

Comparative effectiveness research: Relevance and applications to pharmacy

GLEN T. SCHUMOCK AND A. SIMON PICKARD

The American Recovery and Reinvestment Act (ARRA), signed by President Barack Obama on February 17, 2009, contained \$1.1 billion in funding for “comparative effectiveness research” (CER).¹ The portion to be administered by the Agency for Healthcare Research and Quality (AHRQ), \$300 million, is 10 times AHRQ’s previous annual budget for CER.² Given that AHRQ was the federal agency that sponsored the majority of CER before 2009, the \$1.1 billion investment represents nearly 37 times the previous annual amount spent explicitly on this field by the U.S. government. This new level of funding will drive CER from a position of relative obscurity to one of high visibility and potentially high impact. But what is comparative effectiveness, why is there so much interest in it now, and what does it mean to pharmacists?

This article provides an overview of CER and discusses its relevance to pharmacists and pharmacy-based

Purpose. An overview of the emerging field of comparative effectiveness research (CER) and its relevance to pharmacists and pharmacy-based decision-makers is provided.

Summary. The U.S. government is investing over \$1 billion on CER over the next two years. This investment is in part driven by the recognition that, despite having the highest per capita health care expenditures in the world, the United States does not always perform well on measures of health compared with other countries. There also is increased awareness of the limited information provided by results of traditional randomized clinical trials to inform decisions about therapeutic alternatives as applied in actual practice. Comparative effectiveness studies have two important principal components: (1) the comparison of two or more agents or interventions that are considered true therapeutic alternatives and (2) the examination of effects (outcomes) in actual practice. Comparative effectiveness studies

differ from traditional efficacy studies in several ways, including the research question addressed, comparison groups, patient population, setting, outcomes measured, and validity. Studies that are within the scope of CER can be categorized as primary comparative effectiveness studies or secondary comparative effectiveness studies. CER also can be used to compare medical devices, procedures, health services, or any competing intervention.

Conclusion. Comparative effectiveness is an emerging area of research relevant to many areas of health care, especially pharmacotherapy. The knowledge gained from CER is important to pharmacists when applying drug information and making decisions related to drug therapy.

Index terms: Clinical studies; Control, quality; Decision-making; Methodology; Outcomes; Pharmacists; Pharmacy; Quality assurance; Research

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decision-makers. The specific objectives were to (1) provide an overview of the factors and events leading

to the current national interest in comparative effectiveness, (2) define comparative effectiveness and differ-

GLEN T. SCHUMOCK, PHARM.D., M.B.A., FCCP, is Director, Center for Pharmacoeconomic Research, College of Pharmacy, University of Illinois at Chicago (UIC), and Associate Professor, Department of Pharmacy Practice, College of Pharmacy, UIC. A. SIMON PICKARD, B.S.PHARM., PH.D., is Assistant Director, Center for Pharmacoeconomic Research, College of Pharmacy, UIC, and Associate Professor, Department of Pharmacy Practice, College of Pharmacy, UIC.

Address correspondence to Dr. Schumock at the Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago, 833 South Wood Street (M/C 886), Chicago, IL 60612 (schumock@uic.edu).

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entiate pharmaceutical comparative effectiveness studies from traditional efficacy studies, and (3) describe different study designs that may be considered within the scope of CER and provide examples of each. The current organization of CER efforts by federal agencies in the United States is described.

Rationale for comparative effectiveness

The level of spending on health care in the United States exceeds that of all other countries in the world. In 2007, health care expenditures in the United States rose 6.1% to \$2.2 trillion, or 16.2% of the gross domestic product.³ By 2017, total health care expenditures are expected to reach \$4.3 trillion.⁴ Prescription drug costs are an increasingly important contributor to overall health care spending, increasing from \$5.5 billion in 1970 (7.3% of total spending) to \$227.5 billion in 2007 (10.1% of total spending). However, professional services, including physician services, and hospital care each accounted for a much larger percentage of total health care expenditures in 2007 (31.3% and 31.1%, respectively).³

In 2004, the average amount spent on health care per capita by developed countries, as defined by the Organization for Economic Cooperation and Development (OECD), was less than half of that of the United States (\$2552 and \$6102 per capita, respectively).⁵ By way of comparison, Canada spent \$3165, Australia spent \$3121, the United Kingdom spent \$2508, and Mexico spent \$662 per capita in 2004. In 2007, per capita spending on health care in the United States rose to \$7421.³

