

Issue Brief:

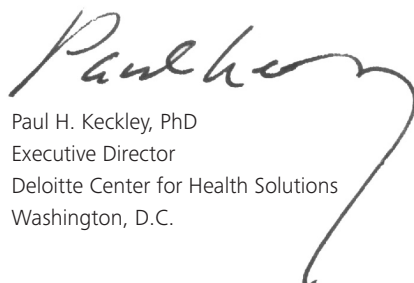
Comparative Effectiveness Research in the United States: *Update and implications*

Foreword

Comparative effectiveness research (CER) is widely discussed, not well understood, a threat to some, and a forceful change for all stakeholders in the U.S. health care system.

CER is not a new idea; many of the world's developed health care systems use a deliberative process to synthesize scientific studies and determine optimal courses of care. By contrast, the U.S. system of CER is fragmented; each health insurance plan, hospital, medical practice, and government program attempts its own research with variable results. Processes vary, results are inconsistent, and applications of CER advisories range from simple information to strictly constructed coverage guidelines.

This Issue Brief offers an update on current CER efforts in the U.S., and explores potential enablers that might facilitate its use as "tools, not rules" in transforming the U.S. health care system..



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Introduction

The rising costs of U.S. health care are unsustainable. In 2009, health care spending accounted for 17.6 percent of the Gross Domestic Product (GDP);¹ an aging population, volume-based reimbursement system, and advances in medical technologies are key drivers of health care spending in the U.S. Furthermore, the lack of quality evidence on the benefits of these technologies in diverse populations has contributed to widespread geographic variation in practice patterns, perpetuating system waste.²

The Affordable Care Act (ACA) of 2010 proposes numerous ways to extract greater value from the U.S. health care system. Among them are delivery system reforms (i.e., value-based purchasing, bundled payments, and reporting quality outcomes), health insurance exchanges, and transparency requirements.³ CER, defined 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 improve the delivery of care⁴, is another.⁵



Glossary: Key Terms

- **Evidence-based Medicine (EBM)** – “A set of principles and methods intended to ensure that, to the greatest extent possible, population-based policies and individual medical decisions are consistent with evidence of effectiveness and benefit.”¹¹
- **Comparative Effectiveness Research (CER)** – “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 improve the delivery of care. The purpose of the research is to help consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.”¹²
- **Clinical Effectiveness Research** – The generation of evidence through use of experimental methods to understand which treatment options are beneficial, for whom, and in what circumstances. CER is a type of clinical effectiveness research, and both are methods used in EBM.¹³
- **Effectiveness** – The outcome or result of applying a particular drug, medical treatment, or service in a particular group of patients;¹⁴ performance of a product under real-life conditions.¹⁵
- **Efficacy** – The ability of an intervention to produce the desired beneficial effect in expert hands and under ideal circumstances; the ability of a drug to produce the desired therapeutic effect.¹⁶
- **Systematic Reviews and Technology Assessments** – The synthesis of evidence gathered across multiple primary comparative or clinical effectiveness studies. Goal is to strengthen the evidence underlying treatment options through structured review of multiple studies.

One of the challenges confronting the U.S. health care system is delivering high-value, effective therapies that provide the best health outcomes.⁶ In a complex web of multiple payers, manufacturers seeking remuneration for R&D investments, and consumerism, this has become increasingly difficult.⁷ With unsustainable high costs of health care, now, more than ever, it is imperative to understand the real-world, incremental value of health technologies in differing patient populations; CER has been proposed as one way to achieve this goal.^{8,9}

CER has been on policy makers’ agenda for a number of years. The enactment of both The American Recovery and Reinvestment Act of 2009 (ARRA) and the ACA reignited the federal government’s interest in CER.¹⁰ Funding from ARRA provided the foundation for the ACA’s newly mandated and immediately effective CER entity, the Patient-Centered Outcomes Research Institute (PCORI). By sponsoring scientifically rigorous CER studies, PCORI will be responsible for assisting patients, clinicians, payers, and policy makers in making informed health care decisions by advancing the quality and relevance of evidence. The CER mandate in the ACA complements other value-seeking provisions of the U.S. health care reform strategy, all of which intend to profoundly impact the quality and value of the health care system. Following ARRA’s appropriation of \$1.1 billion to advance CER in the U.S., the Deloitte Center for Health Solutions in 2009 published an Issue Brief that examined the history of CER in the U.S. and reviewed examples of four national CER programs. This new Issue Brief revisits CER following the enactment of the ACA. It describes the legislative mandate for CER in the ACA, offers suggestions for U.S. policy makers based on lessons learned from international CER experiences, and shares implications for U.S. stakeholders as PCORI takes shape.

**U.S. comparative effectiveness research:
where are we now?**

Pre-Affordable Care Act

ARRA (2009)¹⁷ revitalized CER in the U.S., via a one-off investment of \$1.1 billion allocated to three agencies:

- \$300 million to the Agency for Healthcare Research and Quality (AHRQ)
- \$400 million to the Office of the Director of National Institutes of Health (NIH)
- \$400 million to the Secretary of the U.S. Department of Health and Human Services (HHS)

The ARRA funding was intended to stimulate CER and develop the data structures and systems necessary to support that research. Expenditures by the three agencies were directed towards three significant building blocks necessary to establish a national CER system that addressed clinical questions, integrated CER into clinical practice, and strengthened infrastructure.¹⁸

The AHRQ used its \$300 million on a variety of activities, including improving the agency’s planning process, supporting the development of strategies to incorporate research findings into clinical practice, and generating clinical comparative effectiveness (CE).¹⁹ The NIH committed most of its funding to specific projects that primarily address clinical questions, while HHS focused on strengthening the infrastructure to support CER.²⁰ Figure 1 summarizes how the agencies have spent their ARRA funding thus far.

