

Comparative-Effectiveness Research: New Progress in Assessing the Evidence in Today's Health Care Marketplace

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KEY POINTS . . .

The recognition of comparative-effectiveness research (CER) as a discipline has expanded rapidly in the last decade because of increased focus and funding from the US federal government.

Despite this increased visibility, utilization of CER findings has been limited, due in part to concerns about interpretation and reliability of CER results.

The CER Collaborative Initiative—a joint effort by ISPOR, AMCP, and NPC—is providing key guidance for advancing appropriate use of CER to improve patient health outcomes, including a free web-based, user-friendly toolkit for assessing CER studies.

Assessing the Evidence
for Health Care Decision Makers

Background

While the practice of comparing treatment outcomes can be traced to ancient times, the development of comparative-effectiveness research (CER) as a scientific discipline is a relatively recent phenomenon. In the United States, CER has a pedigree based in health technology assessment, stemming from early efforts by the US Office of Technology Assessment to justify the use of expensive new medical technologies [1].

While definitions may vary based on stakeholder and purpose, the United States National Institutes of Health refers to CER as “the conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat and monitor health conditions. The purpose of this research is to inform patients, providers, and decision makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances.” [2]

Although CER may be conducted using a wide variety of study types, four common types (excluding randomized studies such as pragmatic clinical trials) include 1) prospective observational studies; 2) retrospective observational studies (administrative claims or electronic records); 3) modeling studies; and 4) network meta-analysis or indirect treatment comparison studies (when two or more treatments have not been compared, but each has a common comparator and are compared indirectly using study-level data). For any given intervention, the results of studies using these non-randomized approaches can often augment the data generated by

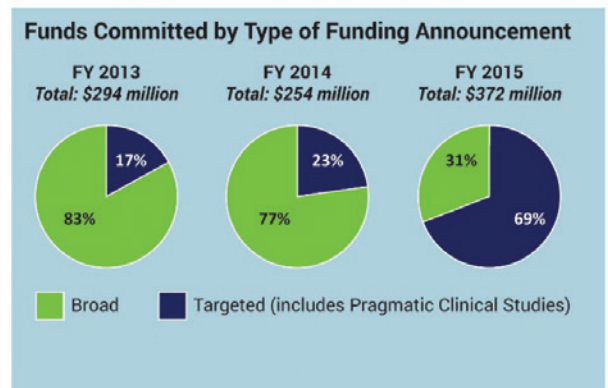
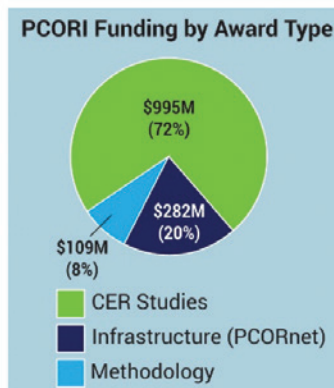
randomized controlled trials (RCTs). Such non-randomized CER data may be used by payers, providers, and patients as they seek to answer the three cardinal questions of evidence-based medicine, as put forth by Archie Cochrane, the pioneer British clinical epidemiologist: Can it work? (efficacy); Does it work in practice? (effectiveness); and, Is it worth it? (value) [3].

The Added Value of CER

One of the fundamental tenets of CER is that it moves beyond tests of *efficacy* (explanatory trials) that assess whether an intervention produces the expected result under ideal circumstances, and focuses instead on tests of *effectiveness* (pragmatic trials or non-randomized study types) that measure the degree of beneficial effect under “real-world” clinical settings [4].

Optimally, CER adds real-world decision-making value at both the *micro* level—selecting the best treatment for a specific patient based on his or her genetic characteristics, disease state, age, comorbid conditions, etc.—and at the *macro* level—selecting the best treatments for a population based on demonstrated efficacy, effectiveness, and value.

The results of well-designed CER studies provide value to decision makers throughout the international community, but are particularly important to those in the United States, where regulatory approval for new-molecule pharmaceutical products is typically based primarily or exclusively on RCTs using placebo-controlled or non-inferiority study designs. And while retrospective types of CER studies are



regularly conducted by non-governmental establishments (such as pharmaceutical manufacturers, managed care organizations, and other private-sector groups), prospective observational CER studies (often seen as more credible than retrospective studies due to fit-for-purpose study design and higher data quality, and are generally much more expensive) are somewhat limited in number and scope. In large part, the primary responsibility for sponsoring large-scale prospective CER studies falls to the federal government [5].