The United States also spends more on pharmaceuticals than do other countries. In 2004, expenditures for prescription drugs averaged \$752 per person in the United States, while the OECD average was \$383. By comparison, per capita prescription drug spending in Canada, Japan, Australia,

and Mexico was \$559, \$425, \$400, and \$138, respectively. Interestingly, U.S. spending on prescription drugs was lower than in OECD countries as a percentage of total health spending (12.3% versus 17.8%, respectively).⁵ While the United States spends more on health care and prescription drugs than other countries, data are mixed regarding the value it gets for the money spent. For example, with a life expectancy of 77.5 years, the United States ranks 22nd among 30 OECD countries, with the average for OECD countries being 78.3 years. The United States also has the lowest survival rate for kidney transplant recipients, the third highest rate of deaths from medical errors, and the third highest infant mortality rate among OECD countries.⁵ On the other hand, the United States is among the top-performing countries in terms of rates of cervical cancer screening,⁶ self-reported health status, breast cancer survival,⁵ and patient waiting times.⁷

The discrepancy between health care spending and health outcomes is also apparent in the regional variations in medical practice within the United States. Differences in medical treatments across the various regions of the United States are well documented.⁸ Not only do these differences suggest a lack of consensus regarding the effectiveness of treatment interventions, they represent an opportunity to reduce costs while improving (or maintaining) quality in areas where decision-making is not informed by outcomes data. Coronary artery bypass graft surgery,⁹ carotid endarterectomy, angioplasty, radical prostatectomy, and back surgery are notable examples of procedures that vary markedly by geographic area without notable differences in outcomes.¹⁰

The need to manage escalating health care costs and concerns about unexplained regional variations in health care in the United States have been cited as forces that contributed

to the outcomes research movement in the United States in the 1990s.¹¹ While comparative effectiveness is an extension of this movement, the current emphasis, at least as it applies to pharmaceuticals, is also fueled by increasing recognition of the failure of the drug development and approval processes to provide data that can help clinicians and policymakers decide among drugs or other interventions used for the same purpose. This issue is discussed in more detail later in this article.

Comparative effectiveness is not limited to the study of pharmaceuticals. Comparative effectiveness studies can examine devices, procedures, health services, or any competing intervention. In fact, comparative effectiveness is not even limited to the health care field.

The need for better information about the comparative clinical and economic effectiveness of health care interventions has been recognized for some time, but the fragmented U.S. health care system and strong political lobbies have created obstacles for government involvement in such efforts. In other countries, the latter issue has not been as much of an impediment to directly addressing efficiency issues in health care. Thus, while the terminology and emphasis may differ, the concept of comparative effectiveness is not unique to the United States. The National Institute for Health and Clinical Excellence in the United Kingdom and the Canadian Agency for Drugs and Technologies in Health, previously known as the Canadian Coordinating Office of Health Technology Assessment, are two of the better-known and well-established organizations outside of the United States that focus on the conduct of systematic reviews of health care interventions to help inform clinical decision-making.¹²

From a legislative standpoint, the recent emphasis on comparative effectiveness in the United States can

be traced to the Medicare Prescription Drug Improvement and Modernization Act (MMA) of 2003.¹³ This legislation and the likely future organization of CER in the United States are discussed later in this article.

Definition and principles of comparative effectiveness

Comparative or clinical effectiveness has been defined differently by various authors and organizations. It typically refers to the generation or synthesis of real-world effectiveness data where one or more treatment options are compared. 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.”¹⁴ CBO also stated that comparative effectiveness studies “may compare similar treatments, such as competing drugs, or may analyze very different approaches, such as surgery and drug therapy” and that “the analysis may focus only on the relative medical benefits and risks of each option, or it may also weigh both the costs and benefits of these options.” It is notable that this definition includes costs. The inclusion of costs is a controversial subject in the United States; as a result, costs are not included in most other published definitions of comparative effectiveness.^{2,15} The Institute of Medicine (IOM) uses the term “comparative clinical effectiveness,” presumably to emphasize the focus on clinical rather than economic outcomes.^{15,16}

At its core, comparative effectiveness has two important components: (1) the comparison of two or more agents or interventions that are considered true therapeutic alternatives and (2) the examination of effects (outcomes) in actual practice. As implied by the first component, comparative effectiveness studies provide information to help clinicians and decision-makers choose among alternative agents or treatments. For

this reason, placebo-controlled studies, for example, are not studies of comparative effectiveness. The second component is perhaps more nuanced and requires an understanding of the difference between the terms *efficacy* and *effectiveness*.

