

Power of observation propels comparative effectiveness research into the mainstream

US agencies are making inroads in the use of comparative effectiveness research to support more robust decision-making. Observational studies are an emerging force in this area and promise to overcome some of the limitations of randomised clinical trials. Such studies have enjoyed some success in fields including cancer, cardiovascular disease and diabetes. Yet some stakeholders fear the advent of the rationing of care, explain Dr Richard Gliklich and Michelle Leavy

In 2009, the debate over comparative effectiveness research (CER) in the US moved from healthcare and policy circles on to the national stage. The new attention largely resulted from the passage in February that year of the American Recovery and Reinvestment Act (ARRA), which allocated \$1.1 billion to support CER in the country.

Interest in CER had been building for several years as stakeholders pointed to the technique as a means of controlling rapidly-escalating healthcare costs and improving patient care. However, the interest and government funding have not come without debate. Some worry about the potential uses of CER, while others question appropriate research methods.

The goal of CER is to provide decision-makers – physicians, patients and payers – with clinical evidence to support treatment and coverage decisions. The US 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. A CER study may compare similar treatments, such as competing drugs, or it may analyze very different approaches, such as surgery and drug therapy.”

CER can take many forms, including randomised controlled trials (RCTs), pragmatic trials, observational studies, patient registries, systematic reviews and meta-analyses.

With the ARRA, the federal government is, for the first time, making a significant commitment to funding a wide range of comparative effectiveness activities. Before the ARRA was passed, Congress funded CER through the Agency for Healthcare Research and Quality (AHRQ). This agency uses the funding to conduct systematic reviews of the comparative effectiveness of various interventions and standards of care. Funding was not available to conduct new studies of comparative effectiveness, however.

Under the ARRA, CER funding can be spent on four major activities: research, human and scientific capital (eg, training researchers and developing new research methods), data infrastructure and dissemination of CER findings.

The ARRA divides the \$1.1 billion allocated to CER between three groups:

- \$400 million for the Office of the Secretary in the US Department of Health and Human Services (HHS);
- \$400 million for the National Institutes of Health (NIH); and
- \$300 million for the AHRQ.

The act also established the Federal Coordinating Council for Comparative Effectiveness Research (FCC) to organise the research conducted or supported by the federal government and called on the Institute of Medicine (IOM) to engage stakeholders and identify research priorities.

In June 2009, the FCC and the IOM both released their initial reports. The FCC report recommended that the funds allocated to the Office of the Secretary be used primarily to support data infrastructure activities. The IOM report recommended 100 research topics as national priorities for CER.

Last autumn, the AHRQ and NIH launched grant programmes for CER funding, based on the recommendations of the two reports. The grant programmes focus on improving CER methods; building infrastructure; developing new evidence through prospective studies and patient registries; supporting translation and dissemination activities; and training researchers. Grants for AHRQ and NIH-funded projects are expected to be awarded this year.

observational studies

Both grant programmes include funding for observational studies of comparative effectiveness. Observational studies are emerging as an important option in CER because they can compensate for some of the limitations of RCTs. Randomised trials are generally placed at the top of evidence

hierarchies, but they present particular drawbacks for CER. The idea of CER is to produce evidence about which interventions work best in typical patient-care settings, for a wide range of patients. RCTs are designed to carefully evaluate which intervention works best in a carefully controlled setting, with a highly selective group of patients. Observational studies, on the other hand, may examine real-world patient care settings, include broad or vulnerable patient populations, and be used for long-term patient follow-up.

pragmatic trials

Pragmatic trials are another alternative to RCTs. Pragmatic studies are designed to provide useful evidence for decision-makers. These trials typically compare clinically relevant alternatives, include diverse study populations, recruit patients from a variety of practice settings and collect a wide range of data on health outcomes. These features fill in many of the gaps associated with RCTs, while preserving the benefits of the experimental study design. Pragmatic trials are an attractive option for CER, but, like RCTs, they tend to be more expensive and time-consuming to implement than observational studies.

understanding physicians

In addition to these limitations, both RCTs and pragmatic trials fail to provide information on physician decision-making. Physicians may choose particular interventions for many reasons, including education, prior experience, culture, incentives and their patients' preference or insurance coverage. Because clinical trials dictate the choice of treatment, they cannot provide information on these factors. Observational studies, on the other hand, leave the choice of intervention in the hands of the physician and can attempt to measure the factors that may influence the physician's choice. Observational studies can also provide information on actual practice patterns.

