

Perspectives on Comparative Effectiveness Research

Views from Diverse Constituencies

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Healthcare sector participants in the US and worldwide offer a rich diversity of views on comparative effectiveness research (CER). CER has been defined – and redefined – by separate stakeholders for various purposes^[1-3] in the context of its potential to help address problems in the healthcare systems of the US and other countries. The demand for evidence about treatment alternatives in terms of both clinical and cost effectiveness in actual clinical practice has stimulated the development and dissemination of comparative effectiveness studies. Many participants in these discussions anticipate that the information these studies provide will, at a minimum, support better decision making and more rational allocation of scarce resources to fund healthcare, with fewer dollars allocated to (relatively) ineffective treatments. The more hopeful believe that evidence from comparative effectiveness studies will directly translate into real improvements in the quality and safety of the healthcare provided to patients.

While the implementation of CER has implications across global healthcare systems, the US focus on CER points to the growing influence of payers and their desire to control spending. Significant funding of the CER initiative from the American Recovery and Reinvestment Act of 2009^[4] indicates that an expected return on investment should be new clinical and economic evidence that will yield better value. In addition, the Patient Protection and Affordable Care Act of 2010^[5] establishes a private, nonprofit entity to oversee publicly financed comparative effectiveness studies, the Patient-

Centered Outcomes Research Institute (PCORI), whose core mission will be to identify priorities for CER, fund these studies and support improvements in CER methodology. A key measure of PCORI's potential impact is its substantial funding: a trust fund with amounts provided from the general fund that will grow to at least \$US150 million in fiscal 2012, with additional funding based on the size of the Medicare population and from new taxes on insurance policies. Altogether, public funding for CER may exceed \$US500 million per year by 2014. Thus, not only will the focus on CER likely change established priorities in the outcomes research arena, but the funding associated with this shift will likely add to the body of analytical evidence alongside existing manufacturer-funded studies that together will describe the key features of alternative medical interventions.

In the future, as the voice of the payer grows louder, both health outcomes research and product development are likely to evolve to address new cost-effectiveness objectives, with implications for those conducting research and developing healthcare technologies. In an era marked by increasing prominence of CER evidence, successful pharmaceutical, biotechnology and medical device manufacturers will need to develop products with unambiguous evidence of economic as well as clinical value relative to alternatives.

The goal of this editorial is to highlight important issues raised by an increased reliance on CER evidence and how they could have an

impact on patients, payers, providers and manufacturers. We conclude with a summary of some of the most critical challenges identified by the contributing authors to this volume, issues that must be addressed in order to translate new evidence from comparative effectiveness studies into meaningful improvements in quality and safety for patients, and cost effectiveness for payers.

1. What is the Definition, Scope and Potential Impact of Comparative Effectiveness Research (CER)?

CER in the US has a lineage that evolved from health technology assessment (HTA), extending back to early efforts by the US Office of Technology Assessment to seek justification for costly new medical technologies.^[6,7] Recently, the Federal Coordinating Council for Comparative Effectiveness Research defined CER as research comparing interventions “in real-world settings.”^[3] This orientation reflects an important change in focus towards research grounded in actual clinical practice, with study inclusion criteria broadened to assess populations representative of the target of treatment, leading to potentially larger, longer and more resource-intensive studies. This shift explicitly favours the external validity characteristic of comparative effectiveness studies over the internal validity that comes from more typical efficacy trials with restricted inclusion criteria.^[8]

The obvious benefit of ‘real-world’ CER for patients is that when physicians apply the results of effectiveness studies cast in such a framework, they are more likely to make appropriate treatment decisions. However, while broadened inclusion criteria can improve applicability to clinical practice, this approach is no panacea.^[9] A given intervention may be more effective on average, yet not be the best choice for a particular patient or sub-population. Heterogeneity in treated populations represents a substantial challenge for CER, as it has for traditional study designs.^[10]

Despite the many dimensions to CER, for many, what may be most often associated with the initiative are head-to-head comparative trials of pharmaceuticals (‘drug A vs drug B’). While these drug-drug comparisons are an important aspect

of CER, from a societal cost perspective, improvements in efficiency that CER advocates seek must also come from elsewhere in the system, including interventions that are not typically subjected to rigorous comparison of outcomes. This is because drug costs represent less than 15% of healthcare spending in the US.^[11] Examples of applications beyond drugs range from surgical or other non-drug medical interventions, to behavioural or policy interventions, and even to system-level changes.^[11] The Institute of Medicine report released in 2009^[12] provides a list of priorities for CER, featuring comparisons across such modalities as surgery and pharmacotherapy and, notably, identifies care delivery as a critical area for CER. Therefore, as CER guidelines are promulgated by regulators, it is important that they be applicable across the range of relevant applications.