Indeed, CER gained prominence in the United States when the American Recovery and Reinvestment Act of 2009 (ARRA) provided \$1.1 billion to the Agency for Healthcare Research and Quality (AHRQ), the National Institutes of Health (NIH), and the Secretary of the Department of Health and Human Services (HHS) to support the development and dissemination of evidence on CER. Additionally, the health reform bill signed by President Obama in March 2010 created a new public-private agency named the Patient-Centered Outcomes Research Institute (PCORI), charged with supporting and overseeing the conduct of CER.

Since it began funding research in 2012, PCORI has awarded more than \$1.38 billion for research and related projects. Roughly \$995 million—72% of the total—has gone to 300+ patient-centered CER studies [6] (Figure 1). Moreover, PCORI-funded CER has evolved in recent years to include mostly targeted studies focused on interventions for conditions that place a particularly high burden on patients, families, and the health care system (Figure 2). These include studies of old and new drugs, medical procedures, and other approaches to prevention, diagnosis, and treatment [6].

Assessing the Evidence

However, the need for CER evidence for health care decision making far exceeds the ability of PCORI or any other institution to fund randomized studies or even prospective observational studies. The much less expensive and time-consuming types of CER studies (e.g., retrospective database studies, modeling studies, and indirect treatment comparisons and network meta-analyses) can still provide useful CER evidence given careful study design, appropriate analytic methods, and transparent reporting. Although publication in a peer-reviewed journal is an important “filter” for study quality, journal and review quality does vary, and the study hypotheses tested in the publication may or may not precisely match the decision that needs to be made. Thus, it is still incumbent on those who want to use the CER evidence to decide on the applicability of that evidence for their particular purposes.

Unfortunately, there are a limited number of accepted principles for the interpretation of observational CER studies for drug formulary and health care decisions. This deficit has been shown to blunt the uptake of such studies by formulary decision makers. For example, Jennifer Graff, PharmD, Vice President of CER for the National Pharmaceutical Council, notes that in formulary decision making “only about 1 in 3 plans were consistently using observational research, and most didn’t have a process to assess the quality of these studies.” [7]

A consensus-based set of principles, combined with educational training and tools, would promote the development, application, and interpretation of appropriate evidence for health care technology and enhance the formulary decision-making process.

As member-based organizations representing the leadership in managed care pharmacy, the research community, and the pharmaceutical industry, ISPOR (International Society for Pharmacoeconomics and Outcomes Research), AMCP (Academy of Managed Care Pharmacy), and NPC (National Pharmaceutical Council) are uniquely positioned to collaborate in advancing the understanding, interpretation, and appropriate use of CER results in a wide variety of payer coverage and formulary decisions.

The CER Collaborative Initiative

In view of their complementary expertise and skill sets, ISPOR, AMCP, and NPC recently joined forces to establish the Comparative Effectiveness Research Collaborative Initiative (CER-CI) for advancing appropriate use of CER to improve patient health outcomes. Each of the three collaborating organizations has a webpage dedicated to CER resources and to the Initiative:

- AMCP: <http://amcp.org/CER/>
- ISPOR: <http://www.ispor.org/askforcesnterpretingorsforhcddecisionmakerstfx.asp>
- NPC: <http://www.npcnow.org/issue/cer-collaborative-initiative>

Goals and Objectives

The goal of the CER Collaborative Initiative is to provide greater uniformity and transparency in the use and evaluation of outcomes research information for coverage and health care decision making by providing user-friendly resources to help decision makers navigate through the various types of study methods used to generate outcomes research information for evidence-based health care decision making.

One of the key goals of the Collaborative was to develop a compendium of papers on “Interpreting Outcomes Research Studies for Health Care Decisions” for the four types of CER studies described above: 1) prospective observational studies, 2) retrospective observational database studies, 3) modeling studies and 4) indirect treatment comparison studies. These interactive questionnaires help decision makers determine whether a given study is: a) relevant to the setting/decision in question, and b) credible enough to include in the overall body of evidence. These papers were completed and published in 2014:

A Questionnaire to Assess the Relevance and Credibility of Observational Studies to Inform Health Care Decision Making Good Practice Task Force Report (a single questionnaire is provided for evaluating both prospective and retrospective observational studies)

Berger ML, Martin BC, Husereau D, et al. Questionnaire to assess the relevance and credibility of observational studies to inform health care decision making: An ISPOR-AMCP-NPC good practice task force report. *Value Health* 2014;17:143-156. (www.ispor.org/observational-health-study-use-guideline.pdf).

