Summary

Comparative effectiveness research has received considerable attention since two pieces of legislation—the American Recovery and Reinvestment Act of 2009 and the Patient Protection and Affordable Care Act of 2010—dedicated significant funds to establish and support a national infrastructure for programs that directly compare the effectiveness of different treatments and care settings on health outcomes.

Behind the government’s decision to substantially increase funding for comparative effectiveness research was a belief that CER, as it is commonly known, could improve health care by discouraging the use of medicines, medical devices and treatment protocols that demonstrate limited benefit to patients. Such assessments, for example, might compare the effectiveness of one hypertension drug to another, leading to reductions in waste and unnecessary, and even harmful, variations in care at a time when the rising costs of health care are widely seen as a problem for the economy.

Though the pharmaceutical and medical device industries as a whole support many principles behind the legislation, they have expressed concern that CER might be used by public and private payers to limit patients’ treatment options. Further, if resources are diverted to studying the effectiveness of treatments for the “average” patient, the needs of patients with rare diseases, minorities, women and children might not receive adequate attention. Similarly, some physicians are worried about government and private insurance companies’ intrusion into the doctor-patient relationship, and its potential to impede their ability to provide patients with the best possible care.
Beyond restricting treatments to those shown to have the greatest benefit for the most patients, opponents of CER also fear that such research might stifle innovation. These fears are understandable. Similar approaches in other countries such as the United Kingdom, France, Germany and Australia have evolved to consider the costs of new drugs, devices and diagnostics in their decision-making. In the United States, the Affordable Care Act was written to prohibit cost considerations from influencing coverage decisions for public health programs including Medicare and Medicaid. However, those investing in new therapeutics and technologies might demand that additional studies be carried out early in the development process, anticipating that these factors will soon be a consideration of public and private health plan coverage decisions. This could potentially increase the development costs and time to market for these products.

Thus far, the government’s priority-setting processes for comparative effectiveness research have received enormous input from stakeholders including industry representatives and trade groups, physicians and other providers, and health care consumers. To fully realize CER's potential to improve health care quality and, perhaps, limit its costs, researchers need to optimize their analytical tools, develop better methods for evaluating health care data on patient outcomes, and improve the databases upon which these analyses are based.

**Introduction**

The U.S. government has been interested in comparative effectiveness research in one form or another since the expansion of public health programs including Medicare and Medicaid in the 1960s. Concerned about the lack of information on health care utilization, costs and service variations, the government established the National Center for Health Services Research in 1968. Ten years later, Congress also created the National Center for Health Care Technology, which, for four years, assessed the safety, efficacy, effectiveness and cost-effectiveness, as well as the social, ethical and economic impacts, of medical technologies. It also advised the Health Care Financing Administration (now the Centers for Medicare and Medicaid Services) on coverage decisions. In 1989, the National Center for Health Services Research became the Agency for Health Care Policy and Research, now the Agency for Healthcare Research and Quality (AHRQ), with an initial appropriation of $97 million.

AHRQ’s original charge and that of its predecessor—to support outcomes research, health technology assessments and practice guideline development geared towards reducing health costs, and ensuring Medicare’s sustainability—has evolved over time and continues to evolve. Currently, its mission is to improve the quality, safety, efficiency and effectiveness of health care for all Americans by supporting research that helps people make more informed decisions and improves the quality of health care services. Recent funding from the Medicare Prescription Drug, Improvement and Modernization Act of 2003 authorized AHRQ to fund comparative effectiveness research.
research on pharmaceuticals, devices and health care services, partly to support sound decision-making under the new Medicare drug benefit. The National Institutes of Health (NIH) and the Department of Veterans Affairs (VA) have been engaged in this research, which AHRQ coordinates through its Effective Health Care Program. Since 2005, Congress appropriated a total of $125 million for the program, including $50 million for comparative effectiveness in 2009.\\n
While there was longstanding and recurring interest in effectiveness research, CER got a significant boost with the passage of the American Recovery and Reinvestment Act of 2009 (ARRA), commonly referred to as the Stimulus Bill. Through ARRA, Congress appropriated $1.1 billion in funding for CER, which included $300 million for AHRQ, $400 million for the NIH and $400 million for the Secretary of the Department of Health and Human Services (HHS). The legislation established the Federal Coordinating Council for Comparative Effectiveness Research, composed of 15 senior federal officials with responsibility for health-related programs. Its mandate was to advise HHS on comparative effectiveness research, including prioritizing funding in this area, and to coordinate CER among relevant federal departments and agencies. ARRA also mandated that the Institute of Medicine (IOM) produce a study that elicited input from a broad array of stakeholders on high priority research topics.

