

COMPARATIVE EFFECTIVENESS RESEARCH: *The Challenge of Getting It Right*

EXECUTIVE SUMMARY

On October 21, 2008, CHI organized a Comparative Effectiveness Research Forum in Mountain View, California. The forum brought together a cross-section of leading academic and industry experts to explore the current state of comparative effectiveness research and its implications for the future. This paper summarizes the forum's highlights and builds upon them by providing insights from additional sources as well as references from the literature.

Comparative effectiveness research (CER) is the application of evidence-based medicine to specific healthcare technologies and treatments in order to find out, among alternative therapies for a given medical condition, which produce the best clinical outcomes. More broadly, CER involves extracting information from various sources (e.g. randomized controlled trials, registries, data sets compiled by managed care organizations) to improve clinical decision-making. At its heart, the CER debate is about medical evidence—what data should count, who should collect and interpret them, how they should be disseminated to physicians, patients and insurers, and how outcomes data should affect practice guidelines, insurance coverage and payments to doctors and hospitals. In the politically charged atmosphere surrounding American healthcare, the debate also involves fundamental questions about the proper role of government and apprehension that, rather than providing the nuanced analyses its proponents envision, CER would mainly be used as a cost-cutting tool.

California Healthcare Institute | April 2009

The California Healthcare Institute (CHI), founded in 1993, is an independent nonprofit organization devoted to researching and advocating policy to forward the interests of California's biomedical community. CHI (www.chi.org) has built a membership of more than 250 leading biomedical companies, academic and research institutions and companies involved in supporting the biomedical community.

The mission of the California Healthcare Institute is to research, develop, and advocate policies and actions that promote biomedical science, biotechnology, pharmaceutical and medical device innovation in California.

CER continues to gain momentum in Washington. The global financial crisis and enormous federal budget deficit, coupled with the strong political desire to reform healthcare, have strengthened support for CER as a component of healthcare reform. Indeed, the recent stimulus bill contained \$1.1 billion for CER over two years, to be divided among three federal agencies. The impetus for government-funded CER comes from congressional leaders and the Obama administration, whose director of the Office of Management and Budget (OMB), Peter Orszag, describes rising healthcare spending as the nation's foremost fiscal problem. He and his colleagues view medical technology as the main driver of increasing costs and thus promote CER as a tool to discourage spending on drugs, medical devices and medical treatments that offer low value.

At the same time, influential groups, including the Institute of Medicine (IOM), the American College of Physicians and the Medicare Payment Advisory Commission (MedPAC) have advocated CER and have convened public/private sector stakeholder meetings focused on the conceptual and practical challenges of creating a CER entity.

Despite much progress, CER remains in an early state of development. Moreover, there are wide gaps between what is known about best practices for different conditions and routine clinical practice. Translating CER research into practice, even when the data are unambiguous, and changing behavior, represents a serious challenge. According to the Congressional Budget Office (CBO), the complexity of planning and generating high-quality CER

information makes the pathway unpredictable. In light of the time needed to conduct CER (including clinical trials), to reengineer coverage and payment policies to reflect the results, and to change physicians' and patients' behavior accordingly, "any potential for substantial cost savings from new research would probably take a decade or more to materialize."¹

Experience from health technology assessment programs in other countries suggests that CER is complex and, if implemented poorly, could undermine patient/provider decision-making, create unintended patient access barriers to optimal care, and discourage the development of innovative medical technologies. In addition, there remains lack of clarity and disagreement on a number of important aspects of comparative effectiveness research. How these issues are resolved will define the policy framework for years to come and determine whether policymakers "get it right" on CER.

Getting CER right will require policymakers to address a range of factors: producing relevant, credible, timely results; incorporating new information in a timely manner; ensuring openness, transparency and accountability; defining an appropriate scope of research; focusing research on clinical outcomes; determining how to approach cost effectiveness; supporting wide dissemination and appropriate application of findings that preserves flexibility at the individual level; and approaching CER evaluations in ways that support continued medical innovation.

In discussions about the scope of CER, no issue is more contentious than the question

of cost effectiveness. Going beyond evidence of clinical effectiveness to evaluate costs raises concerns in three areas:

- *The physician-patient relationship: choosing the best treatment*
- *Ensuring that minorities and sub-populations are appropriately represented*
- *Protecting incentives for medical innovation*

While CER represents a powerful tool for identifying gaps in our knowledge, care must be taken to ensure that patient care and medical decision-making are not overshadowed by payers' decisions to limit access to expensive treatments. Due to the immaturity of the science and complexities surrounding CER/cost effectiveness, more work is needed to determine how to proceed.

