

Balancing Act: Comparative Effectiveness Research and Innovation in U.S. Health Care

A White Paper



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About the New England Healthcare Institute

The New England Healthcare Institute (NEHI) is a nonprofit, health policy institute focused on enabling innovation that will improve health care quality and lower health care costs. Working in partnership with members from across the health care system, NEHI brings an objective, collaborative and fresh voice to health policy. We combine the collective vision of our diverse membership and our independent, evidence-based research to move ideas into action.



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Executive Summary

Comparative effectiveness research (CER) has risen to prominence in the debate over national health care reform. Equally important in this debate is the role of innovation, long the engine for growth and advancement in our health and our health care system. But to date, there has been little discussion about how CER might impact the dynamics of innovation in health care.

CER is, fundamentally, the comparison of two or more health care interventions. The comparison can be between discrete treatments (drug vs. drug, device vs. device); it can encompass combinations of products and care practices; or it can include a review of the structures and systems that comprise the practice, organization and delivery of health care. As such, CER will have an inevitable impact on innovation because, if it succeeds, it will act to winnow out some interventions and promote others.

The landscape of the CER debate changed dramatically in early 2009 with the enactment of the American Recovery and Reinvestment Act (ARRA), also known as the federal Stimulus Bill. In total, the act allocates \$1.1 billion over two years for CER: \$300 million to the Agency for Healthcare Research and Quality (AHRQ) and \$400 million each to the National Institutes of Health (NIH) and the Department of Health and Human Services (HHS), to be distributed at the discretion of the Secretary. Additionally, the act directs HHS to contract with the Institute of Medicine (IOM) to conduct a study to determine “recommendations on the national priorities for comparative effectiveness research.”¹

This new federal commitment to CER is a response to the fact that much of the health care that Americans receive is not grounded in empirical evidence of effectiveness. Recent research found that only 11 percent of the more than 2,700 recommendations contained in practice guidelines issued by the American College of Cardiology and the American Heart Association were supported by “evidence and/or general agreement that a given procedure or treatment is useful and effective.”²

These evidence gaps contribute to uneven health care quality and to dramatic variations in approaches and spending within practices, communities and entire regions of the U.S. The Obama administration and key congressional leaders view CER as one tool to address this variation by gathering data on and promoting what works best in health care.

How CER moves from legislation into implementation holds many implications for innovation across the U.S. health care system. There is a common belief that CER is primarily a tool to evaluate innovative medical technologies (drugs, devices and

¹ United States. Cong. House. 111th Congress, 1st Session. HR 1, American Recovery and Reinvestment Act of 2009. Congressional Bills, GPO Access. Web. 16 March 2009.

² Tricoci P et al, “Scientific evidence underlying the ACC/AHA clinical practice guidelines.” JAMA. 2009 Feb 25;301(8):831-41.

procedures). Yet CER is equally applicable to evaluation of competing medical protocols, care practices and organizational systems – areas where the need for innovation is urgent. Dr. Jack Wennberg of Dartmouth Medical School, the leading U.S. expert on medical practice variation, suggests that federal CER research “must first be aimed at rationalizing care processes.”³

This white paper examines the likely impact that federally funded CER will have on innovation and suggests issues policymakers should consider to achieve the best of both worlds: **vast improvements in the evidence base supporting health care, and sustained development and adoption of valuable innovation throughout the health care system.**

The paper is based on research by the New England Healthcare Institute (NEHI), including a series of focus groups and expert interviews with a wide range of health care stakeholders and an expert roundtable discussion held in Cambridge, Massachusetts in October 2008.

Key Findings: CER’s Impact on Health Care Innovation

The impact of CER on innovation will be shaped in large part by the policy choices facing federal agencies and others as they seek to implement CER activities described only in broad strokes in the ARRA. These critical choices include decisions on the goals, priorities and scope, study methodologies, and application of CER.

- **CER Goals:** There are two basic options facing policymakers on the goals of CER: clinical effectiveness and cost effectiveness. Congress, through the ARRA, has taken a first step by directing HHS and its agencies to make comparative clinical effectiveness the standard of new CER research. This goal is more likely to sustain valuable innovation in technologies than comparative cost effectiveness. Cost-based standards entail greater methodological complexity and provoke a level of controversy that could weaken the ability of the CER program to act as a force for change, particularly in promoting evidence-based innovation where it is most needed: in health care delivery. Despite these concerns, cost effectiveness as a goal of CER is likely to remain a subject of debate. In this event, the debate over cost effectiveness analysis should be reframed as a debate over long-term value, not short-term cost, in order to sustain innovation.
- **Priorities and Scope of CER Studies:** To promote valuable innovation, the CER research agenda should encompass studies of the broader issues of health care practices, organization and delivery in addition to studies of medical technologies. Studying topics where significant evidence gaps exist would also spur innovation. Within any one topic, the scope of the study should also be broad, reflecting the complexity of real-world medical decisions in providing care for diverse patients in diverse settings. Conversely, narrowly scoped analyses focused on comparing

³ The Dartmouth Institute for Health Policy & Clinical Practice, *Improving Quality and Curbing Health Care Spending: Opportunities for the Congress and the Obama Administration* (A Dartmouth Atlas White Paper), December 2008: 7.

individual drugs or devices has the potential to more negatively impact innovation, particularly in medical technologies.

- **CER Processes and Methodologies:** The extent to which CER is conducted using open and transparent processes will have a significant impact on innovation. Open and transparent processes are more likely to yield high-quality research results and will show health care innovators the rules of the road. In addition, a wide array of study methods will be required to produce useful CER findings in a broad range of areas across health care. The preponderance of data and research methods currently available, obtained primarily from randomized clinical trials (RCTs), was developed for narrower purposes. Consequently, investment in the development and selection of new methodologies that move beyond RCTs is critical for innovation. New methods will be needed to identify the impact of innovations not only on the average patient, but also on patients with diverse characteristics. Appropriate methods will be needed to discern the effectiveness of innovations that may need repeated utilization or may need to be combined with other interventions to demonstrate their true value. Finally, different research methods are needed to conduct research on innovations in the practice, organization and delivery of health care.
- **Application and Use of CER Studies:** Congress has directed that – at least for now – federally supported CER studies should not be explicitly linked to or provide the sole justification for coverage and reimbursement decisions. This policy to avoid coverage mandates will help sustain the utilization of new technologies that produce valuable benefits for patients and physicians. Currently, the dissemination of evidence-based findings is currently protracted and uneven. Thus, the CER program must find new and more effective approaches to disseminate CER findings to patients, clinicians and payers in ways that will encourage the adoption of effective innovations and practices. Efficient dissemination and the resulting adoption of effective innovations at the point of care will support and sustain innovation, particularly in health care practices, organization and delivery.