Questionnaire to Assess Relevance and Credibility of Modeling Studies for Informing Health Care Decision Making Good Practice Task Force Report

Caro JJ, Eddy DM, Kan H, et al. A modeling study questionnaire to assess study relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health* 2014;17:174-182. (www.ispor.org/modeling-health-study-use-guideline.pdf).

Indirect Treatment Comparison/Network Meta-Analysis Study Questionnaire to Assess Relevance and Credibility to Inform Health Care Decision Making Good Practice Task Force Report

Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: An ISPOR-AMCP-NPC good practice task force Report. *Value Health* 2014;17:157-173. (www.ispor.org/indirect-treatment-study-use-guideline.pdf).

Online Tools

An end product and main goal of the entire initiative is to develop an electronic user-friendly toolkit for assessing the body of evidence by decision makers: “Assessing the Evidence for Health Care Decision Makers.” The first phase of this work—to create and publish an online interactive tool that enables users to assess the relevance and credibility of individual CER studies—is complete, as detailed below.

“Assessing the Evidence for Health Care Decision Makers”

is a set of public online interactive questionnaires based on the three published questionnaires cited above, and can similarly be used to systematically evaluate modeling, observational, and network meta-analysis/indirect treatment comparison studies (Figure 3). These online questionnaires facilitate greater uniformity and transparency in the evaluation and use of evidence for coverage and health care decision making with the ultimate goal of improving patient outcomes.

The “Assessing the Evidence” tool serves three key purposes:

1. It is a guide to determine whether a study is relevant to the setting and credible enough to include in the formulary decision-making process:

- ✓ Prompts users on what they need to look for in a study
- ✓ Flags fatal flaws that undermine the study’s credibility
- ✓ Prioritizes essential items that are pertinent to the study’s credibility (includes helper questions)
- ✓ Provides instant feedback during the assessment process

2. It is an educational platform to improve users’ study assessment skills

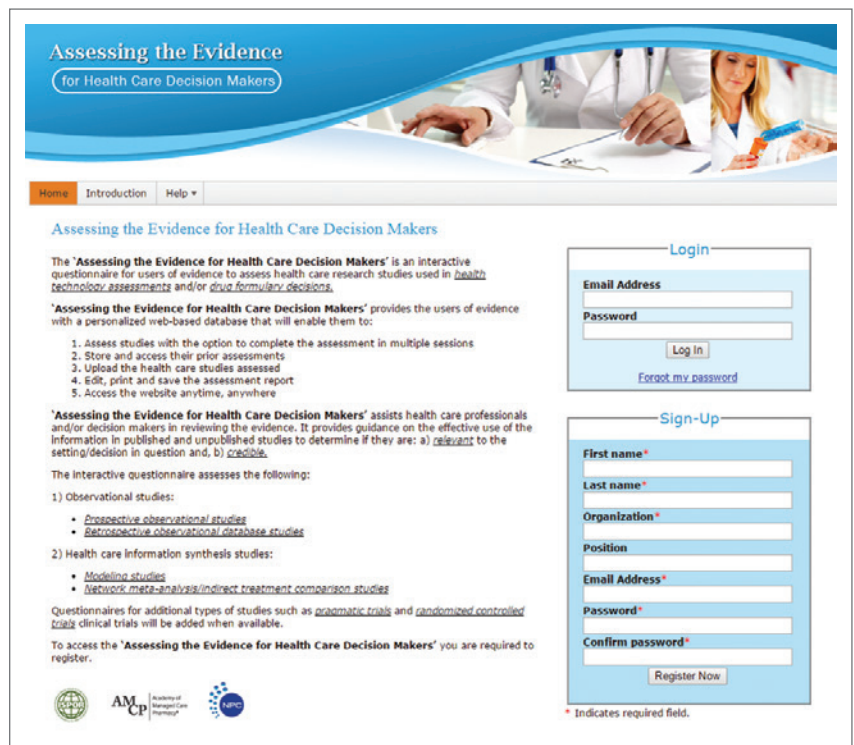
- ✓ Direct links to explanation of terminology and concepts
- ✓ Glossary of terms

3. It provides user-friendly features that allow users to:

- ✓ Build a personal library of assessment reports and uploaded papers
- ✓ Edit, print, and export those personal reports to Excel
- ✓ Access the personal library of work from any internet-connected device
- ✓ Follow step-by-step instructions

Interactive Learning

The interactive website—“Assessing the Evidence for Health Care Decision Makers”—may be accessed at <https://www.healthstudyassessment.org/>. Please note that users of the “Assessing the Evidence” tool must register, thus providing each user with a private, personalized, password-protected web-based database in which to store their assessments and access them from anywhere at any time.



