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COMPARATIVE Effectiveness **RESEARCH** Coming Soon?

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As the political debate on healthcare

reform intensifies, comparative effectiveness research (CER) has increasingly been cited as an important tool for reducing costs and improving quality. The American Recovery and Reinvestment Act put CER on the national radar by setting aside \$1.1 billion for this research, and President Obama has identified a role for more CER. However, opponents argue that CER will be used as a means to control costs by limiting patient access to new therapies and interfering with the medical judgment of physicians.

The Congressional Budget Office (CBO) defined CER as “a rigorous evaluation of the impact of different options that are available for treating a given medical condition for a particular set of patients. Such a study may compare similar treatments, such as competing drugs, or it may analyze very different approaches, such as surgery and drug therapy. The analysis may focus only on the relative medical benefits and risks of each option, or it may weigh both the costs and the benefits of those options.” Thus, the goal is to provide patients, physicians, and payers with evidence to support treatment decisions.

It might come as a surprise that such information is not already available. The Institute of Medicine (IOM) estimates that because comparative effectiveness does not enter into the regulatory approval process, less than half of all medical care is supported by adequate effectiveness evidence. Head-to-head comparisons can be risky for manufacturers. (A recent comparison of statins demonstrated this when the study sponsor’s competitor’s product proved more effective at lowering cholesterol and reducing the risk of mortality.) Research has also revealed that expensive treatments do not always result in better outcomes. Medicare data were recently used to show that large geographic variations in healthcare spending and treatment patterns are not clearly linked to improved outcomes.

Growing Movement for CER in the US

In recent weeks, CER has jumped to the forefront of the healthcare debate with the inclusion of \$1.1 billion in funds for this research in the American Recovery and Reinvestment Act of 2009 (ARRA). While CER is now the subject of much media attention, it is not a new concept. Interest in CER has been increasing over the past several years, stimulated by

concerns about rapidly rising healthcare costs and the sustainability of our Medicare and Medicaid systems, as well as multi-stakeholder interest in evidence-based medicine.

A major demonstration of the importance of comparative effectiveness came in 2000, when the Academy of Managed Care Pharmacy adopted a Format for Formulary Submissions that specifically requested information on the clinical and cost effectiveness of treatments from manufacturers. This format has since been adopted by health plans covering more than 100 million people. The Medicare Prescription Drug, Improvement, and Modernization Act (MMA), passed in 2003, marked the advent of federally sponsored CER by requiring the Secretary of Health and Human Services to support research on “the outcomes, comparative clinical effectiveness, and appropriateness of healthcare items and services (including prescription drugs).”

The Agency for Healthcare Research and Quality (AHRQ) responded to the MMA mandate by creating the Effective Healthcare Program. AHRQ designated 13 Evidence-Based Practice Centers (EPCs) to conduct systematic CER on topics of importance to Medicare, Medicaid, and the State Children’s Health Insurance Program. The reports, available on AHRQ’s Web site (www.ahrq.gov), include comparisons of pharmaceutical products, surgery versus drug therapy or watchful waiting, and treating patients in-hospital, as opposed to on an outpatient basis.

Prior to the passage of the ARRA, increased government interest in CER was already evident on a number of fronts. In 2008, the AHRQ budget for CER was doubled to \$30 million, and the 110th Congress introduced at least six bills to increase government support for CER, including funding of current existing CER and creation of a government entity to conduct new CER. The 2007 CBO report emphasized the need for CER as a means to control costs and improve quality, and recommended that the federal government take a lead role in producing this research. The report also emphasized that CER must be produced independent from political pressure, respected by medical professionals, and accountable to policymakers in order to be successful.

Some of the CBO’s recommendations were taken into account in the ARRA, which has substantially increased the budget at the National Institutes of Health, and their current Challenge Grants in Health and Science Research include

several projects relating to comparative effectiveness. Some \$300 million of the CER funding will go directly to AHRQ's Effective Health Care Program. The new legislation expands the ability of existing government agencies to conduct CER and requires the Institute of Medicine to recommend research priorities. The legislation also creates a Federal Coordinating Council for Comparative Effectiveness Research to provide guidance and coordination between agencies.

