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# Consensus of recommendations guiding comparative effectiveness research methods

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**Consensus of recommendations guiding comparative effectiveness research  
methods**

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## **5 Key Points**

- A systematic literature review identified nine CER methods guidance documents.
- These documents present more than three hundred individual methods recommendations, covering topics such as study design, bias, and statistical analysis.
- Categories of shared methods recommendations were assembled which embodies a consensus of recommendations for CER methods.
- All nine documents recommended transparency and adaptation for relevant stakeholders in the interpretation and dissemination of results.
- Other shared recommendations identified in at least seven documents included transparent operational definitions allowing for replication, assessment of data and study measure validity, inclusion of clinically meaningful and objectively measured outcomes, and focusing on gap in knowledge that are relevant for decision-makers.

## **Conflicts of Interest and Disclosures**

This manuscript was reviewed and endorsed by the International Society for Pharmacoepidemiology Comparative Effectiveness Research Special Interest Group.

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## **Abstract**

**Purpose:** Due to an increasing demand for quality comparative effectiveness research (CER), methods guidance documents have been published, such as those from the Agency for Healthcare Research and Quality (AHRQ) and the Patient-Centered Outcomes Research Institute (PCORI). Our objective was to identify CER methods guidance documents and compare them to produce a summary of important recommendations which could serve as a consensus of CER method recommendations.

**Methods:** We conducted a systematic literature review to identify CER methods guidance documents published through 2014. Identified documents were analyzed for methods guidance recommendations. Individual recommendations were categorized to determine the degree of overlap.

**Results:** We identified nine methods guidance documents, which contained a total of 312 recommendations, 97% of which were present in two or more documents. All nine documents recommended transparency and adaptation for relevant stakeholders in the interpretation and dissemination of results. Other frequently shared CER methods recommendations included: study design and operational definitions should be developed a priori and allow for replication (n=8 documents); focus on areas with gaps in current clinical knowledge that are relevant to decision-makers (n=7); validity of measures, instruments, and data should be assessed and discussed (n=7); outcomes, including benefits and harms, should be clinically meaningful, and objectively measured (n=7). Assessment for and strategies to minimize bias (n=6 documents), confounding (n=6), and heterogeneity (n=4) were also commonly shared recommendations between documents.

**Conclusions:** We offer a field-consensus guide based on nine CER methods guidance documents that will aid researchers in designing CER studies and applying CER methods.

## **Introduction**

As a result of an ever-increasing number of treatment options, real-world evidence is needed to inform clinical decision-making. Consequently, the demand for high-quality comparative effectiveness research (CER) has increased over the past several years. The Institute of Medicine has defined CER as, “the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care”.<sup>1</sup> Inherent in this definition is the head-to-head comparison of treatment approaches used in clinical practice to provide information on which treatments work best, for whom, and in which situations. To comparatively evaluate treatments, a wide range of methods and various study designs, including randomized controlled trials and observational studies, are utilized.

In response to a number of recent CER funding initiatives based in the United States, under the 2009 American Recovery and Reinvestment Act and the 2010 Patient Protection and Affordable Care Act, which established the Patient-Centered Outcomes Research Institute (PCORI), several methods guidance documents have been developed recently.<sup>2-5</sup> Despite the utility of such guides, it remains unclear which documents should be followed and under which circumstances, as consensus between the guidance documents has not been determined. To this end, this review sought to identify CER methods guidance documents, and then identify areas of agreement among CER methods recommendations to create a consensus document that may assist in the design and conduct of high-quality CER, including observational studies and randomized clinical trials (RCTs).

## **Methods**

A literature search was conducted in February 2015 by two independent reviewers (JM, RM) to identify CER methods guides that included specific methodological recommendations for the design and conduct of CER. To identify published, peer-reviewed literature, Pubmed's Medical Subject Heading (MeSH) system and the query "comparative effectiveness research/methods" was used.<sup>6</sup> To find documents that were not published in the peer-reviewed literature, such as industry reports and white papers, grey literature search methods were employed.<sup>7-9</sup> Specifically, we used the query "comparative effectiveness research" in Google and Google Scholar. Websites of organizations involved in CER, including the Agency for Healthcare Research and Quality (AHRQ), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), PCORI, Food and Drug Administration, Health Canada, and National Institute for Health, were also searched. While CER is a newer term to describe an existing discipline that has carried various names, the focus of our search for methods guidelines was specific to this term that was popularized by the American Reinvestment and Recovery Act.