With the passage of the ARRA, the debate has shifted from whether a federal CER program will be authorized to how it will be designed and implemented. To fully preserve and promote innovation, CER policymakers will need to carefully consider the policy options presented in this white paper on the development of study goals, priorities and scope, processes and methodologies, and application and use. To achieve this, an open dialogue is required between federal entities designing and conducting CER and the stakeholders from across the health care system who will be impacted by the study outcomes.

NEHI believes that CER can, and must, be designed in a way that truly identifies those interventions that best meet patient needs. In so doing, it will send a signal to innovators that the CER process will support the development of valuable innovations that are so crucial to improving care processes and treatment outcomes for patients.

The Crucial Role of Innovation in U.S. Health Care

Innovation has long been the engine for growth and advancement in our health and our health care system. Indeed, innovation in medical technology has been dramatic and pervasive. New technologies are credited with such radical improvements as the sharp reduction in mortality from heart disease and cancers in the U.S. since World War II. Continued introduction of innovative medical technologies and access to new therapies that may address unmet medical needs is a life-or-death issue for many patients.

Innovation in medical technologies also plays an important role in the U.S. economy. Three out of every four new drug introductions worldwide are made in the U.S., for example. In the context of the current global economic downturn, identifying ways to control health care costs while sustaining U.S. leadership in medical innovation will be a priority.

Yet innovation in health care goes well beyond innovation in medical technology. Innovations in care practices, delivery systems, benefit design and other areas can be equally dramatic. Recent examples of significant innovations in health care quality include the '100,000 Lives' campaign for patient safety led by the Institute for Healthcare Improvement and executed by U.S. hospitals. And the Asheville Project is an innovative model of chronic diabetes management that markedly improved treatment adherence and health outcomes among patients through partnerships with employers and pharmacists.⁴

Innovation in health information technology (HIT) is also widely seen as a crucial step toward improving safety and efficiency throughout the U.S. health care system. New investment in HIT is a major goal of the ARRA.

Continued innovation at every level of the health care system is considered a necessity for fundamental health care reform. In the words of the Commonwealth Fund Commission on a High Performance Health System for the United States, fundamental health care reform "demands an accelerated rate of innovation and improvement."⁵

⁴ See Chernew ME et al, "Value-based Insurance Design." *Health Aff.* 2007 Mar-Apr;26(2):w195-203. Epub 2007 Jan 30.

⁵ Commonwealth Fund Commission on a High Performance Health System for the United States, "Framework for a High Performance Health System for the United States," August 2006.

CER and the Dynamics of Health Care Innovation

In comparing health care interventions, CER by its very nature will have an impact on innovation in health care; innovation creates the very technologies, care practices and organizational structures that will be subject to CER review. It is critical, then, to understand how health care innovation works, beginning with the differences between innovation in medical technology and innovation in health care practices, organization and delivery.

Innovation in Medical Technology

Medical technologies include a wide spectrum of interventions ranging from pharmaceuticals, medical and diagnostic devices, and surgical and imaging equipment to medical and surgical procedures and other types of therapy. The introduction of new medical technologies is primarily driven by new scientific discoveries (such as the decoding of the human genome) and advances in engineering (such as in electronics that have made magnetic resonance imaging and other imaging innovations possible).

Four key dynamics of innovation in medical technology are:

1) Regulatory oversight influences market availability

Medical technologies are subject to varying degrees of regulatory oversight before they are approved for utilization by physicians and patients. In general, the introduction of new drugs and devices is closely regulated by the FDA through evaluation of clinical trials. New drugs typically face 12-15 years of development before introduction to the market, provided they pass all regulatory hurdles.

In contrast, new surgical and medical procedures do not typically require clinical trials for regulatory approval, although the development of many new procedures is increasingly dependent upon the use of medical devices that are themselves subject to clinical trials and regulatory oversight (implantation of coronary artery stents, for instance). This disparity in regulatory treatment creates a disparity in the availability of data, which has important implications for CER.

2) Upfront investment required

Highly regulated products such as drugs and devices enter the market after years of sustained investment, bearing a higher financial burden to the innovator than less-regulated procedures. To the extent that CER studies create new costs (measured in the delay of market adoption or in new, out-of-pocket costs to the innovator), they could raise the overall cost of developing new technologies, thus inhibiting investment in them.

3) Utilization by physicians and patients reveals best use

Many medical technologies achieve lasting usage and the approval of physicians and patients only after physicians begin to utilize them and discover which new technologies work best with different patients facing varying circumstances. Frequently, medical technologies approved for use in one indication find new or different uses in other indications as a result of repeated, off-label utilization and the resulting experience gained by clinicians. This accumulation of experience among clinicians is perhaps the most important dynamic of innovation from the standpoint of CER policy. For example, in the medical device field, medical lasers initially developed for ophthalmology and dermatology ultimately found new uses in gastroenterology, oncology and thoracic surgery. Similarly, in pharmaceuticals, beta blockers are now widely used as a standard therapy for hypertension despite being originally introduced and approved for treatment of cardiac arrhythmia. Indeed, studies indicate that as many as 20 percent of prescriptions written in physician offices are for off-label use, particularly in cancer care, where drugs initially approved for late-stage disease sometimes evolve into use as first-line or second-line treatments.

In addition, new medical technologies frequently undergo several iterations of redesign and refinement even after they win initial FDA approval and enter the commercial market, as clinicians gain more experience with them. (For example, many artificial joints and cardiac pacemakers now in general use have undergone successive rounds of re-engineering since their first introduction, based on experience gained with clinical use.)

4) Highest value evolves in combination with other interventions

New technologies frequently find their best, highest value use only in combination with other products or procedures, often as a result of utilization with varying combinations of treatments carried out over time. Radiation and chemotherapy for breast cancer is an example. Both were introduced as stand-alone therapies, but have found their best uses in combination with each other. The synergies created by combinations of technologies may result in progress that is difficult to connect to any one specific technology.