In addition to activity on the federal level, some states are also getting involved with CER. The Medicaid program in Oregon is collaborating with the Oregon Health and Science University EPC to produce comparative effectiveness reviews to support Medicaid formulary decisions. Several other states have indicated interest in using similar reviews to shape their Medicaid formularies.

Areas of Controversy

Interest in CER is not without controversy, however. Recently, concerns have been raised regarding the drug approval process, the possibility that CER could inhibit physicians from prescribing certain therapies in the name of cost effectiveness, and appropriate methodologies for CER.

Pharmaceutical companies have seen CER complicate FDA approval. In an unprecedented move, in August 2007 the FDA issued an approvable letter to GlaxoSmithKline requesting additional data comparing the extended release version of Requip CR (ropinirole) with the original immediate release formulation. In 2008, the agency issued a not approvable letter to Vanda Pharmaceuticals for iloperidone, concluding that the drug was no more effective than Johnson & Johnson's product, Risperdal (risperidone).

The issue of whether to include cost in assessments of effectiveness is a major point of contention for government-sponsored CER. Several groups have expressed concerns that CER will become a tool for payers to use in limiting the availability of expensive treatments or procedures. The Biotechnology Industry Organization (BIO) expressed concern that CER could be used to limit the ability of individual physicians to select from a range of treatment options. It also argued that CER should encompass all aspects of healthcare delivery, including preventive services, diagnostics, and medical procedures, as well as drugs, biologics, and medical devices. BIO asserts that the goal of this research should be to improve patient outcomes, not simply to constrain costs. Critics point to the United Kingdom and Australia as examples where national health plans denied coverage of certain treatments based on comparative and cost effectiveness research, prompting public outcry.

AdvaMed also emphasized the importance of maintaining patient access to therapies, and went further by indicating that the focus should only be on clinical effectiveness,

not cost effectiveness. In contrast, the CBO supported including cost in its 2007 report, and the American College of Physicians has argued for the inclusion of cost-effectiveness data as a key component of any national comparative effectiveness program. The new ARRA legislation does not specifically include cost, but a report from House Appropriations Committee raised concerns when it mentioned the possibility of lowering healthcare costs by reducing the use of less effective, more expensive therapies.

In addition to concerns about cost and the perception of government-dictated treatments, some groups have expressed worries that CER would only focus on recommendations for average patients, leaving out minority groups and others not typically studied in clinical trials. In response to those concerns, the legislation specifically states that the research funded through this bill must include women and members of minority groups.

Along with increased interest in CER have come questions about what constitutes good practice for comparative effectiveness research. The demands for information far outstrip the available resources to conduct expensive, highly focused, randomized clinical trials. Instead, observational research is being used to provide information on long term patient follow-up and broad or vulnerable populations not usually studied in clinical trials.

Because the traditional good practice guidance that supports the clinical trial industry doesn't apply well to observational studies, new initiatives have been launched to guide the conduct, evaluation, and reporting of observational CER studies. With seed funding from the National Pharmaceutical Council, Outcome Sciences Inc. spearheaded creation of the GRACE Principles to guide good practice for designing and conducting observational studies of comparative effectiveness through a broad collaboration of academia, industry, and formulary decision-makers. (See www.graceprinciples.org.)

Future Trends

Attention to CER is unlikely to wane as more therapeutic alternatives come to market, some very costly to patients and healthcare systems. President Obama has reiterated his interest in reforming the US healthcare system, and with CER on his healthcare agenda, the buzz about government-sponsored CER is unlikely to subside.

New legislation may increase funding but key questions remain unanswered. What types of research will be required? Who will conduct the research? Will it include cost-effectiveness? How will this research be used by the FDA, CMS, and other payers and decision-makers? Only time will tell CER's definition in these terms, and determine what the full effects of a CER-based system will be.

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