In order to strike a balance between incentives to control costs and efforts to provide the best treatments for patients, several basic principles should apply:

- CER should be developed and guided through stakeholder consensus. All stakeholders—patients, physicians, payers, medical innovators, academic researchers, and others—offer valuable perspectives and expertise and should be included in CER governance and process. Innovators with daily expertise in study design methodology, the ethics of clinical trials and patient recruitment, physician needs and commercialization can provide valuable “real world” expertise.
- The role a national entity will play is critical to the future of the life sciences. CER is complex and expensive; funding must be adequate to produce high-quality information.
- There must be recognition of how the innova-

tion process differs among drugs, devices, diagnostics and procedures. Related to this is the need to understand that *where* and *when* in a product's life cycle CER and other analyses are conducted can make a big difference.

- CER should not focus solely on medical technology. It should address the full spectrum of systems and interventions that affect patients' care: insurance coverage and benefit design, diagnoses, procedures, cognitive services, etc.
- There must be an understanding that no two people are clinically identical and therefore “one-size-fits-all” decision-making is unsuitable for patients. Patients are individuals—there is no such thing as an average patient.
- The CER process must be transparent, and allow for all stakeholders to have a seat at the table. This includes a mechanism for public comment on draft CER reports. This would be consistent with other evidence-review entities such as NICE and AHRQ, and would promote support from various stakeholders.■

BACKGROUND: HEALTH TECHNOLOGY ASSESSMENT IN THE PAST

As early as the 1970s, the U.S. Department of Health and Human Services, through such bodies as the National Center for Health Care Technology, was assessing drugs and devices. The quest for evidence gained traction, above all, owing to the rise of health maintenance organizations (HMOs). In 1985, the Blue Cross and Blue Shield Association set up the Technology Evaluation Center “for assessing medical technologies through comprehensive reviews of clinical evidence.”ⁱⁱⁱ Managed care groups like Kaiser Permanente that contracted with employers to provide all necessary medical services to a company's employees for a fixed price had direct

financial incentives to constrain costs.

Managed care companies wanted not just to control the use of expensive medical services and technologies, they needed to do so in ways that satisfied customers and discouraged litigation. American consumers, after all, detest rationing. And so managed care, which quickly expanded to include much of the traditional indemnity insurance industry, aggressively collaborated with government agencies, physicians, academic medical centers, employers, and even drug and device firms, to develop technology assessment strategies.

Today, various payers, stakeholder groups, members of Congress, and President Obama, have all incorporated comparative effectiveness into their health reform proposals. Several groups have called on Congress to pass legislation creating a new “trusted” Institute, one that is transparent and “legitimate” and would support research comparing the effectiveness of new and existing drugs, devices, biologics, diagnostics, and procedures.ⁱⁱⁱ

Defining Comparative Effectiveness Research

Exactly what is meant by CER differs and there are several definitions in use today:

The Agency for Healthcare Research and Quality: A type of healthcare research that compares the results of one approach for managing a disease to the results of other approaches. Comparative effectiveness usually compares two or more types of treatment, such as different drugs, for the same disease. Comparative effectiveness also can compare types of surgery or other kinds of medical procedures and tests. The results often are summarized in a systematic review.^{iv}

The Congressional Budget Office: As applied in the healthcare sector, an analysis of comparative effectiveness is simply 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. The analysis may focus only on the relative medical benefits and risks of each option, or it may also weigh both the costs and the benefits of those options. In some cases, a given treatment may prove to be more effective clinically or more cost-effective for a broad range of patients, but frequently a key issue is determining which specific types of patients would benefit most from it.^v

S. 3408—*The Comparative Effectiveness*

Research Act of 2008 (Conrad/Baucus): The term means research evaluating and comparing the clinical effectiveness, risks, and benefits of two or more healthcare interventions, protocols for treatment, procedures, medical devices, diagnostic tools, pharmaceuticals (including drugs and biologics), and any other processes or items being used in the treatment and diagnosis of, or prevention of illness or injury in, patients. The term is also described as research evaluating and comparing the implications and outcomes of two or more healthcare strategies to address a particular medical condition.