Challenges for CER Policy

The dynamics of innovation in medical technology present three key challenges for the development of CER policy:

1) Data availability

CER implementation policy faces a challenge in the availability of adequate data. Clinical trial data developed for FDA approval are available as sources of information for CER studies. However, broader-based CER analyses will require new data from prospective studies or from retrospective analysis of broader data sources such as claims data.

2) *Timing*

CER policy must consider critical questions around the timing of CER studies, including: When in an intervention's lifecycle is it most appropriate to subject a technology to comparative review? How can evaluations account for the changing role and value of an intervention over time? Can CER policy allow for appropriate access to technologies by patients and physicians so that valuable experience with the technology can be gained?

3) *Discerning variation*

CER policy must also consider how studies can account for variations in usage, and for synergies achieved through varying combinations of technologies, that may prove important to providing the best care responsive to the varying needs of individual patients.

This challenge in discerning variation is amplified by the ongoing revolution in genomics, which has the potential to transform care by revealing genetic variations that distinguish patient subpopulations from each other and individual patients from one another. Many of these differences are revealing ways that patient subgroups respond differently to a given treatment. With this knowledge, it should become easier to determine which treatment should (or should not) be used for a particular patient or patient subgroup, which is at the heart of the so-called personalized medicine movement. The emergence of personalized medicine represents substantial opportunities and challenges for CER.

On the one hand, CER holds promise in closing the major evidence gaps relevant to personalized treatments. CER studies can help shed light on the clinical utility of new personalized medicine interventions (such as molecular diagnostics) and, ultimately, discern their impact on health outcomes.

On the other hand, the data on genetic variation is still in its infancy. The overwhelming preponderance of existing data on patient response to medical interventions, particularly data from RCTs conducted for regulatory approval purposes, yields findings demonstrating an average patient's response. In the past these generalized results have frequently overlooked variations pertinent to large subgroups, including women, children and minorities, let alone variations pertinent to genetic characteristics. As a result, past CER studies have had to rely on generalized findings and have given rise to the fear that future CER studies will yield "one-size-fits-all" findings. Thus, a major challenge for federal policy going forward is to ensure that new CER studies actively seek out or promote the development of data that fully reflect patient variations, particularly as the revolution in genomics generates more and more data.

Innovation in Health Care Practices, Organization and Delivery

The Commonwealth Fund's call for an "accelerated rate of innovation and improvement" in health care is rooted in findings that innovation in health care systems is slow and uneven. The IOM's seminal report on patient safety, *To Err Is Human: Crossing the Quality Chasm*, notes that, "The lag between the discovery of more efficacious forms of treatment and their incorporation into routine patient care is unnecessarily long, in the range of about 15 to 20 years. Even then, adherence of clinical practice to the evidence is highly uneven."⁶

Three key dynamics play an important role in innovation in health care practices, organization and delivery:

1) Fragmentation

U.S. health care is highly fragmented among providers and payers. Few patients are covered by highly integrated health care systems such as the Kaiser Permanente system, the Intermountain system, the Mayo Clinic and the Cleveland Clinic. Instead, most health care markets are composed of disparate payers and providers with limited incentive to collaborate and share best practices.

2) Localization

Health care delivery is highly localized. Health care markets are extremely diverse relative to the size and influence of payers, hospitals, primary care physicians and specialists. The highly localized nature of U.S. health care contributes to the high degree of practice variation documented in the *Dartmouth Atlas*.

3) Misaligned incentives

Incentives to create, promote and adopt valuable innovations are often weak and poorly aligned. Weak incentives to provide highly coordinated care, essential to the management of chronic conditions, is currently fueling interest in payment reforms that will align the interests of patients, providers and payers.

In the absence of strong incentives for innovation, successful innovation in health care organization and delivery frequently depends upon more idiosyncratic factors such as the culture of individual health care institutions, their receptivity to change and the presence of strong internal leadership ready to promote change.

Challenges for CER Policy

The slow and uneven pathways for innovation in health care organization and delivery pose significant challenges for CER policy. CER policymakers face obstacles in delivering

⁶ IOM, Committee on Quality of Health Care in America. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academy of Sciences, 2001: 145.

CER findings that can be disseminated and adopted by the U.S. health care system much more quickly than the 15-20 year path described by the IOM.

More important, CER policy should deliver findings that are directly relevant to patients and physicians in the daily practice of medicine. Findings should be useful to the physician at the point of care, reflecting the complexity of real-world care delivery. To quote Dr. Jack Wennberg, “The research to address unwarranted variation in the frequency of use of supply-sensitive care for the chronically ill must be radically different from research that is primarily focused on comparing alternative treatment options.”⁷ Former FDA Director and CMS Administrator Mark McClellan has noted that, “Where we really need better evidence, if you look at the numbers, is on evaluating different styles of medical practice, not just head-to-head comparisons of particular treatments.”⁸

Federal CER policy designed to meet such real-world needs should take several factors into consideration, including balancing research priorities between studies of discrete technologies and studies of issues in health care organization and delivery; appropriately scoping studies so they reflect the multiple variables at play in the delivery of effective medicine at the point of care; developing robust methodologies that capture valid comparisons of medical effectiveness at the point of care; and successfully disseminating CER findings to patients and clinicians.

⁷ The Dartmouth Institute for Health Policy & Clinical Practice, *Improving Quality and Curbing Health Care Spending: Opportunities for the Congress and the Obama Administration* (A Dartmouth Atlas White Paper), December 2008: 7.

⁸ John A. Vernon and Joseph H. Golec, *American Enterprise Institute Forum: Pharmaceutical Price Regulation: Public Perceptions, Economic Realities, and Empirical Evidence*, February 17, 2009.

Drivers of CER's Impact on Health Care Innovation

Whether CER will be compatible with innovation depends on how key aspects of CER policy are defined. There are four fundamental aspects of CER policy that will determine its impact on innovation:

- CER goals
- Priorities and scope of CER studies
- Research processes and methodologies for CER
- Application and use of CER findings

CER Goals

Policymakers face two basic options as goals of CER: clinical effectiveness and cost effectiveness. Clinical effectiveness studies demonstrate what works best in health care and would improve quality by providing evidence for better decision making by patients and clinicians. Cost effectiveness studies consider cost in addition to clinical considerations in determining the most valuable health care interventions.