Because of these strengths, observational

studies are increasingly being used for CER. A recent report from AcademyHealth examined the volume and types of CER under way in the US and found that observational studies and patient registries already have a prominent role. In some cases, the registries and studies were designed specifically for CER, whereas in others existing registries and studies have been linked to other data sources to support comparative effectiveness analyses. For example, data from several cardiovascular registries were used in the AHRQ comparative effectiveness review, “*Comparative Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Grafting for Coronary Artery Disease.*”

In cancer research, observational surveillance registries have been linked to other data sources to support comparative effectiveness studies.

Cardiovascular disease registries have been used in a similar manner. For example, a study published in the *Journal of the American College of Cardiology* in 2009 compared outcomes in older individuals receiving either drug-eluting stents or bare-metal stents, using data from the National Cardiovascular Disease Registry linked to Medicare claims data for follow-up information.

Observational studies have also been used in CER in diabetes. A 2007 study of patients enrolled in the Kaiser Permanente Northern California Diabetes Registry compared glycaemic response to antihyperglycaemic therapies in type 2 diabetes.

new guidelines

With the new grant programmes from the AHRQ and the NIH, the role played by registries and observational studies in comparative effectiveness research is likely to increase. This prominent role for observational study designs has sparked new debate about the potential limitations of these studies for this purpose.

As with all observational research, observational CER must address the potential effects of confounding. Study design considerations can help to reduce confounding, while statistical techniques can attempt to account for its effect on the study results.

A further complication to the use of observational study data is the significant variation across studies in terms of their research methods and data quality.

A few recent efforts aim to develop better guidelines for the use of observational

research methods, including patient registries, for CER.

For example, the GRACE Initiative is a collaborative effort to develop good practice principles for observational studies of CER. The GRACE principles document outlines a number of scenarios where observational study designs are appropriate for CER and may provide high-quality evidence. While not specific to CER, the STROBE statement provides guidelines for reporting the results of observational studies that have been widely adopted by biomedical journals. The AHRQ handbook, “*Registries for Evaluating Patient Outcomes,*” describes good practices for patient registry design, operation and evaluation.

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In addition to discussions over methodology, there is debate over other aspects of CER, including how or if the information will be used in the regulatory approval and labelling process and in determining reimbursement policies for medical products. At present, regulatory approval in the US only requires evidence of efficacy, not effectiveness relative to other products on the market. Manufacturers have expressed concerns that requirements for comparative effectiveness data will further delay the drug approval process.

The potential use of CER to determine reimbursement policies has also raised concerns among physician and patient organisations. These groups fear that CER will be used to limit coverage to a small group of treatments that are deemed most effective for most people. This could limit treatment options for patients who do not respond to the treatments covered. The issue of including cost in effectiveness evaluations is particularly sensitive, as many stakeholders worry that cost effectiveness studies are the first step towards a system of rationing care.

expect more debate

Debate over CER methods and their applications will likely continue as more CER is conducted and more evidence becomes available.

The ARRA funding offers healthcare stakeholders, particularly those in

government and academia, a unique opportunity to improve the data infrastructure and research methods for CER, while conducting a large number of new studies.

But, as in all areas of health research, it is probably industry that will ultimately be the largest funder of CER to respond to the demands of key decision-makers. There are many examples where this may occur from formulary committees making decisions about new products, particularly those that are not first-in-class, to health technology assessments.

Public and private funding offers the potential for significant advances within the field of CER, but also brings many new challenges. In particular, it will be important for researchers, funding agencies and other stakeholders to address methodological challenges, determine how the new evidence should be used and find effective means of translating the evidence into practice.

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