Whichever definition is ultimately used, getting it right will require any new federal CER initiative to skillfully resolve the inherent tensions in CER and appropriately balance competing issues.

Other agencies, entities and organizations have their definitions as well.

Whichever definition is ultimately used, getting it right will require any new federal CER initiative to skillfully resolve the inherent tensions in CER and appropriately balance competing issues. Some of the important tensions to be addressed include those that exist between: expectations of what CER can achieve versus the reality of its strengths and limitations; and conclusions based on broad population averages versus differences that exist among individuals and subpopulations due to clinical, ethnic, genetic and other factors. In addition, balancing the issues of quality improvement versus cost-containment as goals of CER is another key consideration for policymakers.

THE PROMISE OF COMPARATIVE EFFECTIVENESS RESEARCH: TEMPERING EXPECTATIONS

Comparative effectiveness research sometimes is viewed as a research tool that can yield clear, unequivocal findings about which test or treatment works “best,” which can then be readily applied in clinical medicine. However, the reality of what CER can accomplish, and how quickly, is more complex.

Consider the compelling points raised by health economist Peter Neumann, director of the Center for the Evaluation of Value and Risk in Health, Tufts-New England Medical Center:

Comparative effectiveness research rarely ‘solves’ a clinical question under investigation. Even the best randomized trials

include selected populations and comparator treatments. Questions about whether a drug works in other population groups or compared to different alternatives remain. Moreover, drugs typically work better in some subgroups than others—often for reasons that are difficult to predict beforehand or explain afterward. The point is not that comparative effectiveness is not worth pursuing but that expectations should be tempered.^{vi}

The complexity of evaluating and applying CER findings also was discussed in a report released by the IOM in December 2008, *HHS in the 21st Century: Charting a New Course for a Healthier America*. “Comparative effectiveness research, like any sharp tool, needs to be used carefully...there will rarely be black and white choices that can guide coverage decisions. In other words, when it comes to care for individual patients, we must accept a gray area,” the report says. Brookings health economist Henry Aaron put it this way:

Effectiveness can be measured many ways. Clear-cut results will sometimes emerge, but many studies will reveal conflicts in which a particular therapy is superior in some respects and inferior in others. Clear information on effects of therapy, while useful, will often justify diverse decisions based on each patient’s values and preferences.^{vii}

Surprisingly little is known about the relative effectiveness of clinical choices. CER can provide valuable guidance in both clinical and coverage-related decision-making. CER research is in wide practice, but its use is diffuse

and inconsistent among federal agencies, private health plans, drug companies, et al. Its adoption into clinical practice is slow. This owes in part to a series of technical and policy-related questions about how CER should be conducted, disseminated and applied to individual treatment and health policy decisions:

- Who should conduct CER?
- How should studies be prioritized?
- How should the studies be designed and conducted?
- How should the results be communicated?
- How should CER results be integrated into clinical practice?
- What should government's role be?

Thus, CER policy must be informed by realistic expectations for what can, and cannot, be achieved. The promise of CER is its perceived ability to inform—to provide the evidence and data necessary to make treatment option decisions that lead to improved clinical outcomes, more efficient resource use and better overall value. But CER is a young, fairly undeveloped science, and in the near future its most immediate benefits may be to identify critical gaps in clinical knowledge.

Even as CER is implemented, it is important that it not divert attention from efforts that utilize effective instruments and methods for attacking the overall cost problems in health-care. These include: more aggressive disease prevention, enhanced chronic disease management, decreased medical errors, decreased hospital infection rates, adherence to quality healthcare measures and improved system efficiencies via investments in health information technology. And there are more flexible, patient-centered

approaches to applying CER results that can inform optimal patient care decisions and, ultimately, better value in healthcare. These include patient treatment decision aids and decision-support tools, as described in the health reform white paper released by the *Dartmouth Atlas of Health* authors.^{viii}

The relationship between cost-savings and CER is complicated. While some level of savings is likely to be achieved via CER, the promise of comparative effectiveness research as a cost-cutting tool is probably overstated and should be carefully considered. In other words, there may be savings in instances where technologies or procedures are being overused, despite the lack of evidence that they work. But just as easily, there could be technologies or procedures that are highly effective, but underutilized, thereby increasing costs. For example:

- Comparative effectiveness research may not save the healthcare system money in the long run if the analyses find that the more expensive interventions or treatment options offer the greater clinical benefit.
- In some instances, research results can have the effect of increasing the utilization of systemically underused items or services, thereby increasing spending in the short term.
- Findings often are not clear and definitive enough to be readily translated to broad savings-generating policy decisions.
- Fully expressing the value equation—explicitly defining costs and benefits of an intervention—is a problem for many interventions. This partly owes to the fact that different patients place different values on various outcomes (e.g. experiencing less pain versus getting out of the hospital sooner).