Across the health care system, there is consensus that better clinical evidence is needed to support decision making at the point of care to reduce variation and promote health care quality. This has generated wide support for clinical effectiveness studies.

Another school of thought advocates including cost or price as a fundamental consideration, in addition to clinical effectiveness, in CER studies. However, there is a concern that cost alone could be used to rule out valuable innovative technologies regardless of their clinical value, could create barriers to market that overlook longer-term evolution in product value, and could shift the research focus from patient/provider concerns to payer concerns.

In practice, even if cost effectiveness is not an explicitly stated goal, CER policy could become a *de facto* means of cost control in two ways. First, if adoption of clinical effectiveness findings results in better health care practices, including reducing unwarranted practice variation, savings would result. The Commonwealth Fund in 2007 estimated that the U.S. health care system could save nearly \$370 billion over 10 years on the strength of a federal CER program budgeted at approximately \$1 billion per year, with savings largely tied to the creation of physician and payer incentives to change practices based on CER findings.⁹

⁹ C. Schoen et al., *Bending the Curve: Options for Achieving Savings and Improving Value in U.S. Health Spending*, The Commonwealth Fund, December 2007: 19-21.

Second, clinical effectiveness studies could be linked indirectly to cost control goals if CER priorities target high-cost interventions or conditions, such as high-prevalence or high-cost diseases, high-cost procedures or drugs, or interventions with rapidly increasing rates of utilization.

Political Climate

The ARRA has broadly endorsed clinical effectiveness as the primary goal of federal CER efforts. In the legislation, Congress directs HHS and its agencies to make clinical effectiveness the goal of studies launched under the new CER program. It makes no mention of other goals such as the relationship of CER to health care cost containment, much less any linkage of new CER studies to the explicit goal of cost effectiveness in medicine.¹⁰ President Obama's budget submission ("A New Era of Responsibility") also links CER studies to a clinical effectiveness goal.¹¹

However, the debate over making cost effectiveness a CER goal is likely to arise again this year as the administration and Congress seek to control health care costs through overall health care reform. If this happens, policymakers may be compelled to rethink how federal CER efforts are organized. Many of the experts consulted suggested that two separate entities or research networks should be set up if the federal government ultimately decides to pursue comparative cost effectiveness as well as clinical effectiveness analysis. This sentiment echoes that of some leading CER proponents, such as former Health Care Financing Administration (HCFA) administrator Gail Wilensky, who has suggested that clinical and cost effectiveness research should be separated into independent, parallel programs.¹² In its December 2007 report on CER, the Congressional Budget Office (led by Peter Orszag, now budget director for President Obama) noted that "having the same organization fund analyses of both clinical effectiveness and cost effectiveness could reduce the impact of any findings about the former – because those findings might be perceived as reflecting cost-control objectives."¹³

Prominent CER proponents dispute the contention that cost effectiveness studies will automatically tend to rule against new or higher-cost technologies. They argue that cost effectiveness analysis may actually favor technologies and treatments that create outcomes of comparatively greater overall value for patients and payers, regardless of the initial cost of treatment. This view of health care value is more consistent with analysis of cost utility. It moves away from comparing the price of Treatment A to Treatment B and takes a more

¹⁰ Cong. Rec. 12 Feb. 2009: H1323-1326 and H1423-1426.

¹¹ Office of Management and Budget. A New Era of Responsibility: Renewing America's Promise. Washington: GPO February 26, 2009. Accessed at http://www.whitehouse.gov/omb/assets/fy2010_new_era/A_New_Era_of_Responsibility2.pdf

¹² Wilensky GR, "Cost-effectiveness information: yes, it's important, but keep it separate, please!" *Ann Intern Med*. 2008 Jun 17;148(12):967-8. Epub 2008 May 15.

¹³ Congressional Budget Office. Research on the Comparative Effectiveness of Medical Treatments. Washington: CBO, December 2007: 26.

holistic or long-range view of patient outcomes, measuring the value of treatments over time as realized by patients, payers and other stakeholders.

Implications for Innovation

Focusing the goal of CER on clinical effectiveness (as opposed to cost control) is most likely to sustain innovation throughout the health care system.

Clinical effectiveness studies would be less controversial, and therefore valuable innovations identified through CER would be adopted more rapidly. Given the controversy over cost effectiveness research, findings from clinical effectiveness studies are more likely to influence medical decision making quickly.

Clinical effectiveness studies better accommodate the lifecycle of innovation. A clinical effectiveness goal is more likely to provide a period of utilization by patients and physicians that will prove an innovation's highest and best value. In addition, the costs of innovations frequently change over time, especially if they move into widespread use, resulting in changes to the relative cost effectiveness of interventions. The clinical effectiveness standard is more likely than a cost effectiveness standard to afford promising innovations a reasonable chance to prove themselves.

Clinical effectiveness studies are more likely to support innovations that address variation among patients. Addressing the cost effectiveness of interventions delivered to a variety of patient sub-groups is inherently more complex than simply determining clinical effectiveness among the same sub-groups. Therefore, clinical effectiveness studies are less likely to rule out innovations that prove effective in treating a patient sub-group.

In the future, the debate over cost effectiveness analysis should be reframed as a debate over value, not cost, in order to sustain innovation.

Despite the concern that cost effectiveness studies would rule out high-potential innovations on the basis of cost, cost effectiveness studies could, in fact, generate positive findings for high-cost interventions if they demonstrate substantial value. Therefore, the debate should focus on long-term value, not simply short-term cost, of innovations.

Priorities and Scope of CER Studies

Priorities: Topics, Relevance and Budget

The impact of CER on innovation will be greatly determined by the interventions policymakers choose to study and the types of research questions that are asked. The selection of priorities for the federal program is viewed as essential given the enormous array of topics that could be studied and the inevitable limits on federal resources. The ARRA recognizes this need and directs the IOM to report back to Congress on national CER priorities by June 30, 2009.¹⁴

The fundamental priorities of Congress and the Obama administration are to fill significant evidence gaps and drive substantial quality improvements in health care. But the endless selection of health care topics to study will require more detailed priority setting.

