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# Why Observational Studies Should Be Among The Tools Used In Comparative Effectiveness Research

**ABSTRACT** Doctors, patients, and other decision makers need access to the best available clinical evidence, which can come from systematic reviews, experimental trials, and observational research. Despite methodological challenges, high-quality observational studies have an important role in comparative effectiveness research because they can address issues that are otherwise difficult or impossible to study. In addition, many clinical and policy decisions do not require the very high levels of certainty provided by large, rigorous randomized trials. This paper provides insights and a framework to guide good decision making that involves the full range of high-quality comparative effectiveness research techniques, including observational research.

Comparative effectiveness has been defined as “the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in ‘real world’ settings.”<sup>1</sup> The Patient Protection and Affordable Care Act of 2010 established a new center, the Patient-Centered Outcomes Research Institute, for comparative effectiveness research. It also called for the creation of a methods committee to “develop and improve the science and methods of comparative clinical effectiveness research.”<sup>2</sup>

One task of the methods committee will be to ensure that these types of studies use rigorous methodologies. Because a good understanding of comparative effectiveness will depend on a range of research methods, the quality of health care decisions emanating from the studies will reflect the quality of their design, implementation, and reporting.<sup>3</sup>

## Types Of Research Methods

There are a number of methods for conducting comparative effectiveness research. These in-

clude systematic reviews of existing evidence and meta-analyses (statistical pooling or other syntheses of the results of multiple studies); experimental studies, such as randomized controlled trials and pragmatic clinical trials that randomly assign interventions; and nonexperimental studies, including retrospective and prospective observational studies that do not assign interventions but leave the choice of treatments up to patients and their health care providers.

A systematic review is a comprehensive review and integration of an existing body of evidence, which may, but does not always, include a meta-analysis. Randomized controlled trials typically enroll a homogeneous population of patients and rigorously monitor their progress. In contrast, pragmatic clinical trials generally enroll a wider range of patients and monitor their progress as they would in routine, real-world clinical practice.<sup>4</sup>

It has long been accepted that randomized controlled trials can provide the least biased estimates of comparative effectiveness. However, the results might not always correspond to what is seen in real-world practice, where physicians apply the treatments to a broader range of patients. Observational studies are often necessary

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to answer important questions about particular populations and conditions. Consequently, the potential contribution of high-quality, large-scale observational studies to comparative effectiveness research is attracting much interest.<sup>5</sup>

We offer examples of clinical scenarios that would benefit from the use of high-quality observational data.<sup>6</sup> In the Technical Appendix,<sup>7</sup> we describe the well-established quality criteria for randomized controlled trials, systematic reviews, and meta-analyses, and we compare those with standards for observational studies.

The impact of comparative effectiveness research on care delivery will depend heavily on achieving greater agreement among experts and stakeholders on the appropriate use of research methods. It will also depend on a shared recognition of what constitutes high quality for such studies.

### The Need For Evidence

The purpose of comparative effectiveness research is to inform decisions about health policy and clinical care. Such information may be used by regulators to approve or disapprove products, by public health agencies and medical societies to create clinical guidelines, by payers to determine coverage policy and patients' costs for medicines, and by clinicians and patients to make decisions about medical care. The information is also used by manufacturers to demonstrate the value of new drugs or medical devices compared to the current standard of care, often through observational studies once the products have reached the market.

Health policy decisions must take account of uncertainty about the quality and availability of evidence to assess a treatment's risks and benefits, as well as uncertainty about the risks to patients that a wrong decision could pose.<sup>8</sup> A question about which type of bandages to stock in a hospital's supply carts would not justify a large randomized controlled trial unless the cost differences among various types were dramatic. However, a decision about approving a new biologic generally requires the high degree of confidence about risks and benefits that a randomized trial can provide.

For serious health conditions that have few if any satisfactory treatment options, decision makers are more willing to accept greater uncertainty in approving or adopting promising treatments. At the other end of the spectrum are preventive services in asymptomatic populations. In those cases, decision makers will expect a high degree of certainty that benefits will outweigh harms, to avoid the possibility of exposing a large, currently healthy population to potential

harm. Most decisions, however, can benefit even from evidence that provides only a moderate level of certainty.

The value of information derived from a comparative effectiveness study or systematic review will depend in large part on how urgently a decision is needed; the body of existing evidence; the additional information that a new study offers; and the timeliness, relevance, feasibility, and cost of obtaining additional information. Typically, randomized controlled trials and systematic reviews of such trials provide the foundation of comparative effectiveness evidence.

However, clinical trials might not involve head-to-head comparisons of treatments or use the most relevant alternatives. Decision makers may want to fill this gap with observational studies—particularly when decisions must be made well before a formal trial could produce results. Currently there is wide variation in decision makers' use of observational studies.

### Methodological Challenges

The reluctance of decision makers to use observational studies stems in part from perceived methodological challenges. Broadly speaking, bias (systematic error) and confounding (mixing different effects together) may lead to erroneous results. For example, when patients with certain prognostic factors—risk factors that affect their chance of having a good outcome—are more likely to receive a new treatment, this introduces a bias. This is because these factors systematically affect the chance that patients will receive a particular treatment as well as the chance that they will benefit from it.