Efficacy is a measure of the capacity of a treatment to produce the desired effect (i.e., can this treatment work for this particular disease and for this particular patient population?). Efficacy assessments occur in a controlled environment, as in a randomized controlled trial (RCT). Effectiveness is a measure of the actual effect of the treatment in practice (i.e., does this treatment work?). Effectiveness assessments account for the variability of patient and environmental characteristics that occurs in actual practice. Accordingly, effectiveness assessments, not investigations of efficacy, fit within the definition of comparative effectiveness.

By defining comparative effectiveness using these two essential components, there are no restrictions on the particular measure of effectiveness (i.e., specific type of outcome) or type of study design used. By this definition, comparative effectiveness studies could include either clinical or safety outcomes, or even economic or humanistic outcomes. However, there is a lack of consensus on the inclusion of economic outcomes and costs in comparative effectiveness studies, with some people arguing that a more narrow definition excludes economic outcomes. Other related terms include *comparative safety*, which focuses on negative versus positive clinical outcomes and may be either distinguished from comparative effectiveness or considered a subcategory within comparative effectiveness. *Clinical effectiveness* and *clinical comparative effectiveness* are sometimes used to highlight the emphasis on clinical outcomes.

While retrospective observational studies are often thought of as the quintessential type of comparative

effectiveness study, comparative effectiveness studies are not limited to this type of design. Comparative effectiveness studies may include prospective clinical trials (randomized or nonrandomized), retrospective observational studies, or syntheses of existing studies using metaanalyses. The only restriction is that the two principle components discussed above are met.

Comparison with RCTs

Sometimes it is easier to define something by what it is not. The characteristics of traditional Phase III RCTs contrast with those of comparative effectiveness studies and help to illustrate the key components of an observational comparative effectiveness study. The basic characteristics of these two types of research are compared in Table 1.

The RCT has long been recognized as the gold standard for evidence on the efficacy of innovative medical care interventions, particularly drugs, and RCTs are required by the Food and Drug Administration (FDA) to market a new drug product. The pivotal Phase III RCT sponsored by a pharmaceutical company in the drug development process has a specific purpose—to establish the efficacy of the new drug (i.e., can the drug work?). Yet, it is now increasingly understood that the traditional RCT does not provide the information necessary for practitioners to understand how an agent works in clinical practice (i.e., does the drug work?).

Another problem with the traditional RCT is that it usually compares the new drug with a placebo or an inferior treatment option rather than the drug or drugs that might be legitimate therapeutic alternatives. Thus, the RCT does not help inform the decision-making process faced by a clinician who must determine which drug is best for the patient, nor does the RCT provide information that allows a formulary committee

Table 1.
Comparison of Traditional Phase III Randomized Clinical Trials (RCTs) and Phase IV Comparative Effectiveness Studies

| Characteristic | Traditional Phase III RCT | Comparative Effectiveness Study |
|-------------------|---|--|
| Research question | Can the drug work? | Does the drug work in normal practice, and how does it compare to therapeutic alternatives? |
| Comparison group | Placebo or inferior treatment | True therapeutic alternatives (e.g., head-to-head) based on current choices available to health care professionals |
| Population | Narrowly selected, usually healthier than patients who will eventually use the drug | Patients who actually use the drug once marketed |
| Setting | Controlled | Normal or actual practice |
| Compliance | Strictly enforced | As in normal practice |
| Outcomes | Often short-term, surrogate, or intermediate endpoints | True outcomes that are relevant to decision-making at the clinical level, policy level, or both |
| Validity | High internal validity but low external validity, not widely generalizable | Lower internal validity than RCT but higher external validity |

to select between two drugs for the same indication. These are the questions that comparative effectiveness studies seek to address.

