

COMPARATIVE EFFECTIVENESS
RESEARCH: Paving the Way for
Evidence-Based Decision Making

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COMPARATIVE EFFECTIVENESS RESEARCH: Paving the Way for Evidence-Based Decision Making

Comparative effectiveness research (CER) is playing a critical role in the shifting health care landscape in the United States. CER presents an exciting opportunity for all stakeholders in the health care system — among them, physicians and other health care professionals, patients, payers, pharmaceutical companies, and policy makers — to work together to pave the way for evidence-based decision making. Understanding the benefits but also the limitations of CER is crucial to its successful implementation.

By ensuring that stakeholders have the objective data and information that is needed to achieve the best possible outcomes, CER is an important step in clinical care that puts patients and their needs front and center. With its emphasis on appropriate use and outcomes, CER will allow us to move beyond anecdotal medicine based on personal experience and toward a shared vision of good medicine.

Background and funding

The year 2010 signaled a propitious change for CER. The federal government, which had funded \$1.1 billion for CER, transferred oversight of that function from the Agency of Healthcare Research and Quality (AHRQ) to the Federal Coordinating Council for Comparative Effectiveness Research. The Patient Protection and Affordable Care Act (PPACA) of 2010 then disbanded the Council and created a new entity, the Patient-Centered Outcomes Research Institute (PCORI), to develop and fund CER (PPACA 2010). PCORI has budgeted \$50 million in 2011 and \$150 million in 2012 for CER. In addition, for the period 2013 through 2019, the PCORI trust fund has been appropriated \$150 million from general funds in addition to fund transfers from the Medicare Federal Hospital Insurance and Federal Supplementary Insurance Trust Funds and from health insurance and self-insured health plans (PCORI 2011a).

PCORI's role is to "help patients, clinicians, purchasers, and policy-makers make better informed health decisions" by conducting research on the quality and effectiveness of medical treatments (PCORI 2011b). PCORI will give AHRQ and the National Institutes of Health (NIH) preference to conduct research and to manage funding, although other entities also can be contracted. In addition to creating and enacting a national CER agenda, PCORI's duties include:

- Establish a standing methodology committee
- Ensure a peer-reviewed process for primary research
- Appoint expert advisory panels
- Provide public comment periods
- Provide publicly available research findings within 90 days after the conduct or receipt of research findings

Critical to an effective CER program is to ensure a high degree of openness of process, data transparency, privacy in accordance with The Health Insurance Portability and Accountability Act (HIPAA) of 1996, adherence to ethical standards, and the avoidance of conflicts of interest.

The dissemination of research findings is an important goal

CER Defined

"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.

- To provide this information, comparative effectiveness research must assess a comprehensive array of health-related outcomes for diverse patient populations and subgroups.
- Defined interventions compared may include medications, procedures, medical and assistive devices and technologies, diagnostic testing, behavioral change, and delivery system strategies.
- This research necessitates the development, expansion, and use of a variety of data sources and methods to assess comparative effectiveness and actively disseminate the results."

Federal Coordinating Council for Comparative Effectiveness Research, Report to The President and The Congress, June 30, 2009

Source: USHHS 2009

— not only must PCORI release such findings in a timely fashion, it must also communicate those findings to clinicians, patients, and the general public in ways that are comprehensible and useful (PCORI 2011a). The findings must also discuss, as appropriate, issues related to specific subpopulations, risk factors, and comorbidities. In addition, many of the priority CER areas are important Medicare cost drivers. The single largest payer in the U. S. marketplace — the U.S. Government — is committed to PCORI's mission.

Toward a common understanding of CER

In its report to the President and the Congress, the Federal Coordinating Council for Comparative Effectiveness Research defined CER as 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" (see sidebar above for full definition). Other definitions of CER also have emerged, and they are useful to review, primarily for the philosophic foundation they all share.

The Institute of Medicine (IOM) defines 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. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.”

IOM, Initial National Priorities for Comparative Effectiveness Research, June 2009

The NIH defines CER as:

“A rigorous evaluation of the impact of different options that are available for treating a given medical condition for a particular set of patients. Such a study may compare similar treatments, such as competing drugs, or it may analyze very different approaches, such as surgery and drug therapy.”

