectiveness. *Am J Manag Care* 2010;16:467-471. [G] • Motheral B, Brooks J, Clark MA, et al. A checklist for retroactive database studies--report of the ISPOR Task Force on Retrospective Databases. *Value Health* 2003;6:90-97. [I] • Cox E, Martin BC, Van Staa T, Garbe E, Siebert U, Johnson ML. Good research practices for comparative effectiveness research: approaches to mitigate bias and confounding in the design of nonrandomized studies of treatment effects using secondary data sources: The International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Retrospective Database Analysis Task Force Report—Part II. *Value Health* 2009;12:1053-1061. [K] • The International Society for Pharmacoeconomics and Outcomes Research. Prospective observational studies to assess comparative effectiveness: ISPOR Good Research Practices Task Force Report (Draft). 2011. [M] • Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. August 2011. [O] • Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol* 2011;64:407-415. [T] • Johnson ES, Bartman BA, Briesacher BA, et al. The incident user design in comparative effectiveness research. Research from the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network. AHRQ January 2012. [Y]
MC Key	4. Contribution to	Patients must often choose a treatment course from amongst several

Criteria: Rationale for and against adoption of the proposed standard	Patient Centeredness	options. In contrast to studies that employ non-use comparator groups, studies that use active comparators provide patients with information about effects of one treatment in comparison with one or more others for similar indication and are most relevant to patients' clinical situation.
	5. Contribution to Scientific Rigor	Avoiding non-use comparator groups can enhance the validity of both randomized trials and observational studies. In randomized trials, a comparator group that receives similar care in all respects except for the intervention of interest, whether the comparator is an inert or active comparator, can mitigate bias by maintaining appropriately blinding. In observational settings, bias can be introduced when the exposed and unexposed groups differ in their prognosis. Active comparator groups can mitigate this bias by comparing patients exposed to the intervention(s) of interest to similar patients exposed to other interventions that may be similarly used.
	6. Contribution to Transparency	The use of active comparators allows treatments to be compared directly with one another and examines their effectiveness in patients with similar disease status and need for treatment, mitigating biases associated with prognosis and effects related to other aspects of treatment (e.g., knowledge of treatment).
	7. Empirical Evidence and Theoretical Basis	Several articles provide empirical evidence describing the pitfalls associated with non-user comparator groups: • Glynn RJ, Schneeweiss S, Wang PS, Levin R, Avorn J. Selective prescribing led to overestimation of the benefits of lipid-lowering drugs. *J Clin Epidemiol* 2006;59:819-828. • Ray WA, Daugherty JR, Griffin MR. Lipid-lowering agents and the risk of hip fracture in a Medicaid population. *Inj Prev* 2002;8:276-9. Rosenbaum has described the benefits of active comparators from a theoretical perspective: • Rosenbaum PR. Differential effects and generic biases in observational studies. *Biometrika* 2006;93:573-586.
Additional considerations	8. Degree of Implementation Issues	The active comparator approach has strong support in the research community. Several issues should be considered when researchers choose whether to implement this approach: • Confounding by indication and other factors related to treatment initiation: In observational studies, patients receive treatments due to both measured and unmeasured factors associated with prognosis, disease duration, and disease severity. Researchers should acknowledge and describe design and analytic approaches to minimize bias among comparator groups. • Settings in which "second-line" or new therapies are used: A patient who is doing well on current treatment may not change or

		"step up" to a new or second line comparator therapy, whereas a patient whose condition continues to worsen or who cannot tolerate current treatment may be switched to the new therapy. To mitigate differences between exposure groups, researchers might define an eligible cohort based on use of common first-line therapy and then define exposure groups based on addition or switch to another product. This improves comparability of disease severity and progression because all required stepped-up therapy. If appropriate active comparators cannot be found then, at minimum, a patient population with demonstrated comparable health services use (e.g., use of prescription drugs, screening tests, or vaccines, as appropriate) should be used to balance active engagement with the healthcare system among exposure groups**.**
	9. Other Considerations	In settings where the definition of active comparators will involve a contrast between a readily available treatment (e.g., prescription drug) and a treatment that may occur with some time delay (e.g., surgery, other procedure), consideration should be given to the definition of the exposure start date. The exposure start date with the least misclassification is the date on which the treatment was prescribed (i.e., date of provider visit). However, the lag time between the provider visit and filling a prescription versus having surgery may be differential, introducing bias. In such situations, it may be preferable to choose the fill date and procedure date and accept non-differential bias from unfilled but prescribed and prescribed but not undertaken procedures. If a non-user comparator group is defined, the rationale for and recognition of biases associated with this choice should be described. Generally, comparing patients who use a treatment to non-users introduces confounding biases related to health system engagement (healthy user bias), disease duration, and disease severity.