Figure 1: Comparative Effectiveness Research activities supported by ARRA²¹

Agency	Funding allocated	Amount spent as of August 2010	Activities supported
Agency for Healthcare Research and Quality (AHRQ)	\$300 million	\$298.9 million	<ul style="list-style-type: none"> • Identified new research topics • Identified clinically useful evidence and gaps in evidence • Tested research findings in clinical practice • Disbursed \$10 million grants for large, pragmatic studies that focused on priority conditions • Invested in registries to collect patient information
National Institutes of Health (NIH)	\$400 million	\$330.0 million	<ul style="list-style-type: none"> • Awarded at least 165 “challenge grants” and “grand opportunity” grants addressing 88 of 100 priority research areas identified by the Institute of Medicine (IOM)
Office of the Secretary of Health and Human Services (HHS)	\$400 million	\$281.5 million	<ul style="list-style-type: none"> • Funded research support infrastructure, including collecting and disseminating data; translating results into clinical settings; monitoring and evaluating research activities; and supporting observational research on community-based care

In parallel, the Institute of Medicine (IOM) was allocated \$1.5 million to investigate and recommend national CER priorities. One hundred high-priority research topics were identified through extensive public consultations.²² To achieve a balanced portfolio of research topics that met both clinical and population health goals, selection criteria included:

- Condition-level criteria (e.g., burden of disease, cost, and variability)
- Topic-level criteria (e.g., appropriateness for CER, gaps in existing knowledge, and the likelihood that the results would improve health)²³

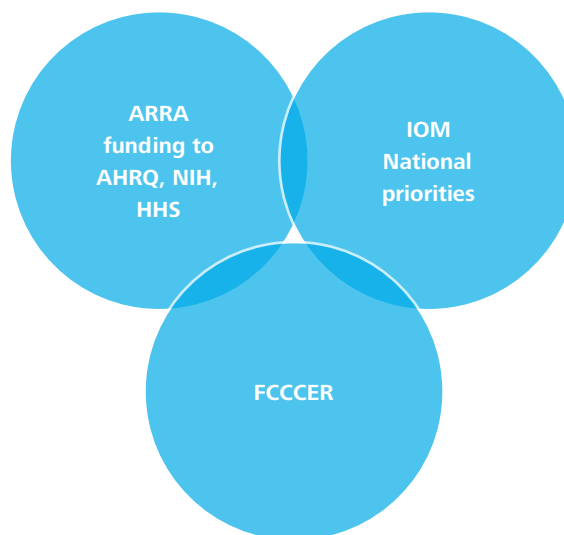
The NIH revisited its portfolio of sponsored projects and determined that 88 of the 100 IOM priorities had been included. NIH has since solicited applications to address the remaining topics; AHRQ has also sought applications that address the IOM priorities.²⁴

A 15-member Federal Coordinating Council for Comparative Effectiveness Research (FCCER), composed of senior representatives of several federal health agencies (e.g., U.S. Department of Veterans Affairs, AHRQ, the Centers for Medicare & Medicaid Services [CMS]), was created to coordinate research and guide investments.²⁵ One of FCCER's significant achievements was its development of a concise definition of CER, to be applied in the new health care reform law:

*"Comparative effectiveness research is the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in 'real world' settings. The purpose of this research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances."*²⁶

Collectively, the interactions of these organizations would set the stage for the most expansive CER effort in the U.S. to date (Figure 2).

Figure 2: Setting the scene for Comparative Effectiveness Research pre-ACA



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The Affordable Care Act

On March 23, 2010, President Obama signed into law the ACA.²⁷ The law established PCORI, a non-profit, non-government entity. Intended to be an independent, transparent body with a flexible and sustainable funding model, PCORI will oversee and set guidelines for CER, replacing the FCCCER established by ARRA. PCORI will be governed by a 21-member board representing a wide range of health sector stakeholders, including clinicians, drug and device manufacturers, payers, and consumers, as well as the Director of the AHRQ and the Director of the NIH, or their designees.²⁸ The board appointees were announced September 23, 2010.²⁹

PCORI will be financed through the newly created Patient-Centered Outcomes Research Trust Fund (PCORTF).³⁰ Initially, PCORTF will be funded through ACA appropriations: \$10 million in 2010, \$50 million in 2011, and \$150 million in 2012. From 2013 through 2019, the trust will be funded through an annual appropriation of \$150 million, which will be supplemented by fees imposed on Medicare and private health insurance companies.

PCORI will establish and carry out a research agenda, which will include systematic reviews and primary research.³¹ PCORI will contract with federal agencies and private sector organizations, with a preference given to AHRQ and NIH, to manage funding and conduct research.³²

Objectives for PCORI's first year in operation³³ include:

- **Objective 1:** conduct an environmental scan to help PCORI determine where it can add unique value and to help PCORI establish the national priorities
- **Objective 2:** develop the "Tier 1" planning grant process
- **Objective 3:** establish the PCORI national priorities
- **Objective 4:** develop the durable Core Research Agenda for patient-centered outcomes research
- **Objective 5:** identify and fund capacity-building research that will fill gaps in research methodology

A 15-member Methodology Committee appointed on January 21, 2011³⁴ will help PCORI develop and update methodological standards and guidance for clinical CER. PCORI also will establish an expert advisory panel on clinical trials and rare diseases to advise on the design, relative value, and feasibility of conducting studies in these areas.

Operationally, the ACA requires that PCORI meet specific requirements³⁵ intended to improve quality, increase transparency, and increase access to better health care. These include:

- **Access:** research must account for potential differences in effectiveness among subpopulations (e.g., genetic, geographic, racial, gender)
- **Quality:** PCORI has to establish a peer-review process for its primary research and publicly post the list of reviewers; it may use the peer-review process of a contracting entity or of appropriate medical journals
- **Transparency and Timeliness:** to ensure transparency, PCORI is mandated to establish comment windows of 45 to 60 days for:
 - PCORI's national priorities and research project agenda
 - The Methodology Committee's methodological standards
 - The peer-review process and draft findings of systematic reviews³⁶

Additionally, PCORI must make research findings public within 90 days. Limitations placed upon PCORI's operations include:

- The creation and use of cost-effectiveness thresholds are explicitly prohibited. This includes the quality-adjusted life year (QALY) or similar calculations.
- Reports and research findings may not be construed as mandates, practice guidelines, or policy recommendations.³⁷ The Secretary of HHS may use CE findings to inform payment or coverage decisions through an "iterative and transparent process;" however, the Secretary may not use findings to deny coverage.