NIH Challenge Grants Program, 2011

Underlying these definitions is the sense that “...all too often, the information necessary to inform these medical decisions is incomplete or unavailable, resulting in more than half of the treatments delivered today without clear evidence of effectiveness” (IOM 2007). The Federal Coordinating Council for Comparative Effectiveness Research in its Report to the President and Congress (USHHS 2009) distinguished between “efficacy” and “real world effectiveness”:

“Comparative effectiveness differs from efficacy research because it is ultimately applicable to real-world needs and decisions faced by patients, clinicians, and other decision makers. In efficacy research, such as a drug trial for U.S. Food and Drug Administration (FDA) approval, the question is typically whether the treatment is efficacious under ideal, rather than real-world, settings. The results of such studies are therefore not necessarily generalizable to any given patient or situation. But what patients and clinicians often need to know in practice is which treatment is the best choice for a particular patient. In this way, comparative effectiveness is much more patient-centered. Comparative effectiveness has even been called patient-centered health research or patient-centered outcomes research to illustrate its focus on patient needs.”

The PPACA defines CER as “research evaluating and comparing health outcomes and the clinical effectiveness, risk, and benefits of two or more medical treatments, services, or times” (PPACA 2010).

Therefore, three strong engines are driving CER: 1) the desire to improve the quality of care through evidence-based medicine; 2) the imperative to be more cost effective; and 3) the need to reflect patients’ and clinicians’ real-world experiences. The CER environment, therefore, will move beyond efficacy and safety data and will demand data via direct comparison to show that a new therapy will perform better than current therapeutic options, that there is a clear and proven benefit for patients in typical day-to-day clinical care, and that decisions are tailored to the needs of individual patients and not just of populations.

Although drugs and biologics represent the largest focus of CER studies, CER will also assess public health and behavioral interventions, surgical procedures, and pharmacologic treatments.

Randomized controlled trials

Randomized controlled trials (RCTs) remain the most common method for assessing the efficacy and effectiveness of a drug or medical technology. In RCTs, two or more interventions are compared, with patients randomly assigned to those interventions. CER requires the use of various types of study designs, depending on the question under investigation, interventions, setting, and feasibility. CER methods for obtaining clinical information include:

- **Mathematical models:** Using computer-based models to simulate treatment outcomes based on information from existing studies
- **Meta-analyses:** Pooling analyses of data from similar studies and reports
- **Systematic reviews:** Structured reviews and summaries of existing studies and reports that do not entail an advanced analysis of known data
- **Observational studies:** Observing individuals or measuring outcomes without attempting to affect them, which can include claims analyses, prospective registries, and patient surveys

An alternative trial design could include “N-of-1” trials in which single-event case studies look at the effect of an intervention on an individual. CER methods differ from RCTs in terms of applicability to large populations and scientific rigor. It is important to note, however, that the U. S. Food and Drug Administration does not consider data from observational studies to be “substantial evidence.”

Goals versus uses of CER

In the United Kingdom, Australia, Canada, and Germany, it has become the norm for these countries to review clinical and cost-effectiveness data. In the United States, CER, for now, will focus on clinical analysis rather than on the economic impact of a new therapy. CER proponents seek to know how a drug or therapy is more clinically beneficial than other available treatments and whether the additional clinical benefits are worth the cost of the new therapy.

According to the IOM, CER aims to replace the “adopt everything for everyone” paradigm with an “adopt when appropriate” paradigm (IOM 2007). The IOM also identifies three different types of inefficiencies to be addressed through CER (IOM 2007):

- **Overuse:** delivering services that provide little or no clinical value
- **Misuse:** using an effective service when it is not clinically indicated
- **Underuse:** failing to deliver appropriate services that provide clinical benefits

The IOM has identified 29 research areas that collectively address broad societal needs (Figure 1). In addition, AHRQ has developed a road map to demonstrate the information needs of CER and how the core elements of CER fit together, distinguishing between clinical efficacy and effectiveness (Figure 2).