In the context of evidence-based medical practice, treatment guidelines frequently present disparate alternatives alongside one another. For example, current treatment of obesity may involve a range of interventions, including behavioural, pharmacological and surgical treatment, goal setting and ongoing monitoring, as shown in a synthesis of recent clinical guidelines for the management of obesity (figure 1).^[13-15] In this example, CER offers the potential to identify which intervention may be more effective, and for which subset of patients (here, based on patients’ body mass index [BMI] and risk factors or comorbid conditions) and also in the context of particular treatment strategies (here, goal setting in advance of treatment and regular monitoring following treatment).

Evaluation of non-drug interventions presents significant methodological challenges, particularly where effectiveness from the perspective of actual clinical practice depends substantially on external factors such as care setting and the way in which a new health technology is used. The effectiveness of diagnostic interventions is particularly difficult to assess because of the indirect linkage with treatment outcomes and the additional challenge of assessing potential harms associated with false positive and false negative results. Historically, clinical studies evaluating the effectiveness of surgical interventions have been uncontrolled case series

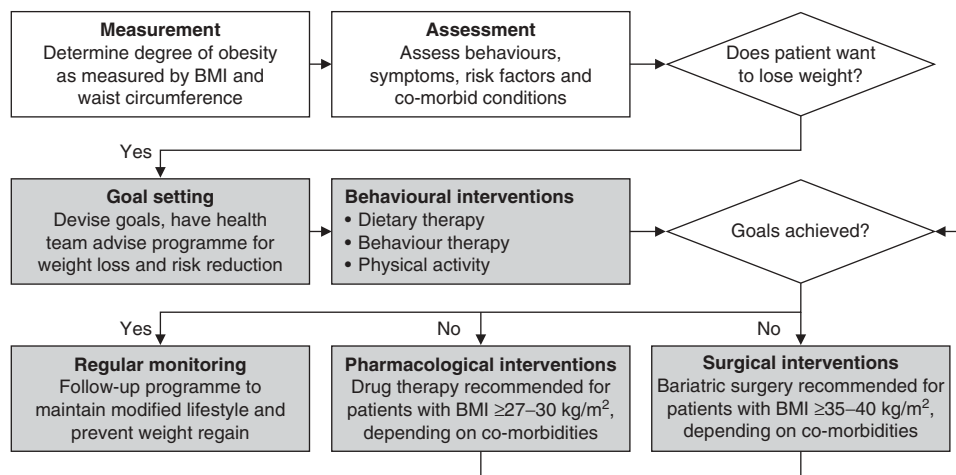


Fig. 1. Synthesis of algorithms for the management of obesity in adults based on recommendations made in recent clinical practice guidelines.^[13–15] BMI = body mass index.

and non-randomized comparative studies; randomized trials of surgery are rarely considered feasible.^[16] Thus, although there may be tremendous potential for improving cost and quality of care by applying CER in areas other than drug-drug comparisons, CER for non-drug interventions will continue to be especially difficult to conduct and interpret, and may therefore diminish any such expected gains.

Drug-drug studies also face significant challenges and many of these issues are the main focus of most of the articles in this special issue of *PharmacoEconomics*.

2. What is the Current State of CER?

It is widely acknowledged that the comparative effectiveness of most therapies is currently unknown.^[17] Commercially funded research has, understandably, been targeted at marketing authorization based on regulatory requirements that often allow for placebo-controlled or non-inferiority study designs. A recent analysis^[18] of publications in the six medical journals with the

highest impact factor considered all randomized trials, observational studies and meta-analyses published over a period of 16 months; a total of 1500 studies. The authors found that less than one-third of studies that evaluated medications were actually comparative effectiveness studies (as defined by the Federal Coordinating Council for Comparative Effectiveness Research as research that compares “the benefits and harms of different interventions and strategies to prevent, diagnosis, treat, and monitor health conditions.”¹ see figure 2). The composition of the comparative effectiveness studies identified also reflects the range of needs for better comparative information, with fewer than half of the studies identified comparing one medication with another (‘drug A vs drug B’ studies). To be fair, in many cases comparative effectiveness studies may not be appropriate, either because treatment alternatives may not exist or because products are still investigational. Still, it seems reasonable to conclude that the majority of clinical studies apparently have not provided comparative effectiveness information to support evidence-based treatment or coverage decisions.