Standard 6: Measure confounders before start of exposure		
Identification and background of the proposed standard	1. Description of standard	Valid CER requires researchers to ensure that differences in outcomes among compared groups are attributable to the therapies themselves and not to differences in the patients who received them. Outcomes risk factors can be balanced using many methods, including randomization, design features, such as matching, and statistical adjustment. In general, **variables for use in confounding adjustment (either in the design or analysis) should be ascertained and measured prior to the first exposure to the therapy (or therapies) under study**. Standard approaches to confounding adjustment can be biased when used to adjust for factors measured after the start of the exposure if these factors are affected by the exposure.
	2. Current Practice and Examples	In expectation, randomization balances all baseline variables. In observational studies, researchers generally attempt to mimic the baseline randomization process by measuring and adjusting for pre-treatment variables: • Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41-55. • Schneeweiss S. Developments in post-marketing comparative effectiveness research. *Clin Pharmacol Ther* 2007;82:143-156. However, some observational studies continue to employ conditional survival models (e.g., Cox proportional hazards models) with time-dependent covariates. Researchers also sometimes adjust for variables measured between the start of exposure and the outcome event date in case-control studies. Both approaches can produce bias when these variables are affected by prior exposure and are causes of or share common causes with the outcome.
	3. Published Guidance	The primary methodological literature uniformly recommends avoiding adjustment for variables affected by prior exposure, which can most easily be achieved by measuring all potential confounders before the start of a treatment: • Weinberg CR. Toward a clearer definition of confounding. *Am J Epidemiol* 1993;137:1-8. • Greenland S. Quantifying biases in causal models: classical confounding vs collider-stratification bias. Epidemiology 2003;14:300-306.
MC Key Criteria: Rationale for and against adoption of the proposed	4. Contribution to Patient Centeredness	Valid approaches to CER are required to produce the most useful information for patients in order to guide treatment choices.
	5. Contribution to Scientific Rigor	Adjusting for variables measured during follow-up (i.e., after the start of a therapy) can introduce bias in the analysis of both randomized

standard		trial and observational study data if these variables both (1) are affected by the exposure; and (2) affect the outcome or share common causes with the outcome. Avoiding this practice can enhance the validity of PCOR/CER. Alternatively, researchers may adjust for variables measured during follow-up if they provide clear rationale for why the variables are not affected by prior exposure or why the variables do not affect or share common causes with the outcome.
	6. Contribution to Transparency	Specifying when variables are measured with respect to the start of exposure increases transparency in PCOR/CER studies by making it clear whether estimated parameters may be biased. When researchers do ascertain variables after the start of exposure, providing a clear rational for why these variables do not depend on prior exposure or using methods to appropriately adjust for them (see "Other Considerations" below) can also enhance transparency.
	7. Empirical Evidence and Theoretical Basis	This standard is supported by both solid theoretical justification and empirical evidence. If a variable is affected by prior exposure and in turn affects the outcome, then the variable is an intermediate on the causal pathway and adjustment for it using traditional methods will distort the true relation between the exposure and the outcome: • Robins J. The control of confounding by intermediate variables. *Stat Med* 1989;8:679-701. If the variable is affected by prior exposure and it shares a common cause with the outcome, then adjusting for it can distort the exposure-outcome relation by opening up a so-called backdoor path: • Cole SR, Platt RW, Schisterman EF, et al. Illustrating bias due to conditioning on a collider. *Int J Epidemiol* 2010;39:417-420. • VanderWeele TJ, Mumford SL, Schisterman EF. Conditioning on intermediates in perinatal epidemiology. *Epidemiology* 2012;23:1-9.
Additional considerations	8. Degree of Implementation Issues	While most patient-centered outcomes research studies and comparative effectiveness studies do successfully measure all potentially confounding variables prior to initial exposure, it is not uncommon to find studies that violate this precept and do not address the problem with appropriate methods (see "Other Considerations" below).
	9. Other Considerations	If the research question pertains to the joint effect of a time-varying exposure, rather than a fixed exposure such as random assignment in an intention-to-treat analysis, then adjustment might be needed for time-varying confounders. Time-varying confounders refer to variables that are affected by prior exposure and that affect subsequent exposure and the outcome of interest. Traditional analytic approaches, such as conditional regression models, can produce biased results when adjusting for time-varying confounding (See:

		Robins JM, Hernán MA, Brumback B, Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11:550-560.). Marginal structural models (MSMs) with inverse probability weights (IPWs), are one example of a causal inference method that can properly account for time-varying confounding, provided relevant time-varying confounders are measured in the data. This method can be used in both randomized trials and in observational studies: • Cook and colleagues used an IPW-weighted MSM in a trial with baseline randomization evaluating the effect of aspirin on cardiovascular mortality. Reference: Cook NR, Cole SR, Hennekens CH. Use of a marginal structural model to determine the effect of aspirin mortality in the Physician's Health Study. *Am J Epidemiol* 2002;155:1045:1053. • Hernán and colleagues demonstrated the beneficial effect of the antiretroviral drug zidovudine on survival of HIV-positive men using an IPW-weighted MSM that properly accounted for time-varying confounding by CD4 count in an observational study. In contrast, a standard survival analysis that adjusted for CD4 count suggested the opposite effect of zidovudine. Reference: Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology* 2000;11:561-570. Multiple guidance documents recommend that IPW-weighted MSMs be used to evaluate time-varying exposures in the presence of time-varying confounding: • European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Guide on Methodological Standards in Pharmacoepidemiology. 2011. [A] • Cox E, Martin BC, Van Staa T, Garbe E, Siebert U, Johnson ML. Good research practices for comparative effectiveness research: approaches to mitigate bias and confounding in the design of nonrandomized studies of treatment effects using secondary data sources: The International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Retrospective Database Analysis Task Force Report—Part II. *Value Health* 2009;12:1053-1061. [K] When estimating the joint effect of a time-varying exposure, one may wish to adjust for time-varying confounders. Using appropriate methods, such as IPW-weighted MSMs, to handle these variables can increase the validity of study results, whereas traditional adjustment approaches will create bias. However, methods to appropriately analyze time-varying confounding, such as structural nested models and targeted maximum likelihood

		approaches, may be unfamiliar to many investigators, which could reduce transparency. Among these methods, IPW-weighted marginal structural models are the most widely used.

Standard 7: Assess propensity score balance		
Identification and background of the proposed standard	1. Description of standard	Propensity scores are a useful method to adjust for many measured confounding variables. A patient's propensity score is his or her probability of receiving a particular treatment, conditional on measured covariates. On average, patients with similar propensity scores in a study tend to have similar distributions of variables used to build the propensity score. When conducting analyses that use propensity scores to balance covariate distributions across exposure groups, researchers should **assess the balance achieved across compared groups with respect to potential confounding variables.** Balance in confounders between treatment groups can be easily assessed after matching on or weighting by the propensity score or within strata of the propensity score.
	2. Current Practice and Examples	Propensity score analyses that do not assess balance across compared groups with respect to potential confounding variables may not fully account for the potential confounding. Examples: • Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083-3107. • Austin PC. The relative ability of different propensity-score methods to balance measured covariates between treated and untreated subjects in observational studies. *Med Decis Making* 2009;29:661-677. • Seeger JD, Kurth T, Walker AM. Use of propensity score technique to account for exposure-related covariates: an example and lesson. *Med Care* 2007;45(10 Supl 2):S143-8. • Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional Propensity Score Adjustment in Studies of Treatment Effects Using Health Care Claims Data. *Epidemiology* 2009;20:512-522.
	3. Published Guidance	No existing guidance documents specifically address assessing balance on the propensity score. However, this standard is supported by recommendations in many methodological papers: • Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083–3107. • Belitser SV, Martens EP, Pestman WR, Groenwold RH, de Boer A, Klungel OH. Measuring balance and model selection in propensity score methods. *Pharmacoepidemiol Drug Saf* 2011;20:1115-1129. • D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998;17:2265-2281.
MC Key	4. Contribution to	Patients require valid study results to make informed treatment