But value is also difficult to express because most interventions have short- and long-term costs, and these costs are spread among various players: patients, families, insurers, physicians, hospitals, governments and greater society.

Resistance to combining cost-effectiveness analysis with CER stems from the fear that those who would use the analyses — principally public and private payers — would focus mainly on the immediate, short-term cost of treatment, ignoring long-term or systemic benefits. If clinical decision-making and cost-cutting efforts are allowed to blend, it is not at all clear (1) who will be making treatment decisions — government, payers, or physicians and patients, (2) how these decisions will be made and (3) what the short and long-term consequences will be.

Comparative effectiveness research, like any sharp tool, needs to be used carefully...there will rarely be black and white choices that can guide coverage decisions. In other words, when it comes to care for individual patients, we must accept a gray area.

- Institute of Medicine

The debate over the CER provisions of the economic stimulus bill in early 2009 illustrates the controversial nature of these issues. Controversial report language surfaced the third week of January from the House Appropriations Committee and ended up in the House economic stimulus package, fueling broad bipartisan concern about the potential impact of CER on patient care. The report language: “By knowing what works best and presenting

this information more broadly to patients and healthcare professionals, those items, procedures, and interventions that are most effective to prevent, control, and treat health conditions will be utilized, while those that are found to be less effective and in some cases, more expensive, will no longer be prescribed.” This underscored the apprehension that many patient groups and others have that patients’ access to treatments may be unduly limited when cost is a factor in coverage determinations.

The tension over CER and cost-containment has remained on display in subsequent congressional hearings. In response to a question on CER at a March 25, 2009, Ways and Means Committee hearing, OMB director Peter Orszag said “we’re not talking about cutting off treatments” or “preventing people from getting the health care they need” based on CER, but “making sure that doctors have the evidence they need.” Similarly, House Energy and Commerce Committee Chairman Henry Waxman, in a speech to the American Medical Association, said:

We all know we have to get costs under control, but the way to do that is not to tell physicians what they can and cannot do or put them in a position where they cannot put the needs of their patient first. What we can do is a better job of giving you better information about what works and how practice patterns differ [across the country,] information that allows you to exercise your best judgment. That in the end will help us improve quality and start to moderate cost increases. I firmly believe that.

In contrast, though, Doug Elmendorf, director of the CBO, told the Senate Finance Committee on March 10, 2009:

To affect medical treatment and reduce health care spending, the results of comparative effectiveness analyses would ultimately have to change the behavior of doctors and patients...Bringing about those changes would probably require action by public and private insurers to incorporate the results into their coverage and payment policies in order to affect the incentives for doctors and patients.

The key points that need to be understood better as they relate to the use of cost-effectiveness analyses in CER include:

Impact on Patients/Clinical Decision-Making

Ultimately, the issue is about putting the needs of patients first. The application of cost-effectiveness analysis should not present a barrier to patients being able to access the medicines that are right for them, as determined by clinical evaluations and the judgment of their clinicians. Cost-effectiveness analysis, by its nature, is a decision tool primarily oriented towards broad policy decisions about whether, or under what circumstances, an intervention should be covered and available to patients. There must be protections in place to ensure that CER will be used to benefit patients.