Each questionnaire includes two main sections: a) relevance, and b) credibility (Figure 4). Credibility is further divided into several domains. Upon completing the questionnaire, the user will be able to make a more substantiated judgment regarding the relevance and credibility of a study to inform a decision. No summary score is provided for the overall questionnaire or for the domains of the credibility section. This was an explicit choice in the design of these questionnaires, since individuals may place greater or lesser weight on the response to any individual question. However, some credibility-focused questions are considered critical; a negative answer to these questions suggests the presence of a “fatal flaw.” It is up to each user to decide how these answers affect the overall credibility of each study.

Finally, the Collaborative set a goal to develop educational modules for health care coverage decision makers on how to use the assessment toolkit for decision makers. These have been produced for the “Accessing the Evidence” tool and are available for public use:

1. Study assessment tool for observational studies.

Presenters: Marc Berger, MD, Pfizer, New York, NY, USA, and Bradley Martin, PharmD, PhD, RPh, University of Arkansas for Medical Sciences College of Pharmacy, Little Rock, AR, USA. <http://www.ispor.org/education/webinars/AssessmentTool-ObservationalStudies.aspx>

2. Study assessment tool for modeling studies. Presenter: J. Jaime Caro, MDCM, FRCPC, McGill University, Montreal QC, Canada, and Chief Scientist, Evidera, Lexington, MA USA. <http://www.ispor.org/education/webinars/AssessmentTool-Modeling.aspx>

3. Study assessment tool for network meta-analysis studies. Presenter: Jeroen Jensen, PhD, Redwood Outcomes, San Francisco, CA, USA. <http://www.ispor.org/education/webinars/AssessmentTool-NetworkMeta-Analysis.aspx>

In addition to these primary benefits, it is likely that the work of the CER Collaborative Initiative will also aid those who design and conduct CER studies—many of whom are ISPOR members—as they seek to understand how decision makers will evaluate their research. By participating in the educational and training opportunities provided by the CER-CI, researchers will be aware of the measures end users will employ to determine a study's value, accessibility, and quality.

Indeed, several groups have cited or adopted the CER-CI approach over recent years. For example, the AMCP Format for Formulary Submissions 4.0 references the CER-CI tools to help decision-makers evaluate and use CER. Students participating in the AMCP Foundation Pharmacy and Therapeutics Competition utilize the CER-CI tools to assess the available evidence and develop formulary recommendations [8]. Finally, in 2017 the Food and Drug Administration cited the CER-CI approach when drug and device manufacturers share health care economic information with payors, formulary committees, and other entities [9].

Additional CER Tools and Educational Resources

A great volume of CER-related information is available today—far beyond what could be mentioned here. Nevertheless, we would like to note three additional resources that may have particular value for our readers:

1. The US National Library of Medicine has produced a library of dozens of **CER-related resources**: www.nlm.nih.gov/hsrinfo/cer.html. Resource categories:
 - Data, Tools, and Statistics
 - Grants, Funding, and Fellowships
 - Guidelines, Journals, Other (Publications/Videos)
 - Key Organizations/Programs
 - Legislation and Policy
 - Meetings/Conferences/Webinars: Upcoming Meetings and Conferences | Webcasts | Past Meetings/Conferences' Archives and Reports
2. The CIPS Knowledge Enterprise (part of the University of Maryland School of Pharmacy Team) has produced, in cooperation with the CER Collaborative Initiative, a **19 credit-hour CER certificate program** (in-person and online trainings): Comparative Effectiveness Research in Decision-Making: <https://www.pharmacists4knowledge.org/cips/CER>. As part of the offering, CIPS has provided a 12-minute free demo module: www.youtube.com/watch?v=sKQqym3XjeU&feature=youtu.be.
3. For several years AMCP has been offering **certificate training** at its Annual Meetings based on the CER Collaborative's work. For more information, see www.amcp.org/CERcertificate/.

Summary

A new era is dawning on the CER landscape. Expanded funding and oversight by the US federal government has led to an amplified awareness of this relatively new scientific discipline. Today, the data produced in prospective/retrospective observational studies, modeling studies, and indirect treatment comparison studies are increasingly important sources of information for clinical practice. Furthermore, the CER Collaborative Initiative—led by ISPOR, AMCP, and NPC—has

made significant strides in providing tools and training that should make these CER study results measurable and meaningful to health care decision makers within the United States and beyond.

In months and years to come, the ISPOR team looks forward to engaging with our stakeholders—payers, providers, patients, health technology developers and assessors, regulators, and others—to build on the progress we've made together in conducting and assessing CER that will help facilitate progressively better-informed health care decisions.

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