Given Congress' apparent determination to rule out CER studies specifically focused on cost effectiveness, while redoubling efforts aimed at health care cost control, CER policymakers may feel impelled to target clinical effectiveness studies on topics that relate to the biggest drivers of health care spending. Studies relevant to high-prevalence diseases or highly utilized services would fit easily into this policy focus, as would a more explicit focus on high-cost diseases, high-cost medical interventions for broad populations, or topics of highest relevance to federal health programs such as Medicare and Medicaid.

Ultimately, the size of each year's CER budget will be a key factor in whether priorities are met. More ambitious priorities will require significant funding. Congress initially appropriated \$1.1 billion as part of the ARRA; it remains to be seen whether Congress will continue to appropriate funding on the same scale for CER in the future.

Scope: Right Questions, Useful Answers

An important question is how narrowly or broadly studies should be targeted. There is a widespread presumption that CER studies entail a direct, head-to-head comparison of discrete items, such as drugs and devices. However, the scope of CER analysis can be broader, and many experts suggest that CER studies *should* be broader in order to compare the different choices that physicians and patients face in the daily practice of medicine.

Dartmouth's Dr. Elliott Fisher provided illustrative examples in speaking to *The New York Times* in February 2009. Fisher suggested that key areas of study for federal CER analysis would be questions such as, "Is it better to treat severe neck pain with surgery or a combination of physical therapy, exercise and medications? What is the best combination of 'talk therapy' and prescription drugs to treat mild depression?"¹⁵

¹⁴ Cong. Rec. 12 Feb. 2009: H1323.

¹⁵ Pear, Robert. "U.S. to Compare Medical Treatments." *The New York Times* 16 February 2009.

Indeed, experts consistently point out that effective health care is not only a question of understanding the clinical decisions made at the point of care, but also the systemic features – such as benefit design and payment systems – that influence and support those decisions. Broadly scoped CER studies could and should address that larger context, and in doing so would help fill an unmet need for good empirical evidence on these systemic issues.¹⁶

Despite their benefits, broadly scoped CER studies will present methodological challenges. First, studies of the real-world effects of any intervention (be it a medical technology or a formulary design) will require methods that reflect real-world use. Broadly scoped studies are, by their very nature, complex and require data that is not routinely collected. Today, the preponderance of available data comes from RCTs, a research technique that typically attempts to isolate the impact of only a few variables, and is considered the gold standard of medical evidence. However, in order to conduct broadly scoped CER studies that are widely accepted by health care practitioners, CER policy will need to develop authoritative approaches on par with RCTs.

Second, studies of care delivery (e.g. practices, organization and delivery of care) require methods that are distinct from those typically used to evaluate medical technology.

Implications for Innovation

The choice of priorities will determine what types of innovations are affected by CER.

Federal CER priorities will be of crucial importance in determining the impact of CER on health care innovation. Those innovations that are studied will naturally be the most affected.

Broadly scoped CER studies are more likely to sustain valuable innovation.

Broadly scoped studies are more likely to capture the complexity and interactions of real-world practice. Broadly scoped studies are more relevant for practitioners at the point of care because they more accurately reflect real-world conditions, and identify the kinds of innovation that evolve when practitioners use new approaches and gain experience in practice. In contrast, narrowly scoped studies are more likely to isolate discrete interventions that may not demonstrate their highest value until they combine synergistically with other technologies and services.

Narrowly scoped studies may negatively impact innovation, particularly in medical technologies.

Due to limitations on the CER budget and pressure to generate study results, CER policy could skew toward narrowly scoped studies – particularly interventions subject to FDA approval – for which data and methodologies are readily available. If this occurs, the result

¹⁶ Pearson SA et al, “Changing Medication Use in Managed Care: A Critical Review of the Available Evidence.” *Am J Manag Care.* 2003 Nov;9(11):715-31.

would be a disproportionate focus on already regulated medical technologies such as drugs and devices. Topics that would not be studied in this case include modes of health care practices, organization and delivery, where innovation is sorely needed.

CER could spur innovation if its priorities include topics on which comparatively little is known.

Physicians often must make their best medical judgments despite limited evidence. Many analysts believe that the nation has chronically underinvested in clinical, translational and health services research¹⁷, resulting in significant evidence gaps throughout medical practice. If CER studies focus on areas in which scientific evidence is limited, they may identify opportunities for newer, better treatment, which would spur innovation in those areas. Studies identifying superior approaches to care delivery and organization will become a force for innovation by creating new standards of practice and performance, thereby reducing the lag time in adoption of new evidence and new evidence-based therapies. They also are likely to support communication of information that is most relevant to the needs of providers and patients at the point of decision making.

Transparency and openness in the establishment of CER priorities will have a beneficial impact on innovation.

Transparency and predictability are vital to innovation. Given the vast number of choices facing policymakers in developing CER priorities, the need for transparency in the process is crucial. Congress signaled a sensitivity to this need in the ARRA by stipulating that the IOM consult widely with stakeholders in drafting its June 2009 report on CER priorities, and in directing the Secretary of Health and Human Services to give stakeholders opportunities to review and comment on CER reports supported by the department.¹⁸

¹⁷ See Woolf SH, "The Meaning of Translational Research and Why It Matters." JAMA. 2008 Jan 9;299(2):211-3.

¹⁸ Cong. Rec. 12 Feb. 2009: H1323-1326 and H1423-1426.

CER Processes and Methodologies

Federal CER policymakers face significant challenges as they select appropriate processes and methodologies for use in conducting CER studies. As noted earlier, the great preponderance of data and analysis currently available to CER researchers comes from examinations of interventions under highly controlled circumstances – not for comparative purposes. Consequently, the expansion of federal CER programs brings to the fore the significant work that remains to be done in developing methods to generate large volumes of real-world evidence on what works best in health care.

Randomized Clinical Trials: The Gold Standard

Growing attention to CER has shown policymakers the need to look beyond the historic gold standard in medical evidence, the RCT.