Criteria: Rationale for and against adoption of the proposed standard	Patient Centeredness	decisions. Appropriately applied design and analytic methods can enhance the validity of outcomes research findings.
	5. Contribution to Scientific Rigor	Treatment effect estimates in observational research depend on being able to account for systematic differences that arise between compared groups. Propensity score approaches can balance covariate distributions across compared groups, minimizing confounding. Illustrating balance across compared groups with respect to important confounders gives empirical evidence that confounding has been mitigated, thus refuting alternative hypotheses that may explain an observed effect.
	6. Contribution to Transparency	Illustrating balance across compared groups with respect to potential confounding variables improves the transparency of analyses that compare the groups with respect to the occurrence of outcomes. Demonstrating balance provides reassurance that important confounders are equally distributed among compared groups.
	7. Empirical Evidence and Theoretical Basis	Balance of covariate distributions across compared groups removes the association between each of the balanced covariates and exposure, preventing confounding by these factors.
Additional considerations	8. Degree of Implementation Issues	Depending on how propensity scores are utilized in an analysis, balance may be easily demonstrated or more difficult to assess. • Propensity score matching: Many studies that employ propensity score matching present balance in terms of a "Table 1" that illustrates the balance for select patient characteristics before and after PS matching. • Propensity score stratification: Tabular comparison of characteristics in each comparison group across strata of the propensity score can be presented to show balance within each stratum. • Other applications of propensity score analyses, such as modeling typically lack such assessment of balance. Suitable approaches to demonstrate balance in the application of these analyses are needed.
	9. Other Considerations	Investigators may not appreciate the options available for illustrating balance, as described above in "Degree of implementation issues."

Standard 8: Assess instrumental variable assumptions		
Identification and background of the proposed standard	1. Description of standard	An instrumental variable (IV) is an observed variable that induces or is associated with variation in exposure such that it approximates randomized assignment to one treatment versus another. When an IV analytic approach is used successfully, bias caused by both measured and unmeasured confounders is mitigated, improving causal inference. **If an IV approach is used, then empirical evidence should be presented describing how the variable chosen as an IV satisfies the three key properties of a valid instrument:** (1) the IV influences choice of treatment or is associated with a particular treatment because both have a common cause; (2) the IV is unrelated to patient characteristics that are associated with the outcome; and (3) the IV is not otherwise related to the outcome under study (i.e., it does not have a direct effect on the outcome apart from its effect through exposure).
	2. Current Practice and Examples	Although the suitability of an IV cannot be explicitly confirmed, there are several approaches to empirically evaluating the IV. Recommendations include: • Reporting the strength of the association between the IV and exposure, either through the report of the Wald statistic or the first-stage model with F statistic and R^2 if the IV estimator is a multivariable model, or through other measures of association (e.g. odds ratios). • Reporting the distribution of patient characteristics across strata of the IV (e.g., means and frequencies) to assess the assumption that the IV is independent of patient characteristics. • Exploring the association between the IV and other concurrent interventions. If the IV affects these other treatments, which in turn affect the outcome under study, then the IV may affect the outcome through another causal pathway in addition to its effect through exposure, invalidating the IV. • Evaluating the sensitivity of the IV estimator to covariate adjustment. If the unadjusted versus adjusted results are different, then the IV may be related to patient characteristics, which can be problematic. <u>Examples</u>: 1. Angrist J, Imbens G, Rubin D. Identification of causal effects using instrumental variables. *JASA* 1996;91:444-455. 2. Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidemiol Drug Saf* 2010;19:537–554. 3. McClellan M, McNeil BJ, Newhouse JP. Does more intensive treatment of acute myocardial infarction in the elderly reduce mortality? Analysis using instrumental variables. *JAMA* 1994;272:859-866.