The Impact on Minority and Underserved Communities

While comparative effectiveness research can play an important role in the provision of useful information for physicians, concern exists over the potential to impact negatively the nation's most medically needy. For example, on April 23, 2008, the Congressional Black Caucus sent a letter to Rep. Charles B. Rangel and Rep. Jim

McCrery, both of the Ways and Means Committee to underscore this concern. The members of the caucus noted that it was vital to:

- “Recognize and account for the variation in outcomes of medical treatments. A growing body of research shows that a ‘one-size-fits-all’ approach to patient treatment is not always the most medically appropriate solution to treating various conditions...Comparative effectiveness research should bolster our understanding of these variations, rather than ignoring them by focusing on population averages that mean little for any individual patient or subgroup. Without this focus, the results of research could inappropriately be used as a rationale for restricting the treatment choices of those who fall outside the average response.”
- “Bolster and expand information and knowledge about quality without restricting access to care. A new government-supported comparative effectiveness group should focus heavily on generating information about how all

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patients—of all racial and ethnic backgrounds—can receive better quality health care and have improved health outcomes. It should, not, however, make decisions or recommendations

about which treatments should be covered and available to patients which treatment are ‘cost effective’ and which provide ‘value’ and which do not, based on limited factors that fail to incorporate or recognize the impact of race, ethnicity, gender, and geography on health and health care.”

The Impact on Innovation

Medical innovation is a long and risky process, and often occurs through a series of incremental gains that change the understanding of an intervention’s value over time. If not conducted and used appropriately, CER can suppress continued medical progress by imposing significant new research hurdles, increasing uncertainty in the research process, and overlooking the progressive nature of medical progress by imposing broad decisions about which treatment is best on average at one time.

It is also important for policymakers to take into consideration the fact that unanticipated clinical benefits can manifest themselves over time. A synthesis of existing information is not adequate to capture the fuller picture of a technology’s effects.

Related to the inclusion of cost-effectiveness analysis in CER is the critical consideration of timing—studying costs and benefits at the point of a product’s launch is extremely problematic in that doing so overlooks (and therefore does not calculate or capture) the unanticipated benefits that occur after widespread adoption of a therapy.

The evolution of cancer treatments illustrates this dynamic. For example, docetaxel was originally approved for breast cancer in 1996,

then approved as a second-line treatment for lung cancer in 1999, and as a first-line therapy in metastatic lung cancer in 2002. It then was approved for inoperable locally advanced head and neck cancer in 2006, and a year later received approval as an adjuvant therapy for operable locally advanced head and neck cancer. Whereas the initial approval in head and neck cancer showed a survival gain of four months, the treatment showed a survival gain of nearly three years compared to the control group in patients with operable head and neck cancer.

When sharing her personal experience with cancer, Virginia Postrel, a contributing editor for *The Atlantic*, wrote:

A more centralized U.S. health-care system might reap some one-time administrative savings, but over the long term, cutting costs requires the kinds of controls that make Americans hate managed care. You have to deny patients some of the things they want, including cancer drugs that are promising but expensive. Policy wonks dream of objective technocrats (perhaps at the “independent institute to guide reviews and research on comparative effectiveness” proposed by Barack Obama) who will rationally “scrutinize new treatments for effectiveness,” as *The New Republic’s* Jonathan Cohn puts it. But neither science nor liberal democracy works quite so neatly.^{ix}

And another (non-cancer) example: ACE inhibitors were launched as antihypertensives. Over time, however, it was discovered that ACE inhibitors, used with drug eluting stents to improve outcomes after left-ventricular remodeling, significantly improved life expectancy.

As a result of aggressive interventional cardiovascular therapy, there have been marked reductions in left-ventricular infarcts, arrhythmias, sudden death and left ventricular ruptures, all of which were never originally anticipated or reflected on the labeling of ACE inhibitors. There must be a process for capturing unanticipated benefits after widespread use.

VCs Recognize Innovation Life Cycle

In its healthcare reform principles, the National Venture Capital Association (NVCA) highlights the value of learning more about what works in healthcare. The group stresses that proposals for comparative effectiveness research must “explicitly recognize the life cycle of technological innovation, specifically that medical practice based on new technology evolves over time and may change significantly before comparative effectiveness studies can be completed.”

Cost-Effectiveness Analysis Would Negatively Impact Innovation

Centralized cost-effectiveness research is likely to have a negative effect on medical innovation. In a 2006 report, U.K. health policy expert Heinz Redwood stated: “It is difficult to see how innovation in the U.S. could escape being harmed if these industries were subjected to mandatory national cost-effectiveness scrutiny in the public sector along the lines of the NICE process.” Imposing centralized mandatory requirements for the appraisal of cost-effectiveness would be “one way of weakening” the leadership status of the U.S. in research and development.