A search result title was assessed for relevance to CER methods by the inclusion of specific words, including "methods," "methodology," "standards," "conducting," "guidelines," and "practices". Subsequently, the abstracts from the results with relevant titles were reviewed. The following information was collected from each abstract: author(s), year of publication, and affiliations. Each abstract was categorized as a CER overview, a presentation of specific analytic methods, or a study of a specific therapeutic topic. Only full-text documents categorized as a CER overview were obtained and analyzed for potential inclusion as a CER methods guidance document. Any document not consisting of a set of formal recommendations on CER methods, or those related to meta-analyses or systematic reviews, were excluded. Guidance documents released as



part of a series or an update were included together as a single guide. Documents published through December 2014 were included in our review.

All recommendations regarding CER methods were extracted from each guidance document by two independent reviewers (JM, RM). The content of each statement was assessed to determine whether the statement provided guidance for conducting CER, and therefore should be considered a CER recommendation. Statements not meeting this criterion were excluded. The list of included recommendations were agreed upon by both reviewers and an additional author (AC).

## **Results**

We reviewed 1,819 Pubmed search results and 360 grey literature results, and identified 248 documents with titles relevant to CER methods. Documents related to a specific therapeutic area (Pubmed n=32, 19.9%; grey n=7, 8.1%) or a specific methodology (Pubmed n=64, 39.8%; grey n=34, 39.1%) were excluded, while CER overviews (Pubmed n=65, 40.4%; grey n=46, 52.9%) were reviewed for inclusion. From this pool of CER overviews, nine CER methods guidance documents were identified, of which five were already known to the authors (Figure 1, Table 1). These nine documents were published between 2009 and 2014. Organizations authored seven of the nine documents, and individual authors wrote the remaining two.

Following the exclusion of statements not meeting the criterion of a CER methods recommendation and splitting statements with multiple recommendations into individual recommendations, there were 312 recommendations. After reviewing all recommendations, 15 categories of shared recommendations were created by two of the authors (JM, AC). All recommendations were then reviewed and placed in a corresponding category or categories, as some recommendations fell in to more than one category. The number of documents with recommendations in each of the

categories were totaled. Specific recommendations within categories of shared recommendations were reviewed in greater detail to identify common themes which were also summed between documents. While the categorization of the recommendations was completed by two authors (JM, AC), all of the authors reviewed and approved these categorizations. Recommendations that did not correspond with any of the 15 categories were considered non-shared recommendations.

Only one shared recommendation category was identified across all nine CER documents, suggesting that the interpretation and dissemination of CER study results should be transparent and adapted for relevant stakeholders (Table 2). Other frequently shared CER methods recommendations included: study design and operational definitions developed a priori and transparent enough to allow for replication (n=8 documents, 89%); focus on areas with gaps in current clinical knowledge that are relevant to decision-makers (n=7, 78%); assess and discuss validity of measures, instruments, and data, including data collection (n=7, 78%); outcomes, including benefits and harms, should be clinically meaningful, and objectively measured (n=7, 78%); appropriateness of exposures and interventions should be assessed and described (n=6, 67%).

Assessment for and strategies to minimize bias (n=6 documents), confounding (n=6), and heterogeneity (n=4) were also commonly shared recommendations between documents. Other shared recommendations supported rigorous literature review to guide study design and planning (n=6, 67%), use of sensitivity analyses (n=5, 56%), involving relevant stakeholders (n=5, 56%), use of appropriate statistical techniques (n=5, 56%), following ethical requirements (n=4, 44%), and improving health care value (n=2, 22%). There were nine individual non-shared recommendations (3% of all recommendations) in five of the nine documents which did not fall in to one of the shared recommendation categories, including protection of the independence of peer review<sup>5</sup>,

time and costs considerations as secondary objectives are defined<sup>10</sup>, and separation of feasibility studies from the main study results.<sup>10</sup>