		4. Schneeweiss S, Solomon DH, Wang PS, Rassen J, Brookhart MA. Simultaneous assessment of short-term gastrointestinal benefits and cardiovascular risks of selective cyclooxygenase 2 inhibitors and nonselective nonsteroidal antiinflammatory drugs: an instrumental variable analysis. *Arthritis Rheum* 2006;54:3390-3398.
	3. Published Guidance	Although IVs have long been used in the economics literature, existing guidance documents provide little support regarding their suitability for valid causal inference in comparative effectiveness research. Documents that mention IVs, include: • European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Guide on Methodological Standards in Pharmacoepidemiology. 2011. [A] • Dreyer NA, Schneeweiss S, McNeil BJ, et al. GRACE Principles: Recognizing high-quality observational studies in comparative effectiveness. *Am J Manag Care* 2010;16:467-471. [G] • Johnson ML, Crown W, Martin BC, Dormuth CR, Siebert U. Good research practices for comparative effectiveness research: analytic methods to improve causal inference from nonrandomized studies of treatment effects using secondary data sources: The International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Retrospective Database Analysis Task Force Report—Part III. *Value Health* 2009;12:1062-1073. [L] On the other hand, the peer-reviewed literature provides considerable guidance for the use of or testing the assumptions for valid IV analyses: • Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidemiol Drug Saf* 2010;19:537–554. • Chen Y, Briesacher BA. Use of instrumental variable in prescription drug research with observational data: a systematic review. *J Clin Epidemiol* 2011;64:687-700. • Glymour MM. Natural experiments and instrumental variable analyses in social epidemiology. In Methods in Social Epidemiology, Oakes JM, Kaufman JS (eds). John Wiley and Sons: San Francisco, CA, 2006;429-468. • Greenland S. An introduction to instrumental variables for epidemiologists. *Int J Epidemiol* 2000;29:722-729. • Grootendorst P. A review of instrumental variables estimation of treatment effects in the applied health sciences. *Health Serv Outcomes Res Methodol* 2007;10:159-179. • Hernán MA, Robins JM. Instruments for causal inference: an epidemiologist's dream? *Epidemiology* 2006;17:360-372. • Martens EP, Pestman WR, de Boer A, Belitser SV, Klungel OH. Instrumental variables: application and limitations. *Epidemiology*

		2006;17:260-267. • Newhouse JP, McClellan M. Econometrics in outcomes research: the use of instrumental variables. *Annu Rev Public Health* 1998;19:17-34.
MC Key Criteria: Rationale for and against adoption of the proposed standard	4. Contribution to Patient Centeredness	Patients require valid study results to make informed treatment decisions. Evidence that strengthens the validity of the analytic approach used to produce results can strengthen the confidence patients have in those results.
	5. Contribution to Scientific Rigor	Assessing the assumptions that underlie whether an IV is valid provides evidence of the methodologic rigor of an IV analysis beyond theoretical justifications and arguments of plausibility.
	6. Contribution to Transparency	Failure to provide empirical evidence that the chosen instrument meets the 3 properties of the IV ignores possible biases that may be associated with a weak or unsuitable IV.
	7. Empirical Evidence and Theoretical Basis	The potential biases associated with violating IV assumptions are well described: • Hernán MA, Robins JM. Instruments for causal inference: an epidemiologist's dream? *Epidemiology* 2006;17:360-372. • Crown WH, Henk HJ, Vanness DJ. Some cautions on the use of instrumental variables estimators in outcomes research: how bias in instrumental variables estimators is affected by instrument strength, instrument contamination, and sample size. *Value Health* 2011;14:1078-1084.
Additional considerations	8. Degree of Implementation Issues	The lack of information on unmeasured characteristics and on the importance of some unmeasured characteristics does not allow for explicit confirmation of IV assumptions. However, efforts to evaluate the IV using measured covariates can strengthen the evidence for the IV's appropriateness.
	9. Other Considerations	Justifying the need for an IV analytic approach (i.e., strong unmeasured confounding) and the theoretical rationale for why the proposed measured covariate is a suitable IV are crucial to causal inference, particularly since the tenability of the assumptions can never be fully empirically verified. Evaluating the IV-outcome association conditional on exposure is not generally advised. See: Hernán MA, Robins JM. Instruments for causal inference: an epidemiologist's dream? *Epidemiology* 2006;17:360-372.