Leaders in the field of personalized medicine have expressed concern that if CER legislation does not explicitly recognize the emerging science of personalized medicine it likely will suppress continued progress in this important field. In a recent letter to Congress, addressing early versions of the economic stimulus bill, the Personalized Medicine Coalition urged lawmakers to correct flaws in the comparative effectiveness research provisions of the economic stimulus bill that “could harm patients” and “stall innovation” in personalized medicine:

Unfortunately, the Comparative Effectiveness Research provisions of the American Recovery and Reinvestment Act of 2009 are written in such a way as to result in one-size-fits-all comparative clinical trials that do not incorporate the targeting of therapies to improve their relative effectiveness based on appropriate segmentation of patients.

Similarly, in a September 2007 letter to the Senate Finance Committee, The National Working Group on Evidence-Based Medicine highlighted the need to focus on patient outcomes, stating:

Cost-effectiveness should not be part of comparative effectiveness studies... We strongly believe this separation is necessary to emphasize the quality of healthcare rather than cost. Moreover, reflecting stakeholder values through cost effectiveness analysis is even more complex and controversial than clinical comparative effectiveness, thus further politicizing any conduct of comparative effectiveness research.

AVERAGE RESULTS VERSUS INDIVIDUAL VALUE

As noted above, the tension between average study results and individual variation in medical needs and preferences underlies some of the thorniest CER policy questions. Creating a framework for CER that ensures it recognizes and supports patient differences rather than obscuring them through “one-size-fits-all” findings will be essential to a credible, sustainable, long-term CER program.

When formulating policy, it will be critical for policymakers and payers to take into account the heterogeneity that exists in individuals, their different (personalized) response to the same treatments, and the recognition that the more we understand about disease, the more we are learning that it is not really the same disease in each person. We now know, for example, that there are a multitude of breast cancers and that different women respond to diagnosis and treatment differently. All patients are individuals; there is no such thing as an “average” patient. Therefore, making decisions based upon averages can have a catastrophic effect on some patients.

Steven Pearson, M.D., president of the Institute for Clinical and Economic Review underscored the importance of this issue in testimony before the Senate Health, Education, Labor and Pensions Committee on Feb. 5, 2009:

The main challenge is getting large bodies of evidence (say 10 different studies on a single topic) synthesized into meaningful results... The problem is that these studies are all going to say slightly different things, and the risk you run in attempting to synthesize large volumes of results is

oversimplifying things and creating a “cookie-cutter” approach to medicine based on effectiveness research. Thus, our greatest challenge is communicating tangible findings without losing the nuance of individual patient variation that certainly exists.

As one example, the science of personalized medicine is showing the role that genetic variation plays as one important factor in determining whether an individual will develop a disease, or how they will respond to particular treatments. To support medical innovation in general, and the emerging field of personalized medicine in particular, CER must acknowledge human variation in response to various treatments and interventions.

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In its health reform white paper, the Personalized Medicine Coalition addresses this issue, calling for comparative effectiveness research that “generates and communicates findings in ways that support personalized medicine by accounting for differences in treatment response and preferences among individuals and sub-groups,” and use of evidence in ways that “support the physician’s ability to optimize individual care based on the range of treatment options.”

THE SCIENCE AND POLICY OF CER

Another key point of debate of CER is whether the agency or entity conducting research should be separated from policy decisions or recommendations based on the research. The inherent complexity of CER and challenges of applying findings to policy decisions are two factors that have made this a prominent feature of the debate. While the stimulus bill report language precludes the use of CER for coverage determinations, the issue is certain to be part of the ongoing debate

Some proposals for CER would connect the research entity more directly to policy decisions, some are silent on the issue, and some include explicit separation of the research and policy functions.

In its June 2007 report to Congress, the Medicare Payment Advisory Commission said, “We emphasize that the entity would not have a role in how public and private payers apply this information—that is, coverage or payment decisions. Instead, it would produce and disseminate comparative effectiveness information to purchasers, providers, and patients who would then decide how to use it.”

Addressing a MedPAC meeting in March 2007, Harvard research Peter Neumann agreed, saying that this separation could help ensure the independence of the entity. “Ensuring the independence of the organization will obviously be critical,” Neumann said. “One way to help insulate the organization is to separate analysts from the decision-makers. That is, maintaining institutional independence between those conducting research and those making reimbursement decisions.”