## **Discussion**

This study provides a synthesis of CER methods guidance documents for the purpose of informing decisions on the development and conduct of quality CER research. This consensus document identifies the most commonly shared expectations of quality CER from an interdisciplinary standpoint, incorporating recommendations from experts in academia, industry, professional societies, and regulatory agencies. Our study identified nine documents with over 300 recommendations for designing and conducting CER. We were able to identify the most frequently shared recommendations which can serve as a summary resource for researchers as they design and implement CER studies.

The documents had varying approaches to recommending specific CER methods. For instance, the Patient-Centered Outcomes Research Institute (PCORI), Agency for Healthcare Research and Quality (AHRQ), and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) present detailed methodological guidance, organized by topic area, which can serve as a how-to guide for researchers attempting to design and conduct CER.<sup>4, 5, 10</sup> In contrast, the American Medical Association (AMA) and American Heart Association (AHA) documents provide less information about study design and analysis and more about health policy, research dissemination, and general principles to guide researchers.<sup>11, 12</sup> Despite their varying perspectives, the documents are unified in their call for the development of CER methods standards. By compiling a list of frequently agreed upon CER methods recommendations, we have facilitated the application of these recommendations for developing CER research based on expert recommendations.

From our list of shared recommendations, it is apparent that some of the most important aspects of quality CER include adaptation of the interpretation and dissemination of study results for patients, providers, and payers; interpretation of study limitation in the context of the population studied; development of a priori study protocols; evaluation of missing data and measure validity; use of clinically meaningful endpoints; use of appropriate measures of exposure and statistical techniques, including sensitivity analyses; assessing and minimizing bias, including misclassification and immortal time bias, confounding, including residual confounding, and heterogeneity; and involvement of relevant stakeholders while following ethical requirements. While a study may adhere to sound CER methodology, the ability to assess the study's quality is severely limited if it does not report sufficient amounts of information. The results of our study support transparency in the protocol and manuscript development process. Furthermore, transparency in statistical analysis is stressed in CER, allowing for not only public critique of methodology, but also study reproducibility.

The synthesis of these nine documents demonstrated a large degree of overlap, as over 97% of individual recommendations were found in at least two documents. Though the documents themselves were not specifically reviewed for contradictions, no contradictions were noted in the extracted recommendations. Additionally, while individual documents may have primary areas of focus for conducting CER, the high degree of overlap suggests a general sense of agreement among the nine documents regarding the most important topics. Though a number of these topics are not exclusive to CER, and may be applied more broadly to pharmacoepidemiology and outcomes research, the emphasis placed on these recommendations by CER experts highlights their importance for CER, particularly when considering how CER contributes to clinical decision-making.<sup>13</sup>

It should be noted that our consensus guide, summarizing key CER methods

recommendations, may be useful in the development of detailed, high-quality, transparent CER that optimizes clinical applicability but does not replace the guidance provided by the individual documents identified. While the concept of consensus as a scientific theory has been controversial in the past, our goal was to present a summary of the overlap between the 312 recommendations from the nine CER methods guidance documents.<sup>14</sup> For specific guidance and additional CER resources, the reader is directed to the individual documents. Now that a consensus of recommendations has been identified, it will be important to identify whether consensus exists for how these recommendations should be implemented and accomplished.

While some recommendations extracted from the guides focus on the reporting of CER studies, they were interpreted as recommendations for the design and conduct for CER. For example, while reporting of limitations and confounders is not necessarily part of conducting research activities, it is an important step in promoting study transparency. With consistent transparency throughout the study process, study quality is improved. Furthermore, in the context of design, confounders and limitations should be considered a priori, so that approaches to minimize confounding and limitations can be implemented in the design phase.<sup>4, 5</sup> One such strategy includes sensitivity analyses, as “residual confounding should be assessed, and approaches to estimating its effect, including sensitivity analyses, should be included.”<sup>4, 15</sup> The utility of sensitivity analyses is also supported by a recent study which identified sensitivity analyses as the single best predictor of quality for studies published in higher-impact journals.<sup>16</sup> The effect of missing data as a potential limitation must also be assessed thoroughly.<sup>4, 15, 17</sup>