By comparing an intervention against a placebo (or standard therapy, in some cases) in two identical groups, RCTs isolate specific effects of the intervention under study, eliminating confounding variables. Thus, RCTs give a high level of confidence that any effects observed are due to the intervention being studied. However, as policymakers seek evidence on the real-world effects of different interventions, new research methods are required. RCTs do not fully capture the complexities of treating patients in real-life situations, which include highly variable patient characteristics and subgroups, often variable adherence of patients and physicians to recommended courses of therapy, and the administration of complementary interventions.

In addition, RCTs have become increasingly expensive and time consuming, as regulatory standards have tightened and statisticians attempt to overcome the limitations of randomized trials by recruiting larger cohorts of patients. The Tufts Center for the Study of Drug Development estimates that the total cost of development for a new biopharmaceutical is over \$1 billion.

Robust comparative RCTs – studying interventions already in the marketplace as opposed to approval trials – can be similarly time consuming and expensive. The ALLHAT trial of competing hypertension and cholesterol treatments is estimated to have cost over \$120 million. And the 15-year Women’s Health Initiative, which evaluated hormone replacement and other therapies, has cost over \$700 million. Consequently, budget limitations alone would mean that the federal CER program will only be able to afford a limited number of true RCTs at a given time.

Other, less expensive forms of CER, such as systematic reviews of existing research and retrospective data analysis, have limitations as well. One challenge is that systematic reviews often use data collected for other purposes – not necessarily for the specific

research question under investigation. Therefore, researchers must try to establish true comparability between disparate previous studies to reach valid conclusions.

In addition, existing studies often have a limited shelf life, given the fact that interventions may change rapidly – particularly interventions based on quickly changing medical technologies.¹⁹

Budget: More Money, More Methods

The size of the yearly CER budget will determine the ability to make investments in studies and study methods. Systematic reviews (synthesis or meta-analysis) of existing data and research are usually less expensive than developing new data through original research. Yet sufficient resources will be necessary to develop methodologies suitable to investigating the broad range of priority topics identified by the CER program.

Timing: How Soon Is Too Soon?

A key issue is the timing of CER analysis in the lifecycle of an intervention: whether CER studies target technologies or other innovations that are relatively new or not yet highly utilized. As noted earlier, many new interventions require some period of repeated utilization by clinicians before they prove (or disprove) their highest and best value for patients. For example, new cancer therapies often are first used in patients who have failed other treatments, and then evolve to second- or first-line treatments.

Conversely, some interventions that appear to be of high value early on may prove to be comparatively ineffective, or even harmful, over a longer period of time. For example, early on, hormone replacement therapy (HRT) became a standard treatment for difficult symptoms of menopause, but closer study in controlled clinical trials over a decade revealed that HRT is actually harmful and counterproductive for many patients.

The Congressional Budget Office recognized these challenges in its December 2008 report to Congress on U.S. health care reform: “One disadvantage of accelerating research on comparative effectiveness is that negative results from early studies might discourage the use of a promising treatment before it has been adequately tested. That might prevent the reinvention and improvement of certain medical technologies that often occur once a treatment has been introduced.”²⁰

Beyond the RCT: New Methods Needed

A robust and balanced CER program will need to develop new and improved methodologies to meet a wide range of study objectives, ranging from the analysis of discrete medical technologies (drugs, devices and procedures) to pathways of health care

¹⁹ For a discussion of comparability issues as they relate to assessment of medical imaging, see Pearson SD et al, “Assessing The Comparative Effectiveness Of A Diagnostic Technology: CT Colonography.” Health Aff. 2008 Nov-Dec;27(6):1503-14.

²⁰ Congressional Budget Office. Budget Options - Volume 1: Health Care. Washington: CBO, December 2008: 86.

including health care practices, organization and delivery. Methodologies must also be available to conduct all modes of comparative analysis, including meta-analysis of existing studies, new research using existing data (retrospective studies), and the conduct of wholly new and prospective trials.

Importantly, innovations in trial designs and statistical methods promise to deliver new methodologies that may yield reliable results at less cost and with smaller trials. For example:

- Adaptive clinical trials that allow statisticians to accurately infer results from early-stage or incomplete data may shorten the time and expense of trials.
- Practical clinical trials test therapies in real-world settings, as they are delivered to diverse groups of volunteer patients by their regular doctors.
- Continued development of patient databases, thanks to growth in electronic medical records and HIT infrastructure, will also allow data mining that will make accurate findings easier and cheaper to produce.

Congress acknowledged this methodology challenge when it enacted the Medicare Improvements for Patients and Providers Act of 2008 (MIPPA). The legislation directs the IOM to study methodological standards for CER in order to identify methods that are “objective, scientifically valid and consistent.”²¹ Methodology development was also a major objective of the CER legislation introduced by Senators Max Baucus and Kent Conrad before the inclusion of new CER authorization in the ARRA. The Baucus/Conrad legislation called for the creation of an expert methodology committee to define, validate and promote development of comparative effectiveness methodologies.²² These issues will likely arise again with any future congressional or administration action providing further details and structure for federal CER activities.

Regardless of the methodologies ultimately pursued, there is a widespread call for openness and transparency in their development and selection. As stated by Brandeis University’s Health Industries Forum, “There needs to be trust in the research findings, the research process, and the entity responsible for prioritizing, funding and disseminating the research.”²³

The Medicare Payment Advisory Commission (MedPAC) echoed this call in a 2007 report to Congress on CER. “To carry out its activities effectively, [a CER] entity needs to develop a clear rationale for selecting the services to study, use rigorous methods and the best

²¹ United States. Cong. House. 110th Congress, 2nd Session. H.R. 6331, Medicare Improvements for Patients and Providers Act of 2008 [Enrolled as Agreed to or Passed by Both House and Senate]. Congressional Bills, GPO Access. Web. 3 March 2009.

²² United States. Cong. Senate. 110th Congress, 2nd Session. S. 3408, Comparative Effectiveness Research Act of 2008. Congressional Bills, GPO Access. Web. 3 March 2009.

²³ Health Industry Forum, “Implementing Comparative Effectiveness Research: The Value Proposition for Patients, Physicians, and the Health Care System,” Conference Report, 25 July 2007. 2.

scientific evidence to conduct its research, and provide for an opportunity for comment and participation from different constituent groups.... Setting up a transparent process that is understandable, clear and documented to produce objective research will be important; people might not use the research if they consider the process subjective and the results biased."²⁴

Implications for Innovation

Investment in new CER methodologies is critical for innovation.