To date, PCORI's Board of Governors has convened four times; most recently, it met May 16 and 17, 2011, in New York City. The Program Development, Methodology, Finance and Administration, and Public Affairs and Communications Committees presented to the board. The Program Development Committee (PDC) reported on its various initiatives that will help define a set of national priorities/research agenda for patient-centered outcomes research, including a landscape review of all ongoing CER projects. The PDC also received approval to explore creating a PCORI Patient Research Network to facilitate conducting CER across the country, using standardized metrics and methods. The Methodology Committee (MC) reported its plans to conduct a landscape review of existing standards for CER and create a "translation table" to summarize best research practices and identify gaps. The MC will be posting a working definition of patient-centered outcomes research on the PCORI website for public comment. The Finance and Administration Committee presented its estimated spend (\$19.3 million) for the current year. The board approved the Public Affairs and Communications Committee's requested name change to the "Communication, Outreach, and Engagement Committee." This committee also updated the board on planned activities to the public and stakeholders as well as announced the first executive director for PCORI, Joe V. Selby, MD, MPH.³⁸

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Vice Chair

- **Steven Lipstein, MHA**, President and Chief Executive Officer, BJC Health Care, a non-profit health care delivery system***

Executive Director

- **Joe V. Selby, MD, MPH**, former director of the Division of Research at Kaiser Permanente Northern California

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- **Lawrence Becker**, Director, Strategic Partnerships and Alliances, Xerox Corporation**
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- **Leah Hole-Curry, JD**, Program Director for the Health Technology Assessment (HTA) program, Washington State Health Care Authority*
- **Arnold Epstein, MD**, the John H. Foster Professor and Chair of the Department of Health Policy and Management at Harvard University School of Public Health, and practicing internist at Brigham and Women's Hospital**
- **Christine Goertz, DC, PhD**, Vice Chancellor for Research and Health Policy, Palmer College of Chiropractic and Palmer Center for Chiropractic Research***
- **Gail Hunt**, President and CEO of the National Alliance for Caregiving
- **Harlan Krumholz, MD**, Harold H. Hines, Jr. Professor of Medicine and Epidemiology and Public Health at Yale University School of Medicine*

Communication, Outreach, and Engagement Committee

- **Sharon Levine, MD**, Associate Executive Director for The Permanente Medical Group of Northern California, a large multi-specialty group practice within Kaiser Permanente's integrated delivery system***
- **Debra Barksdale, PhD, RN**, Associate Professor, University of North Carolina (UNC) at Chapel Hill School of Nursing*
- **Robert Jesse, MD, PhD**, Principal Deputy Under Secretary for Health and National Program Director for Cardiology, Department of Veterans Affairs
- **Grayson Norquist, MD, MSPH**, Professor and Chairman, Department of Psychiatry and Human Behavior, University of Mississippi Medical Center**
- **Ellen Sigal, PhD**, Chairperson and founder of Friends of Cancer Research, a cancer research think tank and advocacy organization***
- **Harlan Weisman, MD**, Chief Science and Technology Officer, Medical Devices and Diagnostics, for Johnson & Johnson***

*First term will expire in 2012

**First term will expire in 2014

***First term will expire in 2016

PCORI Methodology Committee

- **Naomi Aronson, PhD**, Executive Director, Blue Cross and Blue Shield Association Technology Evaluation Center
- **Ethan Basch, MD, MSc**, medical oncologist and health services researcher, Department of Medicine and Department of Epidemiology, Memorial Sloan-Kettering Cancer Center
- **Alfred Berg, MD, MPH**, Professor, Department of Family Medicine, University of Washington
- **David Flum, MD, MPH**, Professor, Department of Surgery and Adjunct Professor, Department of Health Services, University of Washington Schools of Medicine and Public Health; Attending physician, General Surgery, University of Washington Medical Center
- **Sherine Gabriel, MD, MSc**, Professor of Medicine and of Epidemiology, and the William J. and Charles H. Mayo Professor, Mayo Clinic
- **Steven Goodman, MD, PhD**, Professor of Oncology, of Pediatrics, of Epidemiology and of Biostatistics, Johns Hopkins School of Medicine and Bloomberg School of Public Health
- **Mark Helfand, MD, MS, MPH**, Professor of Medicine and of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University; Staff physician, Portland VA Medical Center
- **John Ioannidis, MD, DSc**, the C.F. Rehnberg Professor in Disease Prevention, Professor of Medicine and Director, Stanford Prevention Research Center, Stanford University School of Medicine
- **David Meltzer, MD, PhD**, Director, Center for Health and the Social Sciences, Chief of the Section of Hospital Medicine, and Associate Professor, Department of Medicine, Department of Economics, and Graduate School of Public Policy Studies, University of Chicago
- **Brian Mittman, PhD**, Director, VA Center for Implementation Practice and Research Support, Department of Veterans Affairs Greater Los Angeles Healthcare System
- **Robin Newhouse, PhD, RN**, Assistant Dean, Doctor of Nursing Practice Program and Associate Professor, Organizational Systems and Adult Health, University of Maryland School of Nursing
- **Sharon-Lise Normand, MSc, PhD**, Professor of Health Care Policy, Harvard Medical School and Professor of Biostatistics, Harvard School of Public Health
- **Sebastian Schneeweiss, MD, ScD**, Associate Professor, Department of Medicine, Harvard Medical School and Associate Professor, Department of Epidemiology, Harvard School of Public Health; Vice Chief and Director, Drug Evaluation and Outcomes Research, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital
- **Mary Tinetti, MD**, Professor of Medicine, Epidemiology, and Public Health, Division of Geriatrics, Yale University School of Medicine; Director, Program on Aging, Yale University School of Medicine
- **Clyde Yancy, MD, MSc**, Chief, Cardiology, Northwestern University Feinberg School of Medicine; Associate Director, The Bluhm Cardiovascular Institute, Northwestern Memorial Hospital

Other national comparative effectiveness programs: an operational comparison

While a national CER effort is new to the U.S., it has been under way in other countries for nearly two decades. A number of them have established structures or agencies to examine the effectiveness of medications, medical technologies, medical devices, and treatment strategies to ensure that health care expenditures achieve superior-quality clinical outcomes and economic value for the funds invested. The CER experiences in industrialized nations such as England, Germany, Canada, and Australia provide insights for the U.S.; Figure 3 compares these CER bodies to the current status of PCORI.