The goal of this project was to identify areas of agreement among CER methods recommendations to assist in the design and conduct of high-quality CER. Many of the recommendations were focused specifically on observational research, rather than RCTs. This focus may be a result of the existing clinical trial methods guidance

documents, including guidance from the Food and Drug Administration on Good Clinical Practice and Clinical Trials and the Pragmatic-Explanatory Continuum Indicator Summary ([PRECIS](#)).<sup>18, 19</sup> Several other documents that may be useful in the design and conduct of CER are those specifically focused on reporting of research results, including the Strengthening the Reporting of Observational Studies in Epidemiology ([STROBE](#)) Statement, the [GRACE Checklist](#), and the Consolidated Standards of Reporting Trials ([CONSORT](#)) Statement and Checklist.<sup>20-22</sup> STROBE and GRACE promote dissemination of quality observational study results, while CONSORT provides guidance specific to RCT reporting in order to assess study validity.<sup>20-22</sup> While the aforementioned documents were not included in our analysis as they were either not specific to CER or focused on reporting rather than the design and conduct of CER, they are important resources, particularly for the reporting of and assessment of CER quality. Lastly, it is also necessary to acknowledge international efforts to improve the utilization of effectiveness research methods in clinical decision-making, including the [GetReal project](#) conducted by the Innovative Medicines Initiative (IMI) and the European Medicines Agency's (EMA) Draft [guidance for Post-Authorization Efficacy Studies \(PAES\)](#).<sup>23,24</sup>

There were several limitations in the development of our consensus document. Firstly, selection of the documents utilized in our study was based upon specific search criteria. Thus, while our search returned an expansive list of articles for review, those documents that did not show up based on our search terminology were not included, such as the [Guidelines for Good Pharmacoepidemiology Practices](#).<sup>25</sup> We used specific and reproducible criteria for searching the published literature, however, most of the guidance documents were identified from the grey literature search. Second, it should be noted that the documents reviewed for consensus were the most up-to-date revisions at the time the literature search was conducted. As such, guidance documents regularly updated may have more recent versions, including the [ENCePP Guide on](#)

[Methodological Standards in Pharmacoepidemiology \(Revision 4\)](#).<sup>26</sup> Lastly, the extraction and categorization of shared recommendations was subject to the interpretation of two independent reviewers. In cases of disagreement regarding the extraction or categorization of specific recommendations within a shared recommendation category, a third independent reviewer was used for the final determination. We also mitigated this limitation by having all authors review and approve the categorization of all recommendations.

## **Conclusion**

We conducted a systematic literature review to develop a single guide of recommended CER methods, and identified nine CER methods guidance documents. The shared recommendations identified from this literature review emphasized adequate and transparent CER study planning and development using validated data, appropriate exposure measures, clinically meaningful and objectively measured outcomes, and statistical techniques which minimize bias and confounding. Further, CER should focus on areas that are relevant for decision-makers and adapt the interpretation and dissemination of results for key stakeholders. This overview of synthesized guidance may aid researchers and decision-makers in conducting and implementing quality comparative effectiveness research.