Randomization in experimental studies controls for bias by attempting to balance factors that affect outcomes across the study groups. For this reason, randomized controlled trials are often considered to provide the highest level of evidence, even though randomization is never completely successful in eliminating bias.

Observational studies are more prone to bias, although careful design and analysis can often minimize the impact of bias and confounding on the findings. These studies offer some advantages over clinical trials. One advantage is larger numbers of subjects at an affordable cost. This means that researchers can examine meaningful subgroups and many comparison groups. Another advantage is longer follow-up periods. This makes it possible to examine long-term risks and benefits.

At least two conditions need to be met for an observational study to succeed. First, variability in treatment is needed to make meaningful comparisons; second, the characteristics of the

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groups being compared should have a reasonable amount of overlap. For example, if patients who receive a surgical intervention are almost always healthier than those who are treated with drugs, no amount of statistical adjustments can compensate for the non-surgically treated group's being sicker and at higher risk for adverse outcomes, largely because of those underlying illnesses.

In general, observational methods are most reliable in the detection of larger differences in the results of treatments. The methods are less reliable when the treatments have only modest benefits, particularly when the information comes from relatively small studies.

## Criteria For Determining Which Type Of Study To Employ

There has been continuing controversy about using observational studies to fill evidence gaps in comparative effectiveness research. However, there will always be gaps in the comparative evidence provided by randomized controlled trials, which are expensive, require special facilities and organizational structures, and are not always feasible. To make the most-informed decisions, policy makers will need to rely on a full range of high-quality research.<sup>9</sup>

**RANDOMIZED CONTROLLED TRIALS** For decisions that require a high level of certainty, the best approach will continue to be randomized controlled trials, with perhaps greater emphasis on pragmatic trials.<sup>4,10</sup> Randomized clinical trials are best at determining whether a new drug should be approved for marketing, because they most effectively control for diagnostic and prognostic factors that affect treatment decisions. For widely adopted therapies, head-to-head randomized trials might be the only reasonable way to assess entrenched practices in the health care community.

For example, at one time autologous stem-cell

transplants (that is, transplants of one's own stem cells) were routine in the treatment of metastatic breast cancer. This essentially precluded any attempt to evaluate a comparable nonexperimental treatment within the context of an observational study. A head-to-head trial was required to show that the addition of such transplants to standard chemotherapy did not improve survival.<sup>11</sup> Clinical practice rapidly changed as a result.

Randomized controlled trials are also useful in defining the value of a particular treatment in complex, multi-therapy treatment. Such trials helped clarify the proper dosing, timing of administration, and impact of clopidogrel, an antiplatelet medication used to reduce the risk of thrombosis during coronary angioplasty.<sup>12</sup>

**OBSERVATIONAL STUDIES** In contrast, some comparative effectiveness questions are particularly appropriate for observational studies. Large studies are often essential when treatment effects differ across types of patients and when analyses of subgroups are needed to understand which patients are most likely to benefit. For studies of ultra-rare diseases—those that affect fewer than twenty in one million people—it is typically not possible to conduct randomized controlled trials of new therapies. This is particularly important for disorders without any known treatments.

Observational studies are also useful for examining multiple treatment paradigms simultaneously. For example, hearing loss is treated by a wide variety of approaches, including cochlear implants, assisted listening and electric acoustic devices, and habilitation and rehabilitation methods.<sup>13</sup> A prospective observational study of patients being treated for hearing loss would permit researchers to examine treatment preferences as well as the risks and benefits of the different treatments.

In general, observational studies are best used to evaluate the real-world applicability of evidence derived largely through randomized trials; to study patients and conditions not typically included or studied in randomized trials; to better understand current treatment practices and how patients are assessed in order to design an appropriate clinical trial; and to provide information that can be derived only through larger studies or long-term follow-up.

Observational studies also can contribute useful evidence in other situations where trials have not been or cannot be performed. For example, there are instances when it would be politically or ethically unacceptable to deny access to an intervention, as in the case of vaccines in the face of a threat of an influenza pandemic. Similarly, it would be unethical to expose patients

deliberately to less effective treatments.

Additional examples in which observational studies can contribute useful evidence are described below. These examples include instances where larger studies are needed to understand the real-world benefits of different dosing and routes of administering a drug; when patients' adherence to treatment differs in real-world settings and randomized controlled trials; when a treatment is delivered with different results by providers with different training; and when treatments are off-label—that is, a drug or device is used in ways that have not yet been specifically approved.