Because the goal of a traditional RCT is to determine if the drug can work, the patient population for such trials is carefully selected. As shown in Table 1, patients enrolled in the typical RCT have the disease of interest but are otherwise healthy. The patients studied have few or no concomitant diseases, are within a narrow age range, are not taking other medications, and are likely to comply with the therapy prescribed. Both the population and the procedure to which study participants are exposed are highly controlled in the RCT. Thus, the RCT neither represents the population of patients who will eventually receive the drug once marketed nor the type of follow-up or care usually provided in practice. In contrast, observational comparative effectiveness studies have minimal selection criteria in order to be

more representative of the population of patients who use the drug in actual practice (e.g., patients who may not comply with therapy). For this reason, comparative effectiveness studies tend to have greater external validity compared with RCTs but have lower internal validity.

The types of outcomes included in observational comparative effectiveness studies are different than those included in the traditional RCT (Table 1). Because they tend to be short-term, RCTs are often forced to use surrogate or intermediate measures of effect rather than true outcomes. While surrogate outcomes may often be good indicators of long-term effect, this is not always the case. To the extent that observational studies can be conducted over a time period sufficient to capture long-term outcomes, they provide additional information not available from the results of an RCT. Knowing the differences among agents with respect to true outcomes is clearly of importance to

clinician decision-makers in selecting drug therapy.

Related to the types of outcomes measured in traditional RCTs versus those measured in observational comparative effectiveness studies is the relative inability of the former to detect rare adverse events. Rare adverse drug events are often not detected in traditional RCTs, because the study population is healthier than the eventual population receiving the drug once it is on the market and because the number of patients included in an RCT is not sufficient for such events to be detected. These adverse events become known once the drug is used widely. Observational comparative effectiveness studies are usually not encumbered by issues of sample size, particularly if they are retrospective, and are therefore better suited for the detection of rare adverse events.

While traditional Phase III RCTs have a clear purpose—to provide efficacy data to support market approval of a new drug—RCTs do not typically provide the direct evidence required by decision-makers to select among therapeutic alternatives. Observational comparative effectiveness studies, on the other hand, are designed to generate such evidence and are thus more relevant to actual practice.

Comparative effectiveness study designs

In 2007, IOM released a report on the need for and current status of CER in the United States.¹⁵ This document provided a useful framework for understanding the types of studies that constitute CER. The report used the term *clinical effectiveness* (rather than *comparative effectiveness*) and categorized research as primary clinical effectiveness or secondary clinical effectiveness, with the former defined as “direct generation of evidence through the use of a specific experimental methodology” and the latter as “systematic

gathering and evaluation of primary research information to further the understanding of common conclusions and disparate results.¹⁵

Primary comparative effectiveness. Primary comparative effectiveness refers to studies that generate new empirical evidence through experimental or quasiexperimental means. These studies measure effectiveness rather than efficacy and assess (i.e., compare) therapeutic alternatives.

While comparative effectiveness studies are commonly thought of as retrospective, this is not necessarily the case. Certain prospective clinical trials can be comparative effectiveness studies if the population is representative of the actual use of the drug and if the interventions are representative of actual practice. The terms *large simple clinical trial* and *pragmatic clinical trial* are sometimes used to characterize such studies, which may be randomized or non-randomized.¹⁷ Cluster randomized trials are another type of prospective clinical trial where the clinicians or practice sites are randomized rather than the patients.

A commonly cited example of a prospective comparative effectiveness study is the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).¹⁸ This large, multicenter clinical trial compared the effectiveness of four antihypertensive medications. While patients in the ALLHAT were randomized to different treatment groups, the patients included in the trial were representative of the general population with hypertension and multiple comorbid diseases (rather than otherwise healthy), the comparisons made were of medications commonly used in treatment of hypertension (rather than a placebo comparison), and the study endpoints were true long-term outcomes, such as all-cause mortality, stroke, and combined cardiovascular death (rather than surrogate mea-

asures). Findings of the ALLHAT were believed to have had a profound effect on the treatment of hypertension.¹⁹ Other well-known prospective comparative effectiveness studies include the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE),²⁰ the Women's Health Initiative,²¹ and the Heart Protection Study.²² While highly relevant to clinical practice, pragmatic clinical studies tend to be very expensive to conduct.