It is important to note, however, what CER is *not* meant to do. The PPACA limits how CER can be used and explicitly states

that findings from CER cannot be construed as mandates, guidelines, or recommendations for payment, coverage, or treatment, nor can CER be used to deny coverage. Therefore, there needs to be a common language for CER so that data are collected and used in ways that focus on improving health outcomes. Within this context, CER is a potentially powerful teaching tool and can be a catalyst for quality as opposed to a tool to restrict access to necessary therapies.

In addition to understanding what CER can and cannot do, consider how it can help the various stakeholders. CER has the potential to lessen conflicts of interest among the following six groups of health care participants, which can lead to improved health care for patients through the procurement of more effective information about optimal choices:

- **Patient:** receives appropriate, high-quality services
- **Provider:** makes informed decisions on individualized effective and appropriate treatment
- **Payer:** separates valuable drugs, devices, and therapies from those that offer little or no value
- **Manufacturer:** focuses on products that are beneficial and cost-effective
- **Employer:** identifies therapies that boost employee productivity regardless of their cost
- **Society:** maximizes the use of scarce resources

In the past, drug manufacturers defined the value of products. Today, providers, patients, payers, and government influence value-based decisions. In the near future, the government will likely increase funding for CER, PCORI's role will expand, and the impact of CER on managed care will be significant. It is less certain, however, how managed care will use the growing body of CER evidence to make coverage and reimbursement decisions. Additionally, few mechanisms are available that allow Medicare contractors to implement CER results when making local coverage decisions. Physician acceptance of CER data is another important factor that will affect its impact.

Collecting real-world data

Although it might be tempting to look for one universal standard by which to evaluate CER data, the reality is that there will be multiple standards, simply because multiple audiences with different needs will use the CER data. Internationally, countries that use CER data do so in ways that are suitable for their culture and health care systems. The challenge in conducting CER in the United States, therefore, is how to package and report the collected data that is suitable for the U.S. health care system and its various stakeholders. Data must come from real-world settings and be developed in ways that ensure the information is meaningful, such as cohort analyses. Drug companies, therefore, should ensure that their study designs are built with CER in mind.

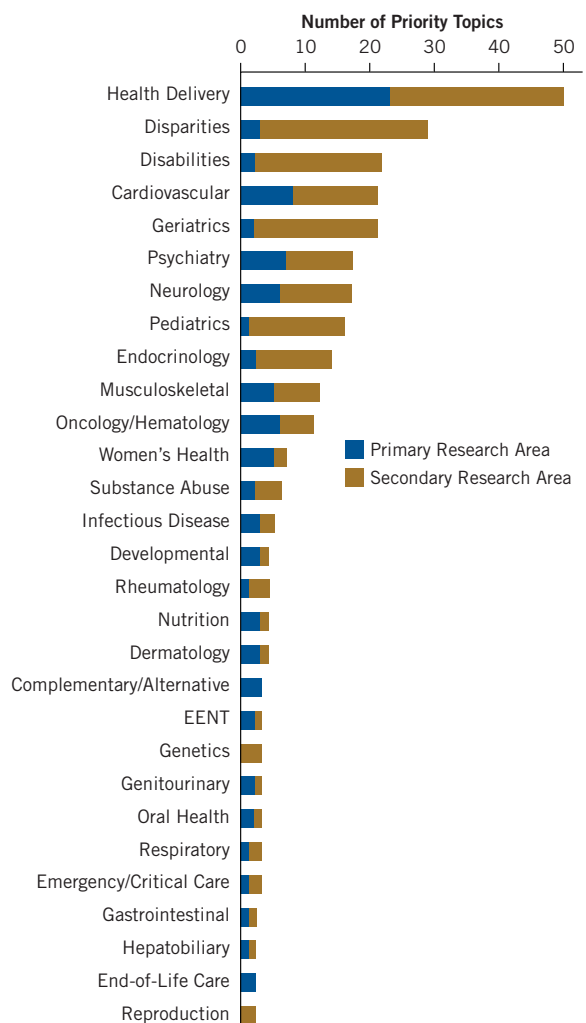
PCORI is empowered to create expert advisory panels, either permanent or ad hoc, to assist in identifying research priorities. It has, therefore, established a 15-member Methodology Committee that consists of physicians, academics, and representatives of groups that conduct CER (see sidebar, page 6). As required by the PPACA, the directors of AHRQ and NIH (or their designees) also serve on the committee (PPACA 2010).