► **WHEN LARGER STUDIES ARE NEEDED:** Although multiple treatment guidelines recommend the use of systemic corticosteroids for flare-ups of chronic obstructive pulmonary disease, the optimal dose and route of administration have not been well defined. Data from observational studies of 84,621 patients that used large linked registries demonstrated that physicians were more likely to administer high-dose intravenous systemic corticosteroids in such cases, but that low-dose oral corticosteroids were equally effective and had fewer side effects.<sup>14</sup> To evaluate these findings in a randomized trial, the trial would have to be very large, with approximately 30,000 patients in the intervention and control groups combined, in order to demonstrate that the treatments were essentially similarly effective—that is, that the differences in treatment failure between high-dose intravenous systemic corticosteroids and low-dose oral corticosteroids were no greater than 1 percent.<sup>15</sup>

► **WHEN TREATMENT ADHERENCE DIFFERS:** Patients are often reluctant to use inhaled steroids, which are considered to be the gold standard for treating asthma. An insurer requested an observational study using administrative claims data for 56,168 asthmatics from US commercial health plans. The study evaluated clinical, economic, and patient-reported outcomes associated with various classes of asthma medications.

The researchers concluded that although inhaled corticosteroids were associated with a lower risk of inpatient admissions and emergency department visits for patients who adhered to the treatment regimen, patients taking oral medications were significantly more likely to adhere to their regimen. Even when the investigators controlled for severity of disease, patients taking oral medications derived greater benefit from treatment than did those taking inhaled medications.<sup>16</sup>

After the study was completed, the insurer decided to continue its favorable reimbursement

level for the oral medication used by the vast majority of its members and to remove its requirement for prior authorization of the drug.<sup>17</sup>

► **WHEN PROVIDERS HAVE DIFFERENT TRAINING:** Implantable cardioverter defibrillators for patients at risk for sudden cardiac death can be implanted by physicians with a wide range of training, from accredited electrophysiology fellowships to less formal training programs. A study of physician certification and outcomes in 111,293 patients showed that patients had a higher rate of procedural complications when the devices were implanted by thoracic surgeons or cardiologists who were not electrophysiologists, compared to when the devices were implanted by electrophysiologists.<sup>18</sup>

Furthermore, among 35,841 patients who met the standard criteria for use of defibrillators with cardiac resynchronization therapy, patients were more likely to receive the indicated resynchronization device when their defibrillators were implanted by an electrophysiologist. That is, electrophysiologists were more likely to implant the appropriate type of device than were non-electrophysiologist cardiologists.

► **WHEN TREATMENTS ARE OFF-LABEL:** Approval by the Food and Drug Administration (FDA) of two drug-eluting stents (that is, stents that were coated with a drug to help prevent their rejection by the body) precipitated the rapid adoption of this technology by interventional cardiologists. Randomized controlled trials showed that drug-eluting stents performed better compared to bare-metal stents.<sup>19,20</sup>

Shortly after that approval, however, new evidence suggested that the use of drug-eluting stents was accompanied by increased mortality and rare but potentially fatal stent thrombosis. The new evidence came from case reports of thrombosis (which were later refuted by additional data from Cypher clinical trials);<sup>21</sup> subgroup analyses of group-level<sup>22</sup> and patient-level data;<sup>23,24</sup> meta-analyses; and observational studies.<sup>25,26</sup> An FDA advisory panel noted that “more than 60 percent of [drug eluting stent] use was off-label.”<sup>27</sup> The panel acknowledged that the use of those stents in sicker patients with more complex heart problems contributed to the higher risk of stent thrombosis and myocardial infarction or death.<sup>21,28</sup>

## Evaluating Comparative Effectiveness Research

Whatever research method is used, investigators need to design, implement, and report comparative effectiveness studies with enough detail so that any patient, health care provider, or health policy decision maker can evaluate the quality of

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the study and its results. Users also need to understand how to interpret unexpected findings, like those that result from exploratory analyses that were not specified as objectives at the outset of a study, and how conflicts of interest can influence the way in which studies are conducted and their results reported.

We examined existing guidelines and collections of best practices for systematic reviews, randomized clinical trials, and observational studies (see the Technical Appendix).<sup>7</sup> Two of these guidance documents address observational studies of comparative effectiveness. The GRACE (Good Research for Comparative Effectiveness) principles<sup>29</sup> provide high-level guidance for decision makers about the design, conduct, analysis, and reporting of observational comparative effectiveness studies. The guidelines of the International Society for Pharmacoeconomics and Outcomes Research address retrospective analysis of databases.<sup>30-32</sup>

Good-practice-guidance documents consistently recommend that researchers specify their objectives at the outset of a study and that they design the study to meet those objectives. Questions remain, however, about the value of ad hoc analyses. Some good practice recommendations assert that a result that had not been specified as an objective of a study should be regarded only as descriptive and could be used to generate hypotheses for subsequent testing.

Supporters of ad hoc analyses counter that evidence should be evaluated whatever its derivation—whether the idea arose from exploratory analyses or prespecified intent. In this view, the value of all studies should be judged on the quality of the research and the scientific evidence, not on when an idea occurred to the researcher.<sup>33</sup>

When employing experimental or observational studies for comparative effectiveness research, decision makers and researchers should under-

stand the extent to which the research methods used and the potential personal and professional interests of the investigators may have influenced the reported study outcomes. Clearly, the methods by which epidemiological analyses account for overt and hidden bias in observational studies will influence the