1 See page 951 of Hochman and McCormick,^[18] which also cites to the Federal Coordinating Council for Comparative Effectiveness Research report to the President and Congress.^[3]

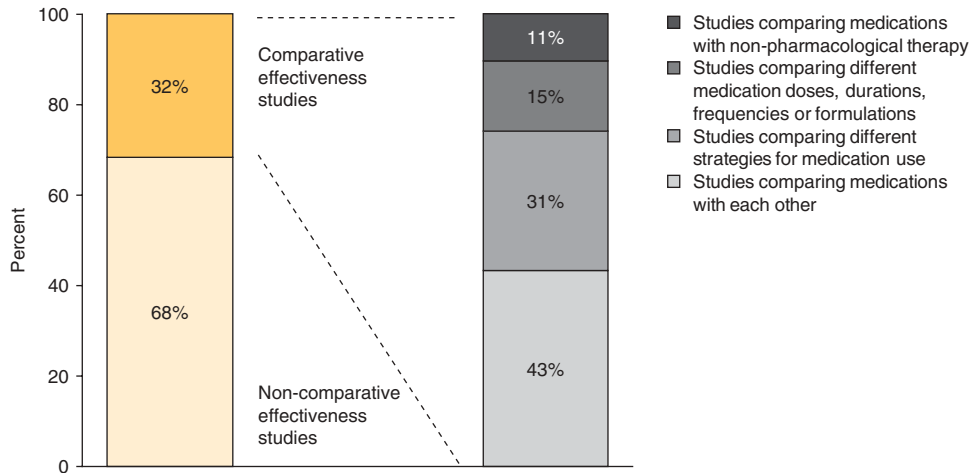


Fig. 2. Prevalence and characteristics of published comparative effectiveness studies, among studies evaluating medications.^[18]

3. How will Evidence from Comparative Effectiveness Studies be Used in the Future?

In light of the ‘public good’² features of comparative effectiveness studies, the availability of more and better CER evidence will presumably lead to its widespread use. Evidence of comparative effectiveness, in theory, should lead to a common understanding of value, and consequently to a common prioritization of treatment alternatives, regardless of who pays for it. Economies of scale and scope should also be evident, such that, given the usefulness of this evidence common to all stakeholders, the cost of CER could be allocated widely, including to both public and private payers. However, we note that there already is a large body of existing evidence with outcomes relevant to payers, including cost-effectiveness, cost-utility and cost-benefit analyses, which has had an uneven impact on coverage decisions. Simply having evidence available, even if it is precisely the information needed, may not translate into optimal allocation of resources.

Even in the context of a single decision-making body with the resources needed to evaluate and make use of complex clinical and economic evi-

dence, substantial challenges exist in applying evidence from CER. Models for the use of CER evidence in the context of HTA can be found outside the US. In this special issue, articles by Levy et al.,^[20] Chalkidou and Walley^[21] and Kamae^[22] provide important perspectives regarding how CER and HTA have developed in much of the industrialized world, specifically the UK in the context of the National Institute for Health and Clinical Excellence (NICE), elsewhere in Europe and Canada, and in the East Asia Rim, with implications and insights for the use of this evidence. This special issue also features an interview with Jean Slutsky,^[23] the director of the Center for Outcomes and Evidence of the Agency for Healthcare Research and Quality (AHRQ), which provides the perspective of AHRQ on how evidence from CER may be applied in the US system and how this may differ from other healthcare systems.

Elsewhere, a recent review^[24] identified some of the many factors that may stand in the way of developing and using evidence for reimbursement decision making, including cultural, political and organizational barriers in responsible authorities worldwide. As discussed recently by Martin et al.,^[25] numerous challenges must be overcome in conducting publicly financed comparative effectiveness

² As discussed by Garrison^[19] in this special issue, a public good is not diminished by others’ use and no one can be effectively excluded from using the good.

studies, including coordination of multiple government agencies as well as public and private payers, all of which may present barriers not typically encountered by pharmaceutical companies in the context of clinical study execution (e.g. reimbursement for the drug). Another recent review^[26] notes the relative absence of mechanisms that could effectively put evidence from CER to work. The authors suggest several strategies to improve the impact of CER, including generating evidence more rapidly and aligning evidence requirements with the needs of regulatory and reimbursement authorities. Although these challenges are daunting, they do seem surmountable given the extraordinary pressure to reduce health-care spending.