Retrospective observational case-control or cohort studies are perhaps the more conventional approach to conducting CER. In these studies, insurance claims data or electronic medical records are often used to assess outcomes in patients treated with one drug or another. Two examples of retrospective comparative effectiveness studies, both investigating the use of β -adrenergic blockers in heart failure, were published in the same issue of the *Archives of Internal Medicine* in December 2008.^{23,24} Go et al.²³ used pharmacy and medical claims data from two large health maintenance organizations and compared survival in patients who received metoprolol tartrate, carvedilol, other β -adrenergic blockers, or no β -adrenergic blockers. Importantly, the multivariate analyses conducted were adjusted for many covariates that were potential confounders. A propensity score (propensity to use carvedilol) was included in the model to attempt to eliminate confounding by indication, an important problem in these types of studies. More information on the statistical methods used in retrospective comparative effectiveness studies can be found elsewhere.²⁵⁻²⁷

Variations of the two types of primary comparative effectiveness studies described above include prospective or retrospective analyses of patient registries and cluster randomized studies. Registries are not a type of study design but are sources of data for comparative effectiveness studies. More information on

the use of registries in CER can be found in the AHRQ report *Registries for Evaluating Patient Outcomes: A User's Guide*.²⁸ Cluster randomized trials are most often used for comparison of the effectiveness of health care services.²⁹ In these studies, physicians, clinics, or sites of care are randomized to alternate interventions rather than individual patients. While cluster randomized studies require special methodological considerations because of the lack of independence among individuals within the same cluster, the primary advantage in CER is that such studies allow for a natural representation of clinical practice.³⁰

Secondary comparative effectiveness. A secondary comparative effectiveness study shares the same basic principles discussed above, but its purpose is to pool results from multiple original studies. Using a systematic method of literature identification, review, and interpretation, secondary comparative effectiveness studies can derive conclusions considered to have greater power than any individual study. Secondary comparative effectiveness studies, including systematic reviews and meta-analysis, are especially useful where there have been conflicting results or controversy, but the primary goal is still to compare alternative treatments from the standpoint of real-world health care decisions. In the case where no head-to-head studies have been conducted, secondary comparative effectiveness studies can present data in a way that allows such comparison.

Many secondary comparative effectiveness studies have been conducted by AHRQ's evidence-based practice centers and are available online.³¹ One recently published example is the systematic review of the comparative effectiveness and safety of insulin products in the treatment of type 2 diabetes conducted by Qayyum et al.³² Based on a review of 45 studies, the authors compared

the strength of evidence for use of various insulin products across outcomes of interest and patient categories. Gaps in the available evidence were also noted by the authors.

This study and other similar comparative effectiveness reviews can be extremely useful in both individual patient care and systemwide health care policy decisions. An extension of these types of reviews is the use of modeling to predict outcomes in a population of patients. Though often associated with economic evaluations, decision models are usually designed to compare one treatment to another and generally assume real-world conditions. The clinical effectiveness of the alternatives being studied is usually an important component of the analysis. For example, Göhler et al.³³ compared the clinical effectiveness and cost-effectiveness of different strategies for managing heart failure using a decision model.

Comparative safety. In the broadest sense of the term, comparative effectiveness can be interpreted to infer that outcomes of interest are both clinical effectiveness and safety. In some cases, however, people will purposefully distinguish between the two. Comparative safety studies are those that focus on the identification or confirmation of previously unknown or suspected rare adverse drug events rather than measures of the beneficial effect of the interventions compared. As noted previously, a limitation of clinical trials is their inability to detect rare adverse events because of limitations in sample size. Observational comparative effectiveness studies are usually not encumbered by issues of sample size, particularly if they are retrospective, and are therefore ideal for detecting rare adverse events.

An example of a comparative safety study is that conducted by Schneeweiss et al.,³⁴ who investigated the risk of mortality associated with the use of conventional and atypical antipsychotics in the

elderly. Using administrative data from the British Columbia Ministry of Health and the British Columbia vital statistics agency, the authors compared mortality in 12,882 seniors who received antipsychotic medications. This study clearly provided results that would not be expected in a typical clinical trial because of the comparison between alternatives, the outcome of interest, and the patient population.

Limitations of comparative effectiveness studies. Each of the comparative effectiveness study designs described above has certain limitations. There are numerous sources of information on the limitations of such studies, but these limitations are not reviewed here. However, it is worthwhile to note the major types of limitations that may be encountered.