Both the Federal Coordinating Council and the IOM published their reports in June 2009. In its report, the IOM provided a comprehensive definition of the term CER. It is, the IOM wrote, “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 IOM noted that CER’s purpose was “to assist consumers, clinicians, purchasers and policy makers to make informed decisions that will improve health care at both the individual and population levels.” This definition, which emphasizes the importance of studying patients in typical care settings and tailoring treatment decisions to the needs of individual patients, mirrors that developed by the Council and has been widely adopted.

In addition to defining CER, the IOM developed a priority list of 100 topics across 29 research areas; half of these topics compare some aspect of the health care delivery system, nearly a sixth of them address racial and ethnic disparities, and nearly a tenth address patients’ functional limitations and disabilities. The IOM also made recommendations on the requirements for a sustainable CER enterprise, such as establishing a national program with authority, overarching responsibility, sustained resources and adequate capacity; actively involving consumers in all levels of the national CER initiative; and developing large-scale data networks to facilitate comparative effectiveness research. Similarly the Federal Coordinating Council identified high-priority research gaps and recommended one-time investments in infrastructure to accelerate the implementation of CER.
Further federal support for comparative effectiveness research came one year later in the Patient Protection and Affordable Care Act of 2010 (Affordable Care Act). The health reform legislation created a public-private, nonprofit organization, known as the Patient-Centered Outcomes Research Institute or PCORI. (It also dissolved the Federal Coordinating Council, which had been created by the Stimulus Bill to coordinate federal activity in this area.) PCORI’s mandate is to “assist patients, clinicians, purchasers and policymakers in making informed health decisions by advancing the quality and relevance of evidence concerning the manner in which disease, disorders and other health conditions can effectively and appropriately be prevented, diagnosed, treated, monitored and managed through research and evidence synthesis that considers variations in patient subpopulations, and the dissemination of research findings with respect to the relative health outcomes, clinical effectiveness and appropriateness of the medical treatments, services and items.”

To do so, PCORI was tasked with identifying national research priorities, contracting with agencies and research institutes, and conducting systematic reviews, assessments and primary research. The head of the Government Accountability Office appointed 19 of PCORI’s 21-member board of governors; the board also includes the directors of AHRQ and the NIH. PCORI is funded by the Patient-Centered Outcomes Research Trust Fund through 2019, which has allocated $10 million for 2010, $50 million for 2011, and $150 million for 2012. Starting in 2013, this funding will come from an annual, per-member tax on Medicare and all private health insurance companies, which is estimated to reach $500 million annually by 2015.

PCORI released a draft report, National Priorities for Research and Research Agenda, for public comment in January. It identifies five areas where CER is needed to support decision-making: assessing prevention, diagnosis and treatment options; improving health care systems; communicating and disseminating research; addressing disparities; and accelerating patient-centered outcomes research and methodological research. The final priorities will guide funding for comparative effectiveness research.

The Controversy

The rising cost of health care is widely viewed as a problem for the economy. U.S. spending on health care totaled $2.6 trillion, or 17.9 percent of the nation’s gross domestic product, in 2010, and is projected to reach $4.6 trillion in 2019. At the same time, achievements in biomedical science have generated an overabundance of diagnostic, treatment and prevention options for patients. However, it is often hard to determine which therapeutic approaches work best for whom, when and in what circumstances. The IOM, in its CER report, wrote that the lack of information to inform such decisions results in “more than half of the treatments delivered today
without clear evidence of effectiveness.” Consequently, there is significant variation in treatment “with costs and outcomes differing markedly across the country.”