Currently available study methodologies do not adequately capture the full value of interventions as used in the real-world. They do not fully account for subtle variations in patient populations or the complexities and confounding factors of real-world medical practice, nor do they adequately compare competing pathways of health care delivery. Consequently, current methodologies may fail to identify valuable innovations or could unintentionally undervalue innovations that do meet specific patient needs.

To maximize innovation, there must be significant and ongoing investment in refining existing methodologies and developing new approaches. However, federal agencies charged with conducting CER studies will face pressure to produce findings immediately, which could compel them to default to existing data and underinvest in the development of new methodologies. But strategic investment in methodologies could be of greater long-term value than defaulting to existing study methods. Therefore, federal policymakers should seek a balance between conducting immediate CER studies and longer-term investment in methodologies.

Poorly timed CER studies may unduly inhibit innovation, and fail to promote valuable innovation.

To sustain innovation, policymakers must be cognizant of the timing of CER studies. A study conducted too early in the lifecycle of an innovation may not capture the true value of an intervention that is demonstrated only through repeated use over time. On the other hand, valuable innovations may languish unadopted without the validation of a timely CER review – for example, a regional innovation in care delivery may not be adopted more broadly without the imprimatur of a CER study.

Supportive policy should also provide for a periodic review of CER findings, since the accumulation of new experience and new data over time may challenge earlier CER findings. CER programs should be integrated with other initiatives such as development of e-health infrastructure – patient databases and registries – that will allow analysts to track health care outcomes over a long period of time.

²⁴ Medicare Payment Advisory Commission. Report to the Congress: Promoting Greater Efficiency in Medicare. Washington: CBO, MEDPAC June 2007: 72.

Innovation in all of its forms in the health care system will be best supported by CER methodologies that move beyond the RCT gold standard.

Because RCTs have substantial limitations in discerning the impact of innovations in real-world practice and require significant financial resources, investment in new methodologies is required if innovation is to be sustained and promoted. RCTs are an invaluable source of evidence on the safety and efficacy of new tests and treatments. However, reliance on RCTs may result in defaulting to studying topics that are most easily studied by RCTs – most likely, medical technologies regulated by the FDA. In addition, the time and expense of RCTs are pushing policymakers to examine alternative study designs.

The development of new methods will allow for better, faster and cheaper analysis of broadly scoped research questions and for analysis of a wider range of topics, including health care practices, organization and delivery.

To support and sustain innovation, the development and selection of CER methodologies must be transparent.

Transparency and predictability are vital to innovation. Given the complexity of developing sound methodologies, the need for transparency is magnified as federal policymakers develop the new CER program. Openness and transparency in the development of CER methods is necessary to create authoritative and credible methods that will create predictability for innovators, providing a market signal by pointing to the most significant opportunities for innovation.

Application and Use of CER Studies

CER's impact on innovation will be greatly shaped by policy choices on CER goals, priorities and scope of studies, and methodology development. But the true impact of CER on innovation will only be realized when the results of CER studies are disseminated and applied throughout the health care system, ultimately reaching patients. But how will CER findings be communicated and to whom? How will they then be applied to health care practice?

Historically, the dissemination and adoption of clinical guidelines, based on sound, evidence-based research, has been uneven and protracted, requiring 15-20 years on average.²⁵ To overcome this slow uptake, federal CER programs will have to do better and employ new and creative efforts to bring CER findings into practice.

CER Findings: Advisory or Mandatory?

The fundamental issue in the application and use of CER findings is whether they are solely advisory or explicitly linked to coverage decisions and other mandates (as in European programs). In enacting the ARRA, Congress made clear its intent that new CER studies *not* be explicitly linked to coverage and payment decisions, either in the public or private sectors. Congress indicated the federal CER program should focus on effectively communicating research results to users – including patients, providers and payers – not on developing federal coverage mandates.

Whether Congress and the administration revisit this issue remains to be seen. Historically, Congress has been reluctant to give the Centers for Medicare and Medicaid Services (CMS) authority to make coverage decisions on any basis other than “medical necessity.”

Relevance Matters

Given Congress' decision to make federal CER findings advisory, findings are more likely to be applied if they address relevant issues in the health care system or can be connected with utilization and payment initiatives already underway. For instance, CER findings could be linked to physician pay-for-performance programs, the design of tiered drug formularies, and the creation of value-based insurance benefits.

Implications for Innovation

Mandates increase risk for innovators.

Health care innovation, particularly in technologies, is more likely to be negatively impacted if CER policies explicitly link CER study findings to yes/no or on/off coverage decisions. Such coverage decisions would remove some interventions from the marketplace. This failure to preserve a basic level of access would eliminate the

²⁵ IOM, Committee on Quality of Health Care in America. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academy of Sciences, 2001: 145.

opportunity for the innovation to prove its value through long-term use, and limit the intervention's use in extraordinary situations where it might be beneficial. In addition, this removal would potentially deter future innovation by creating what is perceived as an additional hurdle for bringing technological innovations to market.

Advisory findings would be a mixed bag for innovation.

Given Congress' decision to keep CER findings advisory in nature, the impact of CER findings on innovation will be determined by two factors: how effectively CER findings are disseminated and whether the CER topics prioritized by federal agencies find a ready audience among payers, patients and providers.

If CER findings are poorly disseminated and utilized, the impact on innovation will be mixed. On the one hand, slow adoption of CER findings may be a form of benign neglect that gives newer medical technologies, in particular, the period of market utilization that is necessary to prove their value. Yet, slow adoption also means that newer, but valuable, technologies may be denied due recognition in the marketplace. In this case, adoption of truly disruptive or breakthrough technologies may be slowed and valuable innovations in health care practice, organization and delivery may languish, as they frequently do now.

If CER findings are effectively disseminated and utilized, the impact on innovation is more likely to be positive. Effective dissemination of CER findings from well-designed studies will increase the adoption of the valuable innovations they identify. An important way to improve dissemination is to link the federal CER program with the parallel federal investment in health care IT, with its focus on clinical decision support. This will help expedite the adoption of CER findings and support valuable innovations by providing clinicians with the most up-to-date information on effective interventions at the point of care.