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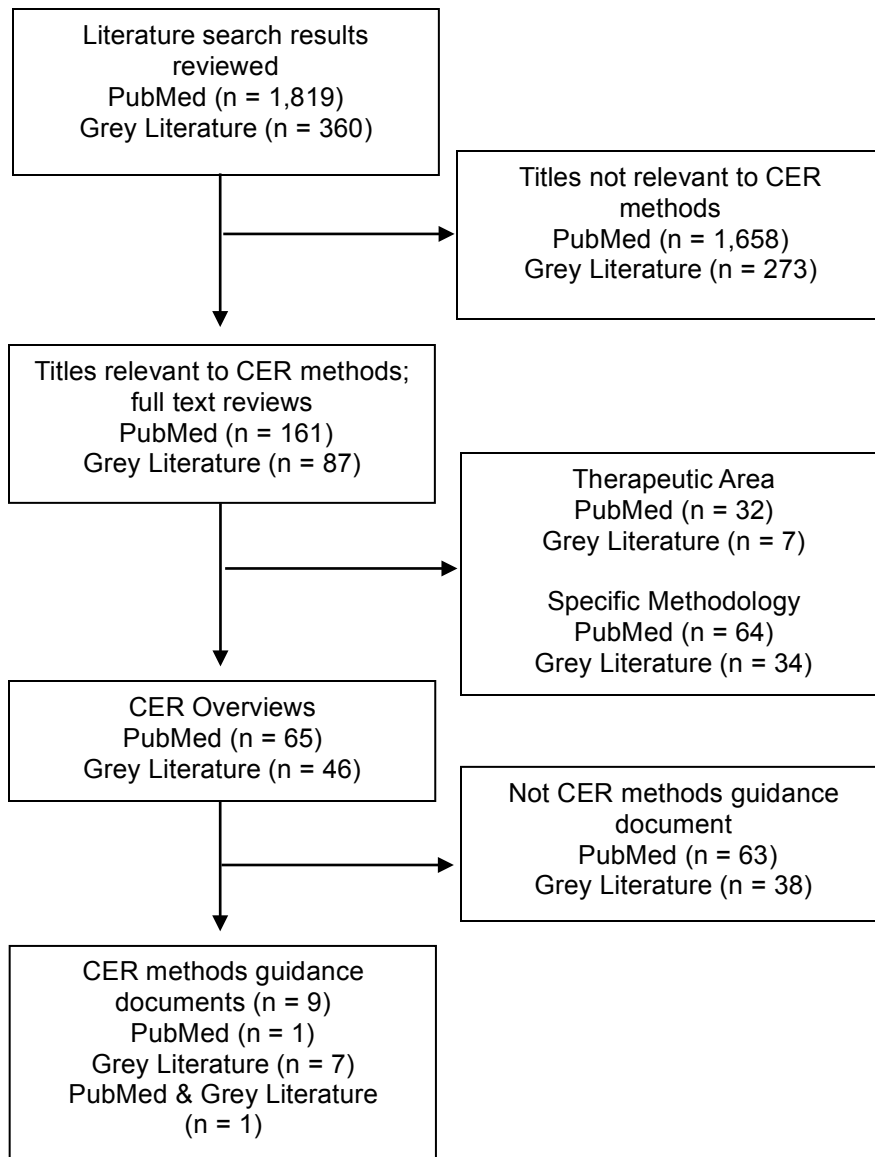


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**Figure 1. Methods guidance document inclusion**



**Table 1. CER methods guidance documents**

Document number	Document title	Authors	Year	Affiliation	Methods recommendations (N)	Document source
1	<a href="#">The American Heart Association's Principles for Comparative Effectiveness Research</a> <sup>12</sup>	Gibbons et al.	2009	AHA	10	Grey Literature
2	Good Research Practices for Comparative Effectiveness Research – Parts I,II,III <sup>15, 27, 28</sup>	Berger et al. Cox et al. Johnson et al.	2009	ISPOR	32	Pubmed, Grey Literature
3	<a href="#">American Medical Association Principles for Comparative Effectiveness Research</a> <sup>11</sup>	AMA	2011	AMA	11	Grey Literature
4	<a href="#">Ten Commandments" for Conducting Comparative Effectiveness Research Using "Real-World Data"</a> <sup>17</sup>	Willke RJ, Mullins D	2011	Pfizer, University of Maryland	13	Pubmed
5	<a href="#">Principles for Planning and Conducting Comparative Effectiveness Research</a> <sup>29</sup>	Luce et al.	2012	Various	13	Grey Literature
6	<a href="#">PCORI Methodology Standards / PCORI Methodology Report</a> <sup>5</sup>	PCORI	2013	PCORI	31	Grey Literature
7	<a href="#">Developing a Protocol for Observational Comparative Effectiveness Research</a> <sup>4</sup>	Velentgas et al.	2013	AHRQ	133	Grey Literature
8	<a href="#">Guide on Methodological Standards in Pharmacoepidemiology (Revision 3)</a> <sup>10</sup>	ENCePP	2014	ENCePP	43	Grey Literature
9	<a href="#">GRACE Principles</a> <sup>21</sup>	Dreyer et al.	2014	GRACE	26	Grey Literature