The Methodology Committee is tasked with developing and

periodically updating “methodological standards” for CER. These standards “shall provide specific criteria for internal validity, generalizability, feasibility, and timeliness of research and for health outcomes measures risk adjustment, and other relevant aspects of research and assessment with respect to the design of research.” The committee will solicit input from relevant experts, stakeholders, and decision makers and will allow for public comment. To reflect the CER goal of collecting real-world evidence, the committee is tasked with ensuring that its standards include appropriate methods to account for and evaluate patient subpopulations.

Other areas of emphasis for PCORI include research training and building greater CER data capacity. AHRQ, working cooperatively with NIH, will establish a training grant program on how to conduct CER appropriately. To build greater data capacity, they will coordinate programs such as the development and use of clinical registries and health outcomes research data networks.

FIGURE 1
The Institute of Medicine’s recommended priorities by primary and secondary research areas



Source: IOM 2009

Pharmaceutical companies and data collection

Ultimately, the benefit for pharmaceutical companies is about demonstrating, through validated data, the true value of their products to their customers. CER raises the bar and creates an environment where a product’s proven value ensures its place within the various therapeutic options that a health plan may have at its disposal. CER data, when thoroughly vetted and accepted, will prevent those drug products that lack or produce inferior data from achieving preferred status. Pharmaceutical companies also will benefit from CER in another important way related to managed care organizations (MCOs) and clinical decision making by helping to establish how CER data are collected and evaluated. Because CER data are about real-world applications, pharmaceutical companies, in partnership with MCOs, can establish benchmarks for how patients, health care professionals, and payers use the data.

Established CER standards will help make MCO decisions more transparent, moving product acceptance and usage away from closed-door contract negotiations and toward a system that explicitly rewards innovative products that demonstrate clear points of differentiation based on superior patient outcomes, cost benefit, quality of life, and other agreed-upon endpoints.

In the past, pharmaceutical companies negotiated clinical trials for a particular drug or drugs that provided data on safety and efficacy and were geared toward FDA approval. Now, data must provide proof of comparative effectiveness. Some stakeholders might want to see more quality-of-life markers or data about categorized subsets of important patient populations. Also, both regulatory and payer needs have to be addressed, and they are different and additive. It isn’t simply a matter of reporting the same data in different ways — new data points have to be collected using validated methods and tools.

The importance of being informed

Ultimately, the investments being made in CER are intended not only to manage health care costs but also to improve clinical care across all therapeutic areas. CER remains in a state of flux, and a common vocabulary and agreement on how to use the data that CER generates are still being developed.

Some of the barriers that could keep CER from reaching its promise are rooted in the clinical study design — moving from study evidence to physician adoption and practice and generating the perception of an innovative technology. Mixed regulatory messages, the inability of