S. 3408 adopted a similar approach, including provisions that required the new research entity to focus on communication of research results and ensured it would not make policy decisions or recommendations. The existing CER program at the Agency for Healthcare Research and Quality, mandated by Sec. 1013 of the *Medicare Modernization Act*, includes similar safeguards. Language accompanying the final CER provisions of the economic stimulus bill stated that such research is not intended “to be used to mandate coverage, reimbursement, or other policies for any public or private payer.” And CER provisions in the House *Children’s Health and Medicare Protection Act* (H.R. 3162) took steps to connect the research entity more directly to policymaking.

THE LIMITATIONS OF CER

Several large comparative trials sponsored by the National Institutes of Health illustrate both the value and limitations of CER. Two of the most important are the ALLHAT and CATIE trials.

ALLHAT

The ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) experience illustrates the limits of comparative drug studies and the danger of the government using these studies to dictate treatment decisions.

In December of 2002, the National Institutes of Health (NIH) published a study in the *Journal of the American Medical Association* (JAMA) that sought to compare the relative benefits of three popular hypertension medicines. The study known by its abbreviated title, ALLHAT, garnered significant media attention because of

its large sample size, government sponsorship, and seemingly novel results. The study was widely interpreted and communicated as showing that older, cheaper drugs called “diuretics” were the best treatment for high blood pressure.

The ALLHAT study exemplifies how conclusions about the comparative effects of treatments based on large population averages can overlook the needs of individual patients.

The ALLHAT study was impressive, taking more than eight years and \$120 million to complete, and yielding valuable findings for physicians, including findings that have led to declines in the use of alpha-blockers. At the same time, several more recent studies, as well as a paper by Dr. David Nash of Thomas Jefferson, Medical College, illustrate the challenges of using this type of comparative effectiveness research in making policy level decisions.

The ALLHAT study exemplifies how conclusions about the comparative effects of treatments based on large population averages can overlook the needs of individual patients. They can serve as one of many useful sources of information to help guide treatment, but should not be used by government agencies to dictate medical decisions.

“It is important to understand that studies look at population averages and not at individual patients,” Nash says. “When prescribing drugs for hypertension,” the article says, “physicians must consider each patient’s unique medical history—metabolic state...kidney function, any heart muscle damage, and heart efficiency

(cardiac output)—because each factor affects the choice of the initial and any subsequent therapy.”

These challenges were echoed in a November 2008 article in the *New York Times*, which noted “The ALLHAT experience is worth remembering now, as some policy experts and government officials call for more such studies to directly compare drugs or other treatments, as a way to stem runaway medical costs and improve care.”

For example, the *New York Times* story noted that the length of time required to complete a trial like ALLHAT means that, in the interim, “medicine moves on.” During and after ALLHAT, “new drugs appeared,” and others “became available as generics, reducing the cost advantage of diuretics.” In addition, “many doctors have shifted to using two or more drugs together.”

“ALLHAT’s main query—which drug to use first—became ‘an outdated question that doesn’t have huge relevance to the majority of people’s clinical practices,’ said Dr. John Flack.”

CATIE

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study, funded by the NIH’s National Institute of Mental Health, was a nationwide public health-focused clinical trial comparing the effectiveness of older (first available in the 1950s) and newer (available since the 1990s) antipsychotic medications used to treat schizophrenia. Overall, the medications were comparably effective but were associated with high rates of discontinuation due to intolerable side effects or failure to adequately control symptoms. One new medication, olanzapine, was slightly better than the other

drugs but also was associated with significant weight gain and metabolic changes. Surprisingly, the older, less expensive medication used in the study generally performed as well as the newer medications. The study, which included more than 1,400 people, supplies important new information that will help doctors and patients choose the most appropriate medication according to the patients' individual needs.

“There is considerable variation in the therapeutic and side effects of antipsychotic medications. Doctors and patients must carefully evaluate the tradeoffs between efficacy and side effects in choosing an appropriate medication. What works for one person may not work for another,” said Jeffrey Lieberman, M.D., CATIE's principal investigator and chair of The Department of Psychiatry, Columbia University and director of the New York State Psychiatric Institute.^x

For example, in commenting on the results of the CATIE trial, the National Institute of Mental Health said: “There is great variability in the response of [patients] to these treatments. A one-size-fits-all policy for treating schizophrenia could be harmful.”