Figure 3: Comparison of NICE, CADTH, IQWiG, PBAC, and PCORI

	UK: National Institute for Health and Clinical Excellence (NICE)	Canada: The Canadian Agency for Drugs and Technologies in Health Care (CADTH)	Germany: Institute for Quality and Efficiency in Health Care (IQWiG)	Australia: Pharmacy Benefits Advisory Committee (PBAC)	U.S.: Patient-Centered Outcomes Research Institute (PCORI)
Stated mission	Offer authoritative guidance on the clinical and cost-effectiveness of new and existing technologies	Provide timely, relevant, rigorously derived, evidence-based information to decision makers and support for the decision-making process	Investigate what therapeutic and diagnostic services are feasible and valuable, and communicate the findings to the health care professions, patients, and the general public	Conduct quality, safety, efficacy, and cost-effectiveness reviews of new drugs (PBAC) and new and established medical devices (Medical Services Advisory Committee, MSAC) to inform government benefit coverage decision makers	Carry out research projects that provide quality, relevant evidence on how diseases, disorders, and other health conditions can effectively and appropriately be prevented, diagnosed, treated, monitored, and managed
Composition of governing board	12 members from cross-sector backgrounds (e.g., academia, public health, consulting, social policy, Department of Health, physician, audit)	13 members, including a number of representatives from health authorities, academia, and the general public	Board of Trustees has 30 members and includes representatives from scientific societies, employers, pharmaceutical companies, and other groups ³⁹	Up to 18 members, with at least one each of the following: consumer, health economist, practicing community pharmacist, general practitioner, clinical pharmacologist, and medical specialist ⁴⁰	21-member Board, with broad range of perspectives and collective expertise in clinical health services research, including epidemiology, decision sciences, health economics, and statistics 15-member Methodology Committee, with experts in health services research, clinical research, comparative clinical effectiveness research, biostatistics, genomics, and research methodologies
Funding source	Department of Health; current funding is USD \$70M ⁴¹	Ministries of Health and Health Canada; annual budget for 2009 was \$23.7M CAD (USD \$19.4M) ⁴²	Annual budget for 2008 and 2009 is 15 million Euros (USD \$19.67M); IQWiG is funded through levies on health care services (via the Statutory Health Insurance [SHI] system); it may accept funding from the Federal Ministry of Health, but seeks no grants or advertising ⁴³	Department of Health and Ageing; USD \$10M annually	From 2010-2012, funding comes from PCORTF; 2010: \$10M; 2011: \$50M; 2012: \$150M From 2013-2019: annual budget is \$150M, funded through PCORTF and fees imposed on Medicare and private health insurance companies

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Scope of assessments	<p>Medical technologies including drugs, devices, and diagnostic tests; clinical guidelines for disease management; public health guidance on disease prevention; information for patients and the public⁴⁴</p> <p>Under proposed UK health reforms, the Health Ministry would negotiate new drug prices directly with manufacturers and final prescribing decisions would be left to individual family doctors, given a capitation-based budget by the government and exempt from following particular decision-making processes</p> <p>Although NICE would continue to provide advice on the optimal use of new drugs, the advice is unlikely to translate into a constitutional right to access⁴⁵</p>	<p>Drugs to provide formulary listing recommendations, medical technologies (e.g., devices, diagnostic agents, equipment, and medical and surgical procedures), and health systems (e.g., telehealth)</p>	<p>Drugs, devices, quality control interventions, surgical procedures, diagnostic tests, clinical practice guidelines and aspects of disease management programs, and evidence-based information for patients⁴⁶</p>	<p>Prescription medicines for subsidy and vaccines for inclusion on the National Immunization Program,⁴⁷ and new and established medical devices (MSAC)</p>	<p>Drugs, devices, procedures, and delivery systems; assessments will evaluate disease prevention, diagnosis, treatment, monitoring, and management</p>
Prioritization process	<p>NICE selection based on predetermined criteria, including broad policy priorities, potential budgetary impact, potential to improve health outcomes, current variation in practice, availability of relevant evidence, and potential of NICE guidance to add value; final approval for review remains with Secretary of State for Health⁴⁸</p>	<p>Health technology assessments (HTAs) are filtered and prioritized by the Advisory Committee on Pharmaceuticals and the Devices and Systems Advisory Committee; selected topics usually are of national interest</p> <p>Common Drug Review (CDR) submissions are made by drug manufacturers, drug plans, or the Advisory Committee on Pharmaceuticals</p> <p>Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) must first focus on the following two priority areas: proton pump inhibitors (for the treatment of gastrointestinal problems) and diabetes management</p>	<p>Federal Joint Committee takes into account the clinical relevance of the health service and the risk and costs associated with it</p> <p>IQWiG may independently select topics for preparing understandable evidence-based health information for patients and public</p>	<p>No prioritization required; committee considers submissions three times a year</p>	<p>The IOM submitted to Congress and HHS a report reviewing 100 high-priority research topics</p> <p>PCORI has yet to establish a formal prioritization process</p>