These are precisely the types of problems that CER has the potential to address. Using CER, AHRQ has generated evidence to inform treatment decisions for numerous conditions, including prostate cancer and osteoporosis. The NIH diabetes prevention trial found that lifestyle changes more effectively prevented the onset of type 2 diabetes than a blood sugar regulating drug called metformin or placebo, and the VA COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial found that percutaneous coronary intervention did not improve the outcomes of patients receiving optimal medical therapy to prevent heart attacks and death.iv

Much of the controversy over such research stems from concerns that the results will only be relevant to “average” patients, at the expense of individuals and subpopulations with different needs, and that the findings will be used to make benefit and coverage decisions, limiting patient choice. There is evidence that the general public is concerned about such impacts on their health care.v These concerns also have led to opposition from physicians, researchers and others involved in health care, bringing them together to form the Partnership to Improve Patient Care. The goal of this umbrella group is to support CER that is centered on patients’ needs and that considers medical innovation part of the solution to cost and quality problems in health care.

Such concerns are highlighted in a Manhattan Institute for Policy Research study, which evaluated the hypothetical impact of changing Medicaid reimbursement policies for antipsychotics based on the results of a 2005 CER trial.vi Called the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE), it found little difference between the effectiveness of older, cheaper antipsychotics from that of more expensive “second generation” drugs. The newer atypical antipsychotics, which have fewer side effects, were developed by the 1990s and are currently one of Medicaid’s largest and fastest growing medication expenditures—rising from $1 billion in 1995 to $5.5 billion in 2005.

Using CATIE data, Manhattan Institute researchers evaluated the effect of limiting coverage to the first generation drugs for 250,000 nonelderly, adult Medicaid enrollees with schizophrenia. They estimated this change in drug coverage would save Medicaid $1.2 billion per year, but noted that these savings would be outweighed by a reduction in patient health and the resulting hospitalizations for those who responded better to the newer drugs and had been denied coverage for them.

Further, the researchers conclude that CER will fail patients because such research does not take in account the variation in response to a given drug from patient to patient or the variation in each individual’s response to different drugs. As optimal therapy varies significantly across patients, comparative effectiveness research
needs to be designed in such a way as to recognize these differences at the individual level, they wrote.

Proponents agree that CATIE should not be used to justify an across-the-board coverage policy, and note that the cost of hospitalizing schizophrenics is high. Comparative effectiveness research, done correctly, focuses on the needs of subgroups—such as the Medicare patients who do not respond to older antipsychotics—and takes these concerns into account. It also “embraces the concept of individualized decision-making, in which the clinical characteristics and preferences of the patient help to determine the choice among alternatives,” wrote Harold C. Sox, M.D., who chaired the IOM committee on CER prioritization, in an *Annals of Internal Medicine* article. vii “Consequently, comparative studies will search for evidence that the response to treatment varies within the study population, a phenomenon called ‘treatment response heterogeneity.’”

**CER’s Impact on Innovation**

In addition to their concerns about CER’s potential to restrict care, many within the health care industry believe that comparative effectiveness research may be bad for business. Specifically, companies that manufacture drugs, devices and diagnostics fear that the government’s investment in and possible inappropriate application of such research has the potential to reduce the rate of medical innovation and consequently quality of life and life expectancy. This possibility stems from the need to increase clinical trial sizes, the complexity of clinical trials, and the number of studies that must be done to meet CER requirements before or in order to obtain approval from the Food and Drug Administration, as well as before or as a condition to be covered by health plans or government. viii They also fear that these requirements might increase clinical development times, delay time to market, and reduce the rate and extent of technology diffusion, thereby raising the costs and risks of development of new therapeutics from an investment perspective.