To improve the quality of care directly, evidence from comparative effectiveness studies will also need to be applied in clinical practice, which will depend largely on changing physician behaviour. In one widely cited example involving alternative approaches to unclogging arteries,^[27] physicians have been slow to incorporate the results of a comparative effectiveness study that was expected to have broad influence on practice.³ Physicians correctly point out the challenges in applying even 'real-world' studies of effectiveness in the context of patient heterogeneity: in a recent editorial, a leading oncologist cited the example of differences in the molecular phenotype of his patients' disease as requiring an individualized approach to treatment, claiming that "CER [can not] keep pace with advances in medicine."^[29] Another aspect of this challenge is the extraordinarily wide geographical variation in medical practices, even in regions with similar populations, culture and access to healthcare.^[30,31]

Clearly, availability of comparative effectiveness evidence will not always be sufficient to have a meaningful impact on healthcare decisions. In this special issue, Kassirer and Wong^[32] review some of the challenges encountered between evi-

dence development and changes in clinical practice. They point out that, even given 'real-world' applicability of CER, the same barriers present for other types of knowledge implementation will factor into widespread application of CER. The authors cite several examples of such delays, including the practice of prescribing β -adrenergic receptor antagonists (β -blockers) for patients who have had an acute myocardial infarction and aspirin (acetylsalicylic acid) for patients with coronary artery disease, both cases where compelling evidence was widely disseminated and the recommended interventions simple and inexpensive. Practical impediments to adoption of CER are also likely to include the difficulties that physicians have encountered in identifying and using the growing number of clinical practice guidelines.⁴ Limits in the ability of individuals to process data may prove to be among the most difficult barriers to translating evidence from CER into practice. Overall, the use of evidence from CER will have a substantial and growing influence on reimbursement policies but perhaps a more diminished and delayed impact on clinical decision making and clinical practice.

4. What are the Implications for Manufacturers?

In this issue, several authors consider the impact of CER from the perspective of manufacturers.^[34-37] The old paradigm for pharmaceutical, biotechnology and medical device manufacturers is that market success depends on the intrinsic clinical value of their products, which is a feature of their biochemical and mechanical characteristics. But value to consumers and payers (and market success) is increasingly measured in health outcomes that may depend on many other factors related to delivery of high-quality care. Evidence of value in an appropriate context must now be developed alongside new health technologies in order to gain

3 The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial demonstrated a lack of reduced risk of death or cardiovascular events from adding percutaneous coronary intervention to medical therapy.^[28]

4 A search of the US National Guideline Clearinghouse^[33] identified over 2400 'evidence-based clinical practice guidelines'.

market access. Berger and Grainer^[34] point out that pharmaceutical innovators must do more than develop drugs that are safe and effective enough to pass regulatory scrutiny – they must now assemble evidence that demonstrates comparative value. Berger and Grainer^[34] also note that new implicit or explicit evidence requirements may necessitate better coordination among the stakeholders who demand this evidence to support resource allocation or treatment decisions. While there are undeniable differences in perspectives among various constituencies, the incentives to create a more effective system are clear for government, payers and manufacturers. Each group will have an important role as partners in an evolving scientific enterprise.

In US markets, demands for evidence of value will be shaped in part by the agenda set by the new PCORI. Unlike the UK NICE, PCORI will not make explicit coverage or treatment recommendations and is proscribed from using a QALY threshold or similar measure in evaluations. Therefore, the activities of PCORI will most directly impact manufacturers through selection and funding of CER on particular topics, which may affect development stage or marketed products. PCORI's research and funding priorities will inevitably focus attention on particular health technologies where evidence of clinical effectiveness is currently uncertain.