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Types of research used	Meta-analyses and systematic reviews of experimental and observational studies; also considers patient surveys and patient and professional expert opinions	Published and unpublished evidence including experimental and observational studies; pharmacoeconomic analyses	<p>Considers randomized control trials (RCTs) in the benefit assessment of drugs; only uses non-randomized intervention studies or observational studies in justified exceptional cases</p> <p>For non-drug therapeutic intervention, considers non-randomized studies in the assessment</p> <p>Cost-effectiveness analysis used only to exclude treatment from coverage if at least one equivalent alternative exists</p> <p>Does not accept confidential commercial information furnished by pharmaceutical companies and subject to publication restrictions⁴⁹</p>	In the absence of one or more direct head-to-head RCTs, preference is to compare two sets of trials where each alternative is randomized with a common reference; cost-effectiveness modeling is generally required ⁵⁰	<p>Systematic reviews and assessments of existing and future research; primary research, such as randomized clinical trials, molecularly informed trials, and observational studies; any other methodologies recommended by the methodology committee</p> <p>By law, analyses will not include cost-effectiveness metrics</p>
Stakeholder involvement	Partners' Council consisting of major stakeholders is appointed directly by the Secretary of State for Health ⁵¹	Patient group input is part of the CDR process	Law requires that providers, experts, industry, and patient groups have an opportunity to comment on methods and recommendations ⁵²	Increasing public involvement in decision making ⁵³	Institute must establish a peer-review process for its primary research (and must make list of reviewers public)
Use of research in coverage decisions	Most treatments that have been reviewed have been recommended for coverage; ⁵⁴ NICE decisions could be overridden by Secretary of State for Health, but this has not yet happened ⁵⁵	Published a total of 454 HTAs and completed 30 reviews of submissions under the CDR in 2008-2009	Recommendations are only advisory and the Federal Joint Committee may decide whether or not to follow the recommendations	The Minister of Health makes all drug coverage decisions; however, the Minister must have a positive recommendation from the PBAC ⁵⁶	<p>Reports and research findings may not be construed as mandates, guidelines, or policy recommendations</p> <p>HHS Secretary may use findings to inform coverage decisions (through an "iterative and transparent process"), but may not solely rely on findings in coverage decisions</p>
Appeals process	<p>Stakeholders may appeal on the following grounds: a) perversity – no reasonable group would have formulated the recommendation; b) violation of procedural rules; c) violation of scope of responsibilities⁵⁷</p> <p>Appeals are heard by a panel of non-executive NICE directors, patient advocates, industry, and National Health Service (NHS) representatives⁵⁸</p>	Every manufacturer whose drug is the subject of a CDR recommendation has the right to file a request for reconsideration	Legal appeals cannot be made on reports as they are not legally binding; however, if the directives based on the reports are developed, approved, and implemented by the Federal Joint Committee, challenging the directives necessitates legal appeal ⁵⁹	<p>Formal process for a "procedural" appeal (when manufacturers feel the rejection was due to an error in procedure)⁶⁰</p> <p>For "merit" appeals, there is an independent review process that reports back to PBAC (rarely used)⁶¹</p> <p>Sponsors may resubmit appraisals or request an independent review of negative recommendations⁶²</p>	Research findings must be made public within 90 days, with a 45-60 day comment period

PCORI vs. NICE, CADTH, IQWiG, and PBAC

PCORI differs in some ways from other established CER bodies.

Mission	International CER bodies primarily serve payer needs, whereas PCORI's analyses will not include cost analyses or assessments of cost-effectiveness. Furthermore, unlike NICE, CADTH, IQWiG, and PBAC, PCORI is a research producer, not a user.
Composition of governing board	In addition to a cross-sector governing board, PCORI will have a 15-member expert methodology committee to ensure the quality and scientific rigor of the studies conducted.
Funding source	The ACA established a growing budget for PCORI via PCORTF. After 2012, the trust fund appropriations are to be supplemented by fees imposed on Medicare and private payers. Currently, PCORI holds the largest budget of all CER bodies but it also has the broadest mandate.
Scope of assessment	Unlike the other CER entities, PCORI will extend assessments to include health delivery systems in addition to drugs, devices, and procedures, taking a holistic approach to improve the value of health care.
Prioritization process	In the U.S., initial prioritization fell to the IOM, which identified the top 100 health priorities for the country. This differs from the other CER bodies, where prioritization of topics is typically based on pre-determined criteria or manufacturer submissions.
Types of studies used	PCORI will be the first national CER body to produce primary research (including conducting clinical trials), not just synthesize it. While conducting prospective trials best fulfills decision makers' needs, time and adequate finances may make it a difficult undertaking. In the absence of primary research, international CER bodies experiment with conditional coverage or coverage with evidence-development strategies, enabling access to therapies until better evidence is available. Since PCORI's research cannot be construed as coverage mandates, the utility of this strategy in the U.S. is uncertain. Unlike NICE, CADTH, IQWiG, and PBAC, PCORI is prohibited from calculating explicit cost-effectiveness metrics (i.e., QALY) or determining explicit cost-effectiveness thresholds. Additionally, PCORI's Methodology Committee plans to include non-traditional and observational studies in its research, necessitating a much broader methodological scope to assessments than other bodies.
Stakeholder involvement	For primary research, PCORI will implement a peer-review process and publish the list of reviewers. Furthermore, unlike NICE, CADTH, IQWiG, and PBAC, PCORI has been established as a high-profile entity tasked to inform the public. Through a series of forums and formal public comment periods, PCORI will increase awareness of its work and obtain public input and feedback prior to adopting priorities, agendas, methodological standards, peer-review processes or dissemination strategies. ⁶³
Use of research in coverage decisions	Research conducted by PCORI may not be construed as guidelines or policy recommendations and HHS is prohibited from basing coverage decisions solely on PCORI's research. International CER experience has found that the inclusion of cost data in CER studies increases the usefulness of technology assessments; however, cost data and the computation of cost-effectiveness metrics such as the QALY are strictly prohibited under the ACA.
Appeals process for recommendations	Unlike other CER entities, any and all U.S. health care industry stakeholders are able to participate in the appeals process. The ACA mandates that all research findings must be made public within 90 days, with a 45-60 day comment period for any and all stakeholders.