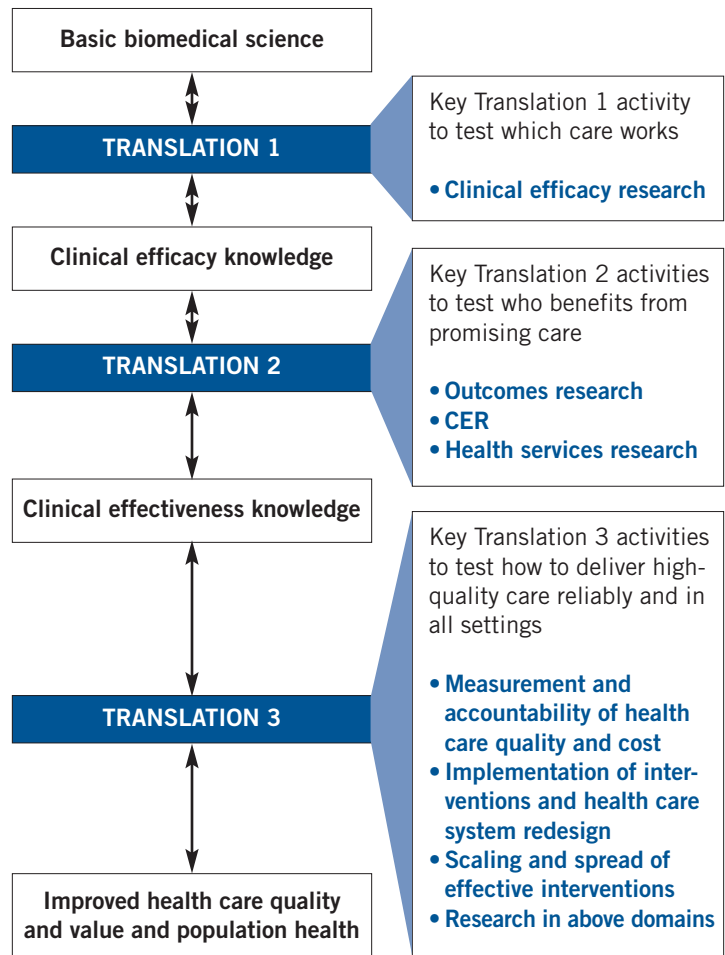
manufacturers to promote CER results, and the lack of a standard grading system to assess the strength of a clinical study are other barriers. Clinical study designs will have to be created with CER in mind and not as a post-trial add-on. Such designs will require protocols that replicate real-world environments with greater population diversity. Other research issues, such as comparing “apples to apples” to ensure that legitimate therapeutic comparisons are being made, also will have to be addressed. Assessments of new technologies also must take into account natural biases for (“new” equals better than existing therapies) or against (“new” equals untested and not as good as established therapies) therapeutic innovations.

CER in action

The effective use of CER in clinical practice is demonstrated in the following three specialty areas:

- Vertebroplasty
- Hypertension
- Advanced Imaging

FIGURE 2
The Agency for Healthcare Research and Quality road map for comparative effectiveness research



Source: Adapted from Dougherty 2008

PCORI's Methodology Committee

Joe V. Selby, MD, MPH, Executive Director

The PCORI Methodology Committee consists of the following members. The Directors of the Agency for Healthcare Research and Quality and the National Institutes of Health, or their designees, also serve on the committee.

- Naomi Aronson, PhD**, Executive Director, Blue Cross and Blue Shield Association Technology Evaluation Center
- Ethan Basch, MD, MSc**, Associate Attending Physician and Outcomes Scientist, 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, Health Services and Pharmacy, University of Washington
- Sherine Gabriel, MD, MSc (Chair)**, Professor of Medicine and Epidemiology and the William J. and Charles H. Mayo Professor, Mayo Clinic
- Steven Goodman, MD, MHS, PhD**, Professor of Oncology, Pediatrics, Epidemiology and Biostatistics, Johns Hopkins School of Medicine and Bloomberg School of Public Health
- Mark Helfand, MD, MS, MPH**, Professor of Medicine and Professor of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University
- John Ioannidis, MD, DSc**, C.F. Rehnberg Chair in Disease Prevention, Professor of Medicine, Professor of Health Research and Policy, and Director, Stanford Prevention Research Center, Stanford University School of Medicine
- Michael S. Lauer, MD**, Director, Cardiovascular Sciences, National Heart, Lung, and Blood Institute
- David Meltzer, MD, PhD**, Director, Center for Health and the Social Sciences and Associate Professor, Department of Medicine and Department of Economics, Harris 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 and Senior Social Scientist at the VA/UCLA/RAND Center for the Study of Healthcare Provider Behavior
- 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, PhD (Vice Chair)**, Professor of Health Care Policy, Harvard Medical School and Professor of Biostatistics, Harvard School of Public Health
- Sebastian Schneeweiss, MD, ScD**, Associate Professor of Medicine and Epidemiology, Harvard Medical School; Vice Chief, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital
- Jean R. Slutsky, PA, MSPH**, Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality
- Mary Tinetti, MD**, Professor of Medicine, Epidemiology, and Public Health and Director, Hartford Center of Excellence in 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