Manufacturers will consider the impact of this attention on their portfolio of products and, where possible, proactively develop evidence of value. CER is likely to be applied intensively and have the greatest impact on certain classes of drug therapies and devices depending upon such drivers as (i) the number of therapeutic alternatives; (ii) the budget impact to payers, whether framed narrowly in terms of drug costs alone or more broadly, on a system-wide basis; and (iii) the perceived level of unmet need. When the number of alternatives is high, comparative effectiveness studies can potentially provide the most meaningful evidence to payers, providers and patients. Similarly, when the budget impact is high, expectations for cost savings and the level of scrutiny is also likely to be highest. However, when the level of unmet need is high, limiting access will be very difficult for payers, even

when evidence of comparative effectiveness may be lacking. As has been the case for NICE,^[38] assessments of effectiveness directed by PCORI for end-of-life care or for treatments for orphan diseases will elicit considerable controversy and potentially may require special treatment, with implications for manufacturers' portfolio strategy.

For products that require substantial financial investments over a long period of time, uncertainty in determining what evidence is necessary for market success can be a strong disincentive for investment. Vernon et al.^[39] point out, also in this special issue, that, as evidence requirements grow in complexity, so too will drug development costs, thereby creating a disincentive for innovation. Vernon et al.^[39] observe that increasing access to products in the short term may have the unintended consequence of reducing access to new and innovative products in the future.

In addition to adjusting to new demands for evidence of value, another great challenge facing manufacturers today is personalized medicine. As Thomas et al.^[35] point out in this special issue, CER with a narrow focus on cost containment could work at cross purposes with personalized medicine. This is particularly true if coverage and treatment decisions become dominated by a so-called 'average effects' approach, where effectiveness in smaller population subsets may go unrecognized by CER focused on broad populations. Epstein and Teagarden^[36] describe a promising combination of CER and personalized medicine in two ongoing studies that evaluate clinical outcomes from pharmacogenomic testing of patients. The first of these studies is designed to measure outcomes of patients genotyped for markers that predict a safe dose of warfarin;^[40] the second evaluates the effectiveness of testing patients in advance of treatment for variants of a gene that predicts responsiveness to clopidogrel. These post-marketing studies are at a promising intersection of CER and personalized medicine, using real-world populations to evaluate the effectiveness of personalized medicine interventions, with results that will have clear implications for the decisions of providers, payers and patients. As Epstein and Teagarden^[36] note, future comparative effectiveness studies in a world with more molecular

diagnostic information will most likely make greater use of observational studies that retrospectively compare effectiveness of health interventions for patients with different pharmacogenetic profiles, expanding the use of registry and claims databases. Although such retrospective study designs have not been the gold standard for evidence of safety and efficacy, there is already precedence for using such data in drug labelling changes.^[41] A clear implication for manufacturers is that research into the comparative effectiveness of their products may come after launch, may change treatment patterns and product labels, and increasingly may be sponsored by payers.

5. What are the Implications for Policy?

Much of the recent interest in CER clearly stems from the potential policy issues raised by new information generated from these studies. A number of potential policy impacts have been discussed above, most notably in three areas: (i) the use of CER in coverage determinations made by payers; (ii) the use of CER in decisions made by providers in medical practice; and (iii) new evidence requirements related to the impact of CER on manufacturers, with consequences for innovation and social welfare.

Several articles in this special issue address challenges in effectively applying this knowledge,^[19,42-44] in particular, focusing on what decision rules might be used for CER in the context of public policy analysis. Cutler and Ericson^[43] consider a situation where price is substantially above marginal cost (viz. for branded pharmaceuticals) and ask what application of cost-effectiveness study results would maximize social benefits. The authors formulate a decision rule that considers social costs. Drawing on examples of statin use and targeted treatments for kidney cancer, they demonstrate that the social cost of a drug is actually well below the market price, which can yield a different cost-effectiveness result. This work implies that application of cost-effectiveness analysis in a policy setting (for example, using a cost-per-QALY threshold such as the one adopted by NICE) would be improved by considering true social costs. Garrison^[19] focuses

on the use of quantitative benefit-risk analysis and health outcomes modelling as a method to assess evidence developed from CER and to support regulatory decision making. The author uses the case of the type II diabetes mellitus treatment rosiglitazone (with noted elevated cardiovascular risk) and discusses the December 2008 US FDA guidance^[45] on safety testing in diabetes. The FDA guidance was developed with numerical guidelines designed to limit the number of cardiovascular events (rather than to reach a threshold of net health benefits), and requires additional safety testing of investigational diabetes drugs conducted in 'real-world' populations, thus bringing CER into the realm of regulatory policy. In the case of rosiglitazone, Garrison argues, the product may have a better overall benefit-risk profile than other marketed diabetes treatments.