Lessons learned from comparative effectiveness research experiences in other industrialized nations

Common approaches to establishing national CER bodies in the UK, Canada, Australia, Germany, and other countries provide important lessons for the U.S.' developing CER efforts. These include:

- Mandated structural opportunities for involving a range of health care sector stakeholders in evaluative and decision-making bodies
- Operational independence of the evaluative body, including an arm's-length relationship from the government
- Methodological and scientific rigor and transparency of research process and outcomes, including open and public accountability
- Structures and processes by which decisions and recommendations can be appealed and subjected to additional scrutiny and accountability
- Priority-setting and timeliness of research relates to the health care objectives of the government and society at large
- A commitment to clinical implementation and patient benefit, including ways to facilitate the uptake of new technologies, products, and clinical processes for timeliness of research, optimal outcomes, and greater efficiencies
- Investment of sufficient resources for the CER body and its activities

Political endorsement, early stakeholder engagement, professional buy-in through scientific rigor, transparency, timeliness and public accountability appear to be the key ingredients for a successful national CER strategy.^{64, 65}

Sector-specific issues for U.S. comparative effectiveness research

The implementation of PCORI impacts all U.S. health care stakeholders. Across industry sectors, there is a need for the delivery of timely, methodologically rigorous research that is applicable to a multitude of broad populations and key subpopulations.

Consumers

PCORI aims to conduct "patient-centered" outcomes research that is responsive to the preferences, experiences, and values of patients whose lives are impacted daily by various diseases or conditions.⁶⁶ PCORI will provide consumers (via public forums, publications and, possibly, via tools such as personal health records) with information they can use to guide their treatment decisions. As a result, such decisions will likely shift from being physician-driven to consumer-driven. According to respondents of Deloitte's *2009 Survey of Health Care Consumers* who prefer their physicians to be more prescriptive and authoritative in treatment decisions, this shift could be unsettling to consumers.⁶⁷

Additionally, for some consumers, a national CER effort appears to be a means of rationing health care and limiting access to potentially important therapeutics. Some patients fear that CER recommendations based on the average deviate from personalized medicine may further add to health disparities.⁶⁸ This fear of treatment rationing could increase, as translating CER into practice may include financial incentives (i.e., lower co-pays) for patients that opt for treatments deemed to be of high value.⁶⁹

Manufacturers/Life Sciences Organizations

For pharmaceutical and medical device manufacturers, CER conducted by a quasi-independent agency could create uncertainty about the fate of their products; non-supportive findings could substantially impact business.⁷⁰ In a new value-driven health care system, manufacturers will need to offer technologies that demonstrate real value to payers, providers, and patients. Product differentiation and value story development will need to occur throughout the product lifecycle, from discovery to launch.⁷¹ Safety and efficacy demonstrated under ideal conditions will no longer be sufficient to gain and/or maintain market access; incremental value over other treatment options will become the decision point.⁷²

One hurdle for life sciences organizations is obtaining access to data that describes real-world utilization of their products and those of their competitors. Retrospective medical claims analyses to study utilization of their product and competitors' limit inferences of causality and blunt claims of CE. Until health information exchanges (HIEs) are fully functional, life sciences organizations will need to build their own clinical informatics capabilities to conduct CER that may inform value-based product development. In addition, manufacturers should be prepared for the onslaught of comparative studies of their products generated by PCORI and the FDA's Sentinel Initiative; conducting CER with the same methodological rigor as PCORI is a sensible way forward.⁷³

Some fear that innovation may suffer due to CER, as return on R&D investments will be less certain.⁷⁴ International experience, however, indicates that a predictable CER process and decision-making algorithm may actually encourage innovation by allowing manufacturers to see what product features are valued and rewarded.⁷⁵ In this new environment, a departure from the tried and true will be necessary for success. This includes employing a CE lens throughout all stages of product development and securing a smaller, but more compliant, portion of the patient pool.⁷⁶

Historically, product value has been based on safety and efficacy as demonstrated in strict laboratory conditions. PCORI's research, in contrast, will evaluate health outcomes in real-world settings. Hence, manufacturers will need access to real-world and real-time data to monitor product performance and gain a true sense of CE. Sophisticated clinical informatics capabilities that allow manufacturers to tap into broader datasets to monitor user outcomes can provide important insights into commercial strategy and may even improve return on investment.^{77,78} Furthermore, clinical informatics can facilitate and expedite clinical trial recruitment, simulate clinical trials to eliminate some in-vivo trials, and provide a stronger foundation for outcomes research.⁷⁹ Pre-market evaluations performed under a CER lens (including competitor studies in real-world settings) can substantially guide product development and ensure a competitive advantage at launch.⁸⁰

The ACA also suggests a greater emphasis on personalized medicine – the right treatment for the right patient at the right time – and CER complements this direction. Manufacturer strategy will focus on gaining greater compliance within a subgroup of patients who attain optimal health outcomes by using their product rather than achieving average compliance across a larger patient population.⁸¹ If outcomes are not achieved, manufacturers seeking broad coverage for new technologies may be faced with more stringent CER evidence requirements by policy makers or have to engage in other negotiating strategies, such as coverage with evidence development or risk-sharing agreements.⁸²

Providers

For health care providers and provider organizations, understanding CER findings and their application to patient populations will be important as payment reforms and outcomes transparency become the norm.⁸³ For example, value-based provider payment systems may reward physicians for using the most effective therapies, and bundled payment systems may use CER to inform the most effective and efficient mix of services for episodes of care. In pay-for-performance approaches, provider bonuses may be determined by compliance with CER findings or quality metrics may be informed by CER results. Additionally, during a time of malpractice reform, using CER-based guidelines in clinical decision making could protect providers from legal consequences.⁸⁴

Tying reimbursement or economic incentives to CER and evidence-based medicine (EBM) might prove most effective for translating research into practice and influencing prescribing patterns over time. Barriers to EBM adoption have been related to the current fee-for-service (FFS) physician reimbursement system; higher physician reimbursement for procedural treatment than non-procedural treatment, despite evidence that a non-procedural treatment is similar or more effective; physician resistance to EBM, wherein individual patient nuances are perceived to be overshadowed by clinical recommendations that work for the average; and continuing education programs sponsored by drug/device manufacturers.⁸⁵ Hence, successful implementation of CER appears highly dependent on linking practice patterns to economic incentives.