Primary comparative effectiveness studies that are nonrandomized suffer the same limitations as other observational research. Chief among these is the fact that only associations, not causality, can be inferred from such data. Lack of randomization may lead to issues of potential selection bias and of confounding. Confounding by indication is a particularly difficult issue that was addressed more fully elsewhere.²⁶ Retrospective comparative effectiveness studies that use administrative databases are limited to the accuracy of coding within the claims data which are known to be highly variable, particularly with respect to diagnoses where miscoding may be problematic. Secondary comparative effectiveness studies may have limitations similar to those of other systematic reviews or meta-analyses. These can include problems in literature identification, publication bias, and issues in methods of analysis.

While not a limitation, it is also worth noting that CER is not a substitute for efficacy studies—both have important contributions to make in understanding pharmaco-

therapy. Beyond CER, there is the important work of dissemination and translation of findings, and from that standpoint CER may be considered necessary but not sufficient for improving the health care system.

Current and future organization of CER

In the United States, the recent emphasis on comparative effectiveness can be traced to MMA Section 1013, which gave AHRQ the authority to “conduct and support research with a focus on outcomes, comparative clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services.”¹³ Presumably, the impetus behind this charge was the considerable expense incurred on behalf of the Centers for Medicare and Medicaid Services with the implementation of the Medicare Part D drug benefit, as well as the desire to ensure that Part D providers make formulary decisions that are informed by considerations of the comparative effectiveness of alternative agents. The initial funding designated in 2005 to AHRQ of \$15 million annually for CER was increased to \$30 million in 2008 by Congress,^{2,12} signaling continued interest by lawmakers in the program. AHRQ’s funding for comparative effectiveness appears to have increased dramatically with passage of the ARRA, which also broadens the pool of government agencies involved in CER, with \$400 million going to the National Institutes of Health (NIH) and \$300 million going to the Secretary of the Department of Health and Human Services.¹

At the time of writing, some information was known about how these agencies will spend the ARRA funds, but readers are encouraged to seek updated information as it becomes available. For its part, NIH announced a limited grant competition that includes high-priority topics within the area of comparative effectiveness.³⁵ In addition to allo-

cating \$400 million to the Secretary of Health and Human Services to support CER, the ARRA mandated that IOM produce and submit a consensus report by June 30, 2009, that provides specific recommendations to Congress and the Secretary for expenditure of these funds. The IOM Committee on Effective Research Priorities, acting on behalf of the Secretary of Health and Human Services, is conducting a study to recommend national priorities for CER.³⁶ The ARRA also mandates the establishment of a Federal Coordinating Council for Comparative Effectiveness Research to “foster optimum coordination of comparative effectiveness and related health services research conducted or supported by relevant Federal departments and agencies, with the goal of reducing duplicative efforts and encouraging coordinated and complementary use of resources.”³⁷

AHRQ has not yet announced how it intends to use its new funds.³⁸ However, the method by which AHRQ has carried out its authority to conduct and support CER in the past is clear.^{2,12}

In brief, AHRQ has organized its comparative effectiveness efforts under an umbrella called the Effective Health Care (EHC) program.³⁹ The EHC program has three aims: evidence synthesis, evidence generation, and evidence dissemination. The efforts around evidence synthesis are orchestrated by a group of centers called the Evidence-based Practice Centers (EPCs), which predate the EHC program by nearly a decade.⁴⁰ The current 15 EPCs (appendix) contract with AHRQ to conduct systematic reviews and meta-analyses of important clinical topics. The reports generated, called comparative effectiveness reviews, provide comprehensive appraisals of existing evidence and identify important gaps in evidence that require future research. The EPCs and the reports that they generate are arguably the

most well-recognized components of AHRQ’s EHC program.

Evidence generation—or primary CER—is orchestrated under the EHC program by two separate groups of centers. The first group is called the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) centers. As described by AHRQ, the DEcIDE network “conducts accelerated practical studies about the outcomes, comparative clinical effectiveness, safety, and appropriateness of health care items and services.” The network currently comprises 13 centers (appendix). Key components of these centers are access to electronic health information databases and possession of the expertise and capacity to rapidly conduct CER using these databases. To date, most of the work conducted by these centers has used retrospective designs, although prospective studies are currently under way as well.