Conclusion

Over the past year, the expanded federal commitment to CER has grown from concept to imminent reality. With CER poised to become a critical tool for improving health care decision making and health outcomes, there is a need to balance its implementation with its potential impact on the all-important force of innovation in health care. Innovation, in all its myriad forms, is broadly considered crucial to the continued success of the U.S. health care system, and therefore any negative impacts from CER must be carefully considered and mitigated.

Implemented poorly, federal CER efforts run the risk of stunting innovation in U.S. health care. If constructed and practiced well, expanded federal CER could provide vital guidance to health care practitioners at the point of care while also spurring innovation across health care, from medical technologies to care delivery models.

This white paper, representing the consensus of a broad range of health care stakeholders across the health care spectrum, presents guiding principles for how to implement a CER program that sustains innovation. As they lead the implementation of CER, the Secretary of Health and Human Services and other policymakers should make support of innovation through CER an explicit goal, beginning by carefully considering the policy challenges detailed in this paper. In doing so, they will achieve the best of both worlds: vast improvements in the evidence base supporting health care decision making, along with sustained development and adoption of valuable innovation throughout the health care system.

Appendix I: Expert Interviews

Jeff Allen, PhD, *Executive Director, Friends of Cancer Research*

Omar Amirana, MD, *Partner, Oxford BioScience Partners*

Bart Barefoot, *Senior Manager, Public Policy and Advocacy, GlaxoSmithKline*

Andy Hartsfield, *Vice President, Public Policy and Advocacy, GlaxoSmithKline*

Gigi Hirsch, MD, *Executive Director, MIT Center for Biomedical Innovation*

Kenneth Kaitin, PhD, *Director, Tufts Center for the Study of Drug Development*

Beverly Lorell, MD, *Senior Medical and Policy Adviser, King & Spalding LLP*

Serena Lowe, *Executive Director, Health Policy, EMD Sorono*

Bryan Luce, PhD, *Senior Vice President, Science Policy, United Biosource*

Peter Neumann, ScD, *Director, Center for the Evaluation of Value and Risk in Health, Tufts Medical Center*

Steven Pearson, MD *Director, Institute for Clinical and Economic Review, Harvard Medical School*

Stacia Reidy, *Director, Government Affairs and Public Policy, Vertex Pharmaceuticals*

Jonathan Rosen, PhD, *Executive Director, Institute for Technology Entrepreneurship and Commercialization, Boston University School of Management*

Amit Sachdev, *Senior Vice President, Corporate Affairs and Public Policy, Vertex Pharmaceuticals*

Harry Selker, MD, *Executive Director, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center*

Appendix II: Focus Group Participants

Focus Group 1- August 14, 2008

Alejandro Aparicio, MD, *Director, Division of Continuing Physician Professional Development, American Medical Association*

Brian Carey, *Partner, Foley Hoag LLP*

Carolyn Langer, MD, *Medical Director, Medical Management and Policy, Harvard Pilgrim Health Care*

Jonathan Rosen, PhD, *Executive Director, Institute for Technology Entrepreneurship and Commercialization, Boston University School of Management*

Samantha Rosman, MD, *Pediatric Emergency Medicine Fellow, Boston Medical Center; Trustee, American Medical Association*

Focus Group 2 - August 19, 2008

Bart Barefoot, *Senior Manager, Public Policy and Advocacy, GlaxoSmithKline*

Jack Evjy, MD, *Medical Advisor, Massachusetts Medical Society*

Mahesh Krishnan, MD, *Executive Director, Medical Policy and Global Health Economics, Amgen*

Serena Lowe, *Executive Director, Health Policy, EMD Serono Inc.*

Barry Zallen, MD, *Medical Director, Blue Cross Blue Shield of Massachusetts*

Focus Group 3 - August 21, 2008

Linda Harpole, MD, *Vice President, Global Health Outcomes, GlaxoSmithKline*

Alison Lawton, *Senior Vice President, Global Product Access, Quality Systems & Regulatory Affairs, Genzyme*

Sandy Leonard, *Senior Director, Health Care Relations, AstraZeneca Pharmaceuticals*

Dennis Meletiche, PharmD, *Director, Health Outcomes and Market Access, EMD Serono Inc.*

Appendix III: Executive Roundtable Participants

October 7, 2008 – Cambridge, MA

Moderator

Clifford Goodman, PhD, *Senior Vice President*, The Lewin Group

Participants

Jeff Allen, PhD, *Executive Director*, Friends of Cancer Research

Richard Bergström, *Director General*, Swedish Association of the Pharmaceutical Industry

Joshua Boger, PhD, *Chief Executive Officer*, Vertex Pharmaceuticals

Randy Burkholder, *Associate Vice President, Policy*, Pharmaceutical Research and Manufacturers of America (PhRMA)

Alexandra Clyde, *Vice President, Health Policy & Payment*, Medtronic

Jonathan Fleming, *Managing General Partner*, Oxford BioScience Partners

Scott Gottlieb, MD, *Resident Fellow*, American Enterprise Institute

Joseph Heyman, MD, *Board Chair*, American Medical Association

Mark Horn, MD, *Senior Director, Worldwide Medical Policy*, Pfizer Inc.

Kenneth Kaitin, PhD, *Director*, Tufts Center for the Study of Drug Development

Paul Lammers, MD, *Chief Medical Officer*, EMD Serono, Inc.

Cato Laurencin, MD, *Dean*, University of Connecticut Medical School

Thomas Lee, MD, *Network President/CEO*, Partners HealthCare System/Partners Community HealthCare

Beverly Lorell, MD, *Senior Medical and Policy Adviser*, King & Spalding LLP

Bryan Luce, PhD, *Senior Vice President, Science Policy*, United Biosource

Joseph Martin, MD, PhD, *Lefler Professor of Neurobiology*, Harvard Medical School

David Nexon, *Senior Executive Vice President*, Advamed

Robert Nierman, MD, *Medical Director for Clinical Coverage*, Tufts Health Plan

Steven Pearson, MD *Director, Institute for Clinical and Economic Review*, Harvard Medical School

James Schibanoff, MD, *Editor-in-Chief*, Milliman Care Guidelines

Ralph de la Torre, MD, *President and Chief Executive Officer*, Caritas Christi Health Care

Barry Zallen, MD, *Medical Director*, Blue Cross Blue Shield of Massachusetts

Notes

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