Additionally, according to the American Medical Association (AMA), a high-quality health care system can only be sustained on a secure, interoperable health information technology (HIT) network. A HIT network can provide real-time, clinically relevant data and decision support tools via electronic health records (EHRs) in the hands of providers at the point of care and increase evidence-based decision making. Meaningful use incentives through ARRA could facilitate provider efforts to build this infrastructure.⁸⁶

Payers

Payers (both private and public) already use several sources to inform coverage decisions and benefit design (e.g., technology assessment organizations, internal analyses, federally funded assessment centers, and Medicare/Medicaid decisions) and are supportive of PCORI's efforts. CER performed by a federally supported, non-profit organization could strengthen the evidence base in important ways; specifically, by expanding the number of head-to-head trials, comparisons of new technologies versus existing technologies, and comparisons between various treatment modalities (procedure vs. drug therapy vs. physical therapy). A key benefit of PCORI's research for payers is how it could influence physician reimbursement and the delivery of high-value health care⁸⁷ by informing value-based insurance product design through the identification of high-value and low-value interventions.

Federal and State Government

Inadequate incentives for academic physicians and administrative burden on community physicians have contributed to a decline in clinical investigators since 2001. Coupled with a system already at capacity evidenced by outsourcing of clinical trials abroad, the demands the new surge of CER will place on the research enterprise may not be sustainable. Additionally, patient participation in trials is in decline due to lack of involvement by their community physicians and fear of receiving inactive treatment during the study (although CER may overcome this barrier, as it intends to conduct trials with only active comparators). Additionally, CER may require more complex trial designs to study a multitude of outcomes in a “real-world” setting, requiring large samples, longer trial durations, and greater costs. Incentives to engage academic and community physicians will be necessary to execute PCORI’s objectives.⁸⁸

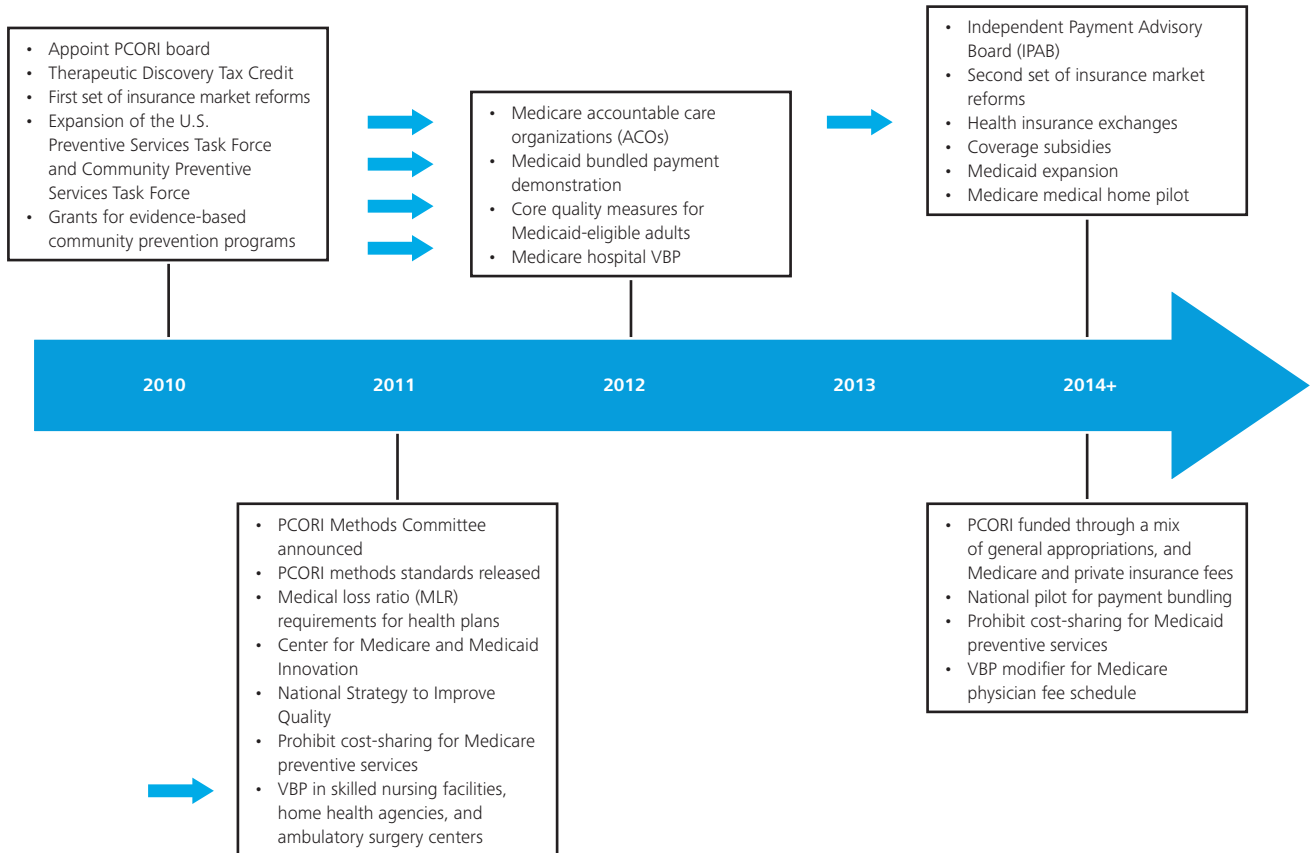
PCORI’s CER efforts may have a greater impact on physician practice patterns if they can influence clinical practice guidelines. According to the Deloitte Center for Health Solutions’ *2010 Global Survey of Health Care Consumers*, academic medical centers and physicians are the two most trusted sources for information about the effectiveness and safety of treatment options. Other sources of information, including the government, were rated lower.⁸⁹ Given these findings, successful CER implementation will likely hinge on integrating the findings into clinical guidelines.⁹⁰

Policy Questions

- How will PCORI deliberations be integrated into HHS’ National Strategy for Quality Improvement annual report to Congress?
- To what extent will CER findings be used in coverage and denial decisions by Medicare, Medicaid, CHIP, military health, and health insurance exchange plans?
- How will CER findings be integrated into payment reforms?
- How will CER influence and/or be integrated into NIH funding priorities?
- How will PCORI research priorities be reflected in FDA approval processes, given that its research will not use control vs. placebo methodologies?
- How will information from meaningful use of electronic health records populate or inform PCORI recommendations?
- How will life sciences R&D change to use comparative analytics? How will this relate to their decisions to offshore R&D operations to conserve cash and mitigate risk?
- How will PCORI be funded from 2019 and beyond?