The Centers for Education and Research on Therapeutics (CERTs) are another group of AHRQ-funded centers that focus, at least in part, on CER. First authorized by Congress in 1997 as part of the FDA Modernization Act of 1997 (Public Law 105-115), the program has grown from 4 initial centers to the current contingent of 14 centers and one coordinating center (appendix). The mission of CERTs is to conduct research and provide education that advances the optimal use of drugs, biologicals, and medical devices. Each CERT focuses on a broad therapeutic theme, which represents areas where limited comparative information exists on the risks, benefits, and interactions of new and older therapeutic agents.

While the future organization of CER could deviate from the current structure that has been implemented by AHRQ, it appears that there will be continued investment in this type of research and a thoughtfully constructed, cohesive program has been developed. As noted earlier, CER has potentially far-reaching implications

for the practice of pharmacy and appropriate drug prescribing. Therefore, it is essential that pharmacy-based researchers and institutions participate and hopefully provide leadership in these initiatives. Scholars with backgrounds in pharmacy or who are based in colleges or schools of pharmacy are the designated lead or principal investigators in at least one center in each of the three initiatives (EPCs, DEcIDE centers, CERTs).

Discussion

CER has the potential to be extremely important to physicians, pharmacists, health care provider organizations, pharmaceutical manufacturers, employers, insurers, and government agencies. Because many of these studies focus on pharmaceuticals, they are particularly important to pharmacists and pharmaceutical policy decision-makers. By providing data on the effectiveness of therapeutic alternatives for a variety of outcomes, these studies can assist pharmacists and other health care professionals in making more informed prescribing recommendations, as well as improve the evidence base for formulary committees. Comparative safety studies can also identify or confirm previously unknown or suspected rare adverse drug events not reported in Phase III clinical trials.

Comparative effectiveness studies also have the potential to serve as an important source of guidance on cost-effectiveness decisions or contribute data to economic analyses. By providing useful information to decision-makers, CER may help mitigate increases in spending on pharmaceuticals or overall health care spending. CBO estimated that CER could reduce direct spending by the federal government (Medicare and Medicaid) by \$0.1 billion between 2008 and 2012 and by \$1.3 billion between 2008 and 2017.¹⁴ However, these estimates were made

before the recent large investment in CER. It remains unclear to what degree CER may result in the actual slowing of growth in pharmaceutical or other health care expenditures in the coming years.

It is important for pharmacists and pharmacy decision-makers to understand and to monitor the results of new comparative effectiveness studies and, when appropriate, to apply the evidence at the patient level (e.g., prescribing) and the systems level (e.g., formulary decisions). Well-trained researchers with a clinical background such as pharmacy combined with skills relevant to outcomes research will likely find opportunities to engage in primary or secondary CER, its dissemination, or both. With the shared goal of improving decision-making at every level of the health care system, pharmacy and other professions can use CER as an opportunity to be more efficient and more accountable.

Conclusion

Comparative effectiveness is an emerging area of research relevant to many areas of health care, especially pharmacotherapy. The knowledge gained from CER is important to pharmacists when applying drug information and making decisions related to drug therapy.

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10. Stanford University, Stanford, and University of California, San Francisco, CA; principal investigator: Douglas K. Owens, M.D., M.S.
11. Tufts University—New England Medical Center, Boston, MA; principal investigator: Joseph Lau, M.D.
12. University of Alberta, Edmonton, Alberta, Canada; principal investigators: Terry P. Klassen, M.D., M.Sc., FRCPC, and Brian H. Rowe, M.D., M.Sc., CCFP(EM), FCCP.
13. University of Connecticut, Storrs, CT; principal investigator: C. Michael White, Pharm.D.
14. University of Ottawa, Ottawa, Canada; principal investigator: David Moher, Ph.D.
15. Vanderbilt University Medical Center, Nashville, TN; principal investigator: Katherine Hartman, M.D., Ph.D.