Source: PCORI 2011b

Vertebroplasty is a treatment for osteoporotic compression fractures in which bone cement is injected into a vertebra to restore its natural shape and to relieve pain. Dramatic regional variations exist compared with the national average of 0.73 procedures per 1,000 Medicare enrollees. Because it has been difficult to establish the true value of the procedure, CER could help create some agreed-upon parameters. In fact, given the controversy generated by the published results of two randomized trials of vertebroplasty in the *New England Journal of Medicine (NEJM)*, a CER-focused discussion would be welcome. Weinstein (2009) chronicled the use of vertebroplasty and found that it had doubled during the 6 years of observation, from 4.3 to 8.9 per 1,000 persons in the United States. This increase occurred despite a seeming lack of evidence supporting the procedure's short-term efficacy. According to data from one study (Buchbinder 2009), vertebroplasty had no statistically significant advantage over a "sham" procedure, with patients in both groups (stratified by site of procedure, sex, and symptom duration) reporting a significant reduction in pain. The second study (Kallmes 2009) found no statistical significance between vertebroplasty and "sham" treatment at 1 month.

Hypertension therapies also have been fraught with controversy. The National Heart, Lung and Blood Institute sponsored the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) to determine whether newer (at the time) antihypertensives were superior to standard therapy (USHHS 2011). The ALLHAT study recommended using diuretics instead of angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers as first-line therapy and caused a strenuous debate. Used properly, CER could address several critical issues raised by the ALLHAT study: If a diuretic is used as the initial therapy, which class of drugs should be added next? Or should treatment begin with two drugs (most patients require at least two drugs to reach their goals), and if so, which two drugs would be recommended?

From a CER perspective, the end goal — lowering blood pressure regardless of the therapeutic approach — should be the number one priority. Hypertension is on the rise (65 million adults, according to the Centers for Disease Control and Prevention [CDC 2011]), with the majority of cases undiagnosed, untreated, or not adequately controlled (Hajjar 2003). The initial CER priority list compiled by the IOM focused on conditions such as hypertension where the real world shows that the greatest barrier to achieving the end goal isn't which drug to use but rather accessing treatment in the first place.

Advanced Imaging is another area where use has substantially increased, quadrupling since 1995 (Lauer 2009), with computed tomography (CT) outstripping magnetic resonance imaging (MRI) scans. An issue with CT scans is that the procedure, unlike MRIs, exposes patients to radiation; it has been reported that up to 2 percent of cancers may be attributable to radiation exposure during these scans (Brenner 2007). To measure the impact of cumulative doses of radiation on specific organs, Brenner used claims data from UnitedHealthcare to assess patients that had received multiple scans over the 3-year study period. These are patients who typically are not monitored over time; therefore, few data exist to demonstrate appropriate and optimal use of advanced imaging. This scenario presents a clear opportunity for CER to introduce assessment and analy-

sis into an area where there hasn't been significant research and where there could be long-term health ramifications.

Conclusion

The promise of CER is to generate robust evidence to guide health care decisions with the aim of better quality health care and improved patient outcomes. To achieve this goal, stakeholders from across the health care continuum — patients, care providers, payers, pharmaceutical manufacturers, and policy makers, to name a few — will need to collaborate and partner in new ways.

Through its emphasis on appropriate use and outcomes, CER puts the needs of patients at the center of decision making. This emphasis will allow stakeholder discussions to go well beyond anecdotal medicine or price-based discussions and to focus on how to optimize the health of our communities.

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It's All About the Real World: Efficacy Versus Effectiveness

WellPoint has taken up the CER challenge, asking for and using real-world data to assist in its decision making. The organization has conducted its own "Real World Impact Assessment" of different drug classes through retrospective claims data.

WellPoint has used CER analysis to reassess and change the way oral asthma medications are approved for use. Spurred by data that showed oral asthma medications being used as front-line therapy (not as part of the FDA-approved drug indication or the NHLBI's asthma treatment guidelines), WellPoint's health outcomes research group, HealthCore, found that users of oral asthma controllers appeared to have better clinical outcomes than did the inhaled corticosteroid group. WellPoint removed prior authorization restrictions on the oral asthma therapies based on HealthCore's study of 55,000 medical and pharmacy claims, along with 800 quality-of-life surveys. The study demonstrated that better outcomes among those taking oral therapies could be traced to greater adherence to the therapy.

Ultimately, WellPoint was trying to determine "which therapy was best for members in the real world and align our formulary appropriately."

Source: Drugs.com 2008, WellPoint 2011

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