Also in this special issue, Meltzer et al.^[44] consider the value of the results generated by comparative effectiveness studies from various perspectives. Using a value-of-information approach, the authors estimate the prospective value of study results to patients, payers and providers (including manufacturers) in three alternative cases: (i) when results identify one intervention as superior; (ii) when results identify a subset of patients in which interventions are more effective; and (iii) when results indicate that alternative interventions are similarly effective. Each of these cases has relevant implications for different stakeholders. Patients appear to benefit most consistently, either from identifying a superior intervention or from price competition that should result when alternatives are shown to be equivalent, but the value of these benefits in each case is not necessarily the same. In general, providers and payers are seen to benefit from CER only in certain cases or only in the short run.

As the articles referenced above demonstrate, important policy decisions regarding CER, including prioritization of research funding and decisions regarding product safety and regulatory involvement, may not use transparent decision rules or thoroughly evaluate the harms and benefits from an appropriate perspective. Situations will arise in which comparative effectiveness studies with different sponsors or perspectives will

compare the same treatment interventions and come to different conclusions, potentially introducing additional complexity to health policy decisions. In any case, there will undoubtedly be cases in which application of CER will not necessarily lead to better health outcomes for patients, and a better understanding is needed regarding the appropriate analytical basis for such critical policy decisions.

6. How can Research Methods Adapt to Meet New Demands for Evidence?

As is reflected in the charter of PCORI, substantial innovation and improvements in methods will be necessary to realize the potential for CER. Several articles herein address this challenge.^[46-49] As the Council defined it, CER can take numerous forms, including retrospective analysis such as systematic reviews, decision analyses and claims studies; and prospective clinical studies such as randomized clinical trials (RCT). One particular approach to designing RCTs to meet the objectives of CER is to use pragmatic or practical clinical trials (PCTs). Mullins et al.^[48] describe the following distinguishing features of PCTs: inclusion of active comparators (clinically relevant alternative interventions), evaluation in a diverse population of study participants from heterogeneous practice settings and collection of data on a broad range of health outcomes relevant to patients. Most important, to be useful to decision makers, PCTs must assess the relative value of alternative treatments.

For retrospective analyses, a number of methodological innovations exist that can help meet the objectives of CER, including statistical and modelling techniques that make possible indirect comparisons of technologies not evaluated in a head-to-head clinical study. In one approach, Caro and Ishak^[47] describe a simulation modelling approach to combine evidence from distinct trials in order to affect an indirect or simulated head-to-head comparison. Events in the simulation are based on equations derived from patient-level data (at least for the index trial); trial publications or meta-analyses may be sufficient for comparators. Signorovitch et al.^[49] apply an alternative

approach in an indirect comparison of adalimumab and etanercept, two treatments that separately were demonstrated to be superior to placebo for treatment of severe psoriasis. In this approach, an indirect comparison was made by adjusting patient-level data from adalimumab to match the baseline characteristics of patients in the etanercept trial. Both approaches are improvements over methods that use only aggregate data that may come from very different patient populations, and thus should support significantly better inferences about the relative value of treatment alternatives so important to decision makers in the context of CER.

7. Conclusions

With so much focus on CER as a component of healthcare reform legislation in the US, the proliferation of expectations is likely to continue. Better informed decisions, based on superior evidence, are to be expected, yet substantial barriers stand between increased knowledge and meaningful improvements in both quality and safety for patients. The contributors to this special issue have, in their research, identified a number of potential important challenges. How will evidence from CER be used in decision making by regulatory and reimbursement authorities and by physicians? How will effectiveness be evaluated in the context of other health technologies, given the significant challenges in conducting and interpreting comparative effectiveness studies other than drug-drug comparisons? Given patient heterogeneity, CER could limit access to the right drug for the right person – will the application of results from comparative effectiveness studies appropriately address patient differences? What will be the reaction to CER if it leads to increased costs (such as if the results of the research find that a specific drug has a better efficacy/safety profile but is more expensive than its alternatives)? New demands for evidence of effectiveness will introduce additional cost and complexity for manufacturers; how will CER have an impact on incentives for innovation? And, most importantly, what will be the net impact on patient welfare?

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