Appendix—List of the Agency for Healthcare Research and Quality (AHRQ)-funded centers conducting comparative effectiveness research

Evidence-based Practice Centers (EPCs)

1. Blue Cross and Blue Shield Association, Technology Evaluation Center, Chicago, IL; principal investigator: Naomi Aronson, Ph.D.
2. Duke University, Durham, NC; principal investigator: John W. Williams Jr., M.D.
3. ECRI Institute, Plymouth Meeting, PA; principal investigator: Karen Schoelles, M.D., S.M.
4. Johns Hopkins University, Baltimore, MD; principal investigator: Eric B. Bass, M.D., M.P.H.
5. McMaster University, Hamilton, Ontario, Canada; principal investigator: Parminder Raina, Ph.D.
6. Minnesota EPC, Minneapolis, MN; principal investigators: Robert L. Kane, M.D., and Timothy J. Wilt, M.D., M.P.H.
7. Oregon Health and Science University, Portland, OR; principal investigator: Mark Helfand, M.D., M.S., M.P.H.
8. RTI International—University of North Carolina at Chapel Hill, Chapel Hill, NC; principal investigator: Meera Viswanathan, Ph.D.
9. Southern California EPC—RAND, Santa

Developing Evidence to Inform Decisions about Effectiveness (DECIDE) centers

1. Acumen, LLC, Burlingame, CA; principal investigator: Thomas E. MaCurdy, Ph.D.
2. Brigham and Women’s Hospital, Boston, MA; principal investigator: Sebastian Schneeweiss, M.D.
3. Duke University, Durham, NC; principal investigator: David B. Matchar, M.D.
4. Harvard Pilgrim Health Care, Harvard Medical School, Boston, MA; principal investigator: Richard Platt, M.D.
5. Johns Hopkins University, Baltimore, MD; principal investigator: Albert W. Wu, M.D.
6. Outcome Sciences, Cambridge, MA; principal investigator: Richard E. Gliklich, M.D.
7. RTI International, Research Triangle Park, NC; principal investigator: Suzanne West, Ph.D.
8. University of Colorado at Denver and Health Sciences Center, Aurora, CO; principal investigator: David West, Ph.D.
9. University of Illinois at Chicago, Chicago, IL; principal investigator: Glen T. Schumock, Pharm.D., M.B.A.
10. University of Maryland at Baltimore, Baltimore, MD; principal investigator: Bruce C. Stuart, Ph.D.
11. University of North Carolina at Chapel Hill, Chapel Hill, NC; principal investigator: Michael D. Murray, Pharm.D., M.P.H.
12. University of Pennsylvania School of Medicine, Philadelphia, PA; principal investiga-

- tor: Sean Hennessy, Pharm.D., Ph.D.
13. Vanderbilt University Medical Center, Nashville, TN; principal investigator: Marie R. Griffin, M.D.

Centers for Education and Research on Therapeutics (CERTs)

1. Brigham and Women’s Hospital, Boston, MA; principal investigator: David Bates, M.D., M.Sc.
2. Cincinnati Hospital Children’s Medical Center, Cincinnati, OH; principal investigator: Carole Lannon, M.D., M.P.H.
3. Duke University Medical Center, Durham, NC; principal investigator: Eric Peterson, M.D., M.S.
4. HMO Research Network, Seattle, WA; principal investigator: Richard Platt, M.D., M.Sc.
5. Rutgers, The State University of New Jersey, New Brunswick, NJ; principal investigator: Stephen Crystal, Ph.D.
6. University of Alabama at Birmingham, Birmingham, AL; principal investigator: Kenneth G. Saag, M.D., M.Sc.
7. University of Arizona CERT at The Critical Path Institute (C-Path), Tucson, AZ; principal investigator: Raymond L. Woosley, M.D., Ph.D.
8. University of Chicago, Chicago, IL; principal investigator: David Meltzer, M.D., Ph.D.
9. University of Illinois—Chicago, Chicago, IL; principal investigator: Bruce L. Lambert, Ph.D.
10. University of Iowa, Iowa City, IA; principal investigator: Elizabeth A. Chrischilles, Ph.D.
11. University of Pennsylvania School of Medicine, Philadelphia, PA; principal investigator: Brian L. Strom, M.D., M.P.H.
12. University of Texas M. D. Anderson Cancer Center and Baylor College of Medicine (Houston CERT), Houston, TX; principal investigator: Maria E. Suarez-Almazor, M.D., Ph.D.
13. Vanderbilt University Medical Center, Nashville, TN; principal investigator: Wayne A. Ray, Ph.D.
14. Weill Medical College of Cornell University, New York, NY; principal investigator: Alvin I. Mushlin, M.D., Sc.M.
15. CERTs Coordinating Center: Kaiser Permanente Center for Health Research, Portland, OR; principal investigator: Mark C. Hornbrook, Ph.D.