Though there is no empirical evidence that innovation has been stifled in countries using comparative effectiveness research, there have been numerous attempts to quantify its potential negative impact on investment in new medical technologies in the United States. ix These studies rely on many broad assumptions about future economic growth and market prices. Using empirical models to establish a direct relationship between pharmaceutical returns on investment and clinical development costs, a study published in the *Drug Information Journal* estimated that comparative effectiveness research could reduce research and development spending by $32 billion over 10 years. x Another concluded that investment in new and improved pharmaceuticals, devices and equipment would be reduced by about $10 billion per year between 2014 and 2025, an amount equal to about 10 to 12 percent of current spending on research and development. xi
Further, many opponents believe that comparative effectiveness research in the United States will evolve to explicitly consider costs and cost-effectiveness when making decisions or recommendations, similar to the experience of many countries internationally. The United Kingdom’s National Institute for Health and Clinical Excellence, or NICE, was established with a mandate to make coverage decisions. France’s Haute Autorité de Santé, Australia’s Pharmaceutical Benefits Scheme, and Germany’s Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, found that their ability to complete assessments was limited when costs were not included in their considerations. In response to industry’s concerns, the final language of the Affordable Care Act, similar to the Stimulus Bill, forbids the government from using quality-adjusted life-years or QALYs and other cost-effectiveness estimates to determine coverage, reimbursement or incentive programs in the Medicare program. (QALYs are a measure of the value of health outcomes as a function of both the length of life and quality of life and are used by NICE in its decision making).

Finally, there are also calls for oversight of the dissemination of comparative effectiveness research to physicians and other care givers—a process referred to both as counter-detailing and academic detailing—similar to the government’s regulation of pharmaceutical detailing. AHRQ, through its Effective Health Care program, shares its findings about medications and other therapeutics by contracting with academic detailing organizations, whose clinical consultants visit physicians, pharmacists, nurses, other clinicians and health care system decision makers nationwide. CER proponents believe this step is central to realizing the benefits of such research; its opponents want a level playing field with specific rules and regulations to govern the behavior and activities of AHRQ’s detailers.

Despite these concerns, the Pharmaceutical Research and Manufacturers of America, or PhRMA, the industry’s trade association, has come out in support of comparative effectiveness research. “When done well, comparative effectiveness research is a valuable tool for both promoting improved quality of care and supporting doctors and patients in their decision-making process about which treatment is right for the patient,” said Rick Smith, PhRMA’s senior vice president of policy, at a Feb. 27 forum on PCORI’s draft priorities. “This means making sure CER studies are high quality, are put in the context of the full range of available information, and account for the wide variability in patient needs and preferences.”

**The Way Forward**

Though considerable opposition to the government’s support of comparative effectiveness research remains, there appears to be widespread agreement that it would be beneficial to have more information about the relative clinical benefits of various drugs, devices and treatments.

International experience with CER has identified three ingredients for the success of organizations engaged in this research: strong political endorsement, early engagement with stakeholders, and demonstrable commitment to quality and
evidence-based practices in order to gain professional approval. Further, CER organizations need to be independent of government, insurance agencies and industries; transparent in the selection of topics, generation of evidence and final decision-making; inclusive; maintain scientific rigor; and timely; and they should establish a means of contestability.

Even with such structures in place, these bodies’ achievements have not come easily. The international experience has found that “… intense controversy, negative press and rapid transformation are intrinsic to the enterprise. An organization that manages to avoid controversy and criticism is probably not fulfilling its role of being useful to decision makers.”

The challenge for CER leaders in the United States is to ensure that their work is fair, accurate and transparent in its evaluation of medical procedures and processes. CER study questions, unlike traditional, investigator-initiated research, must continue to be prioritized through a multi-stakeholder process. These studies also need to move beyond traditional clinical trial approaches, which compare one drug to a placebo in controlled settings, to “designs that better account for diverse patient populations and health care settings, with methods that draw on and link alternative data sources,” said Clifford Goodman, PhD, senior vice president, The Lewin Group Center for CER, at a symposium on the topic. Only once the value of information resulting from CER studies has been demonstrated, will the federal efforts in this area gain broad public support.

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Chalkidou, Tunis, Lopert et al., “Comparative Effectiveness Research and Evidence-Based Health Policy: Experience from Four Countries,” 2009.