AHA, American Heart Association; AHRQ, Agency for Healthcare and Research Quality;

AMA, American Medical Association; ENCePP, European Network of Centres for

Pharmacoepidemiology and Pharmacovigilance; GRACE, Good Research for

Comparative Effectiveness; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; PCORI, Patient-Centered Outcomes Research Institute

**Table 2. Categories of shared CER methods recommendations**

<b>Shared CER Methods Recommendations</b>	<b>Document Numbers*</b>	<b>N (%)**</b>
<b>Interpretation and dissemination of CER study results should be transparent and adapted for relevant stakeholders</b>	<b>1-9</b>	<b>9 (100)</b>
Interpret results in the context of the population studied		5 (56)
Adapt presentation of results for different stakeholders		4 (44)
Interpret results in the context of limitations		2 (22)
<b>CER study design and operational definitions should be developed a priori and be transparent to allow for replication</b>	<b>1-4, 6-9</b>	<b>8 (89)</b>
Operational definitions should be included in the study protocol and deviation from protocol definitions should be described		5 (56)
Present sufficient information to allow for replication		2 (22)
<b>CER should focus on areas with gaps in current clinical knowledge that are relevant to decision-makers</b>	<b>1, 3-8</b>	<b>7 (78)</b>
<b>Validity of measures, instruments, and data, including data collection methods, should be assessed and discussed</b>	<b>2, 4-9</b>	<b>7 (78)</b>
Evaluate data validity		5 (56)
Evaluate missing data		4 (44)
<b>Outcomes, including benefits and harms, should be clinically meaningful, objectively measured, and transparently reported</b>	<b>1, 4-9</b>	<b>7 (78)</b>
Outcomes should be clinically meaningful		4 (44)
Outcomes should be objectively measured		2 (22)
Outcomes should be patient-centered		2 (22)
<b>Exposures and interventions should be adequately described and assessed for appropriateness</b>	<b>2, 5-9</b>	<b>6 (67)</b>
Incident user design should be utilized if possible		2 (22)
<b>Assess for and implement strategies to minimize bias</b>	<b>2, 4-5, 7-9</b>	<b>6 (67)</b>
Minimize misclassification bias		4 (44)
Studies should be free of immortal time bias		3 (33)
<b>Assess for and implement strategies to mitigate confounding</b>	<b>2, 4, 6-9</b>	<b>6 (67)</b>
Assess for unmeasured, missing, or residual confounders		4 (44)
<b>Rigorous review of the literature should be performed to guide CER study design and planning</b>	<b>1-3, 5, 7-8</b>	<b>6 (67)</b>
Review all relevant treatment approaches, including new treatments		4 (44)
<b>Consider sensitivity analyses, including changes in the exposure, outcome, confounder, or covariate definitions or classifications</b>	<b>2, 6-9</b>	<b>5 (56)</b>
<b>Relevant stakeholders should be involved in the planning and conduct of CER</b>	<b>3, 5-8</b>	<b>5 (56)</b>
<b>Utilize appropriate statistical techniques, defined a priori in a statistical analysis plan, according to study design and endpoints</b>	<b>2, 4, 6-8</b>	<b>5 (56)</b>
Develop a comprehensive statistical analysis plan prior to study initiation		3 (33)
Present statistical assumptions		3 (33)
Describe the statistical modelling approach		3 (33)
<b>CER should follow ethical requirements and conflicts of interest should be fully disclosed</b>	<b>3-4, 7-8</b>	<b>4 (44)</b>
<b>Assess for and report heterogeneity</b>	<b>4, 6-8</b>	<b>4 (44)</b>
<b>CER should focus on improving health care value</b>	<b>1, 3</b>	<b>2 (22)</b>

\*Column values correspond to document number in Table 1.

\*\* N (%) of guidance documents which include the specific recommendation.