Figure 4 depicts how PCORI's work will intersect with other provisions in the ACA that are high on stakeholders' agendas.

Figure 4: Timeline of ACA provisions



➡ = point of intersection between CER and other provisions in health reform

Comparative effectiveness research's impact on health care costs

The true impact of CER on total health care costs is indeterminate, at best. It is difficult to make comparisons among countries due to the myriad of factors that influence health care spending and major structural differences among health systems.⁹¹ In the UK, the purpose of CER was to improve health services' quality and accessibility, not necessarily cost containment. And while NICE guidances may have increased the average cost-effectiveness of treatments covered by NHS, there is no evidence that total spending or the rate of cost increases has been reduced.^{92, 93} Similarly, in Australia, CER was not intended as a cost-containment strategy but a means of obtaining better value for money spent and greater efficiency. Hence, net increases in expenditures following coverage for a new drug represent better value for taxpayer money.⁹⁴

Studies of CER's impact on total U.S. health care spending have thus far demonstrated limited effects. Following a proposal by the Children's Health and Medicare Protection Act of 2007 that would have established a Center for Comparative Effectiveness Research within AHRQ, the Congressional Budget Office (CBO) estimated that CER would generate modest practice changes and reduce total federal spending on health care by less than one percent over 10 years. The CBO estimates assumed that CER results would not affect policy or coverage decisions (similar to the ACA's restrictions on PCORI), which contributed to the modest impact.^{95, 96} A more recent analysis by Basu and Philipson that examined Medicaid spending on antipsychotic drug treatments (one of the largest drug classes in a major U.S. public subsidy program) indicated that CER may increase quality of care but also increase spending when all patients achieve the same treatment effect. Moreover, the study found that when treatment effects are inconsistent across patients, CER may increase spending as well as adversely impact health outcomes based on how markets react to quality information. The authors suggest that more research be conducted to understand how CER should be stratified and thus determine "the right treatments for the right subpopulations."⁹⁷ Pearson and Bach have proposed a tiered payment model for Medicare in which services with evidence to suggest superior health benefits compared to alternates receive higher payments; services with comparable outcomes would be reimbursed equally; and new services without this evidence would receive usual payment rates until more evidence is available.⁹⁸

While data on the impact of CER on total health care spending is inconclusive, there is clear evidence of its positive impact on the quality and value of health care services. Moving forward, more research is needed to better understand CER's total impact on the U.S. health care system.

Implications for stakeholders

Manufacturers/Life Sciences Organizations

- Employ a CE lens during all stages of drug development and marketing; technologies with high incremental value are likely to be rewarded.
- Develop robust clinical informatics capabilities; these can prove useful for all stages of drug development, from understanding the competitor landscape, to developing the value story, and monitoring post-launch product performance.
- Shift R&D strategy away from average performance in large populations to patient segments in which optimal outcomes and high compliance rates are achievable.

Providers

- Pay attention to CER as the industry's movement toward ACOs, EBM, and transparency of outcomes continues; provider performance will likely be measured on EBM, the basis of CER.
- Leadership should make sure that all physicians in the organization understand what CER is and in what context the research is appropriate.
- Avoid cherry-picking CER results that support business objectives. In the new value-driven health system, patient outcomes and satisfaction will likely be critical to securing economic incentives.

Consumers

- Consumers will also need to pay attention to CER as they are likely to become confused by the barrage of information and controversy over whether certain types of studies (i.e., databases) are sufficiently conclusive.
- High-value technologies may prove beneficial for consumers and they should monitor the research to make informed decisions about their health care.

Payers

- Monitor implementation of CER findings, particularly as they relate to payment reforms and performance measurement.
- Utilize a CER quality and value lens in when developing new products and services.

Federal and State Government

- Consider offering incentives to engage sufficient academic and community physicians to carry out PCORI's research agenda.
- Monitor the CER studies that are contracted out to independent and academic research organizations for timeliness, as career researchers specialized in large trials may require more lengthy statistical analyses to control for various factors.
- Consider further research to understand exactly how and in what capacity CER may reduce total health care costs and improve health outcomes.

Conclusion

Overall, based on international experience and empirical data, CER's impact on reducing health care costs is inconclusive; however, there is clear evidence of its positive impact on the quality and value of health care services. That said, CER's role flies in the face of most consumers' expectations, especially those accustomed to depending on their physicians for treatment guidance.

In the U.S., the effectiveness of CER and its facilitator, PCORI, is dependent on three key factors:

1. Educating consumers about evidence-based care and its association with improved outcomes for patient populations;
2. Creating meaningful information technologies and real-time tools to equip providers, consumers and payers in decisions about care;
3. Maintaining the independence of PCORI and overall CER processes from political and regulatory endeavors that might compromise their mission and scope.

CER, through PCORI, is about tools, not rules, to enable the U.S. health care system to better align its diagnostics and treatments with evidence. CER also is about the dynamic process of creating, synthesizing, and reporting findings to equip consumers to be active participants in their care. CER is necessary and worthwhile, although the challenge of implementing it and gaining stakeholder acceptance may prove daunting.

All data presented in this document were accurate as of May 2011.

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