Patient advocacy groups have raised concern that at least one state has proposed making use of CATIE and similar results to establish a restrictive, one-size-fits-all policy on access to schizophrenia medicines. Addressing the issue at a conference in March 2007, Jennifer Bright, head of the National Working Group on Evidence-Based Healthcare, said: “If we think that's good public policy or good personalization of treatment, it's really scary to come to that conclusion.”

COMPARATIVE EFFECTIVENESS RESEARCH: WHAT IT WILL TAKE TO GET IT RIGHT

While CER represents a powerful tool for identifying gaps in our knowledge, care must be taken to insure that patient care and medical-decision making are not overshadowed by payers' decisions to deny access to critical treatments.

In order to strike an appropriate balance between incentives to cut costs and efforts to provide the most appropriate treatments for patients, it is imperative that realistic expectations be set and that the following be taken into consideration:

- CER should be developed and guided through stakeholder consensus. All stakeholders—patients, providers, payers, medical innovators, academic researchers, and others—offer valuable perspectives and expertise and should be included in CER governance and process. Innovators with daily expertise in study design methodology, the ethics of clinical trials and patient recruitment, physician needs and commercialization can provide valuable “real-world” expertise.
- The role a national entity will play is critical to the future of the life sciences. It must be adequately funded in order to provide for the necessary caliber of information.
- There must be agreed upon definitions of the terms.
- There must be a recognition of, and appreciation for, the innovation process—and how it differs among drugs, devices, diagnostics and procedures. Related to this is the need to understand that *where* and *when* in a product's life cycle CER and other analyses are conducted

can make a big difference. Again, there is no one simple, single answer.

- Comparative effectiveness research should not focus solely on medical technology. It should address other important aspects of health care such as the use of IT, the effects of insurance benefits on the quality of care a patient receives, and the many disparities in patient outcomes based on the use of different procedures, services and patient management.
- There must be an understanding that no two people are clinically alike and therefore “one-size-fits-all” decision making is dangerous for patients. Patients are individuals—there is no such thing as an average patient.
- The process must be transparent, and allow for all stakeholders to have a meaningful seat at the table. This includes a mechanism for the public to have an opportunity to comment on draft CER reports. This would be consistent with other evidence-review entities such as NICE and AHRQ, and would promote support from various stakeholders.

ADDITIONAL WORK IS NEEDED ON ADDRESSING THE OUTSTANDING ISSUES ASSOCIATED WITH CER AND COST EFFECTIVENESS

Due to the immaturity of the science and complexities surrounding CER/cost effectiveness, more work is needed to determine how to proceed; because the impact of poor policy decisions in these areas can harm patients, stifle innovation, squander limited resources, and in the long run, end up increasing healthcare costs. CER legislation should support the types of programs that will solve the myriad problems that have been presented in this paper.

The ultimate impact of CER will depend upon the shape and scope (i.e., structure, placement, funding and authority) of the national CER entity as well as its priority topics and research methodologies and outputs—and how payers and others use this information to inform their policy and payment decisions.

Comparative effectiveness research has the potential to contribute to the evidence base that supports better healthcare decision making. But CER is deceptively complex and if we commit to investing valuable resources, we must commit to “getting it right.”

REFERENCES

- ⁱ Congressional Budget Office, Research on Comparative Effectiveness, 12.
- ⁱⁱ E.J. Emmanuel, V.R. Fuchs, A.M. Garber, “Essential Elements of a Technology and Outcomes Assessment Initiative,” *Journal of the American Medical Association*, no. 11 (298): 1323-1325.
- ⁱⁱⁱ In addition to the work undertaken by AHRQ and the BCBS Technology Evaluation Center (TEC), the Drug Effectiveness Review Project (DERP) has published 28 original and 45 updated comparative drug class reviews since its formation in 2000.
- ^{iv} <http://effectivehealthcare.ahrq.gov/tools.cfm?tooltype=glossary&TermID=118>
- ^v CBO Report: Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role. December 2007.
- ^{vi} Neumann PJ, Getting better value for our health spending. NIHCM Foundation. July 2007.
- ^{vii} H.J. Aaron, Serious and Unstable Condition: Financing America’s Health Care (1991), 50-51.
- ^{viii} <http://www.dartmouthatlas.org/>
- ^{ix} Virginia Postrel, “My Drug Problem,” *The Atlantic*, March 2009.
- ^x NIH press release Sept. 19, 2005, “NIMH Study to Guide Treatment Choices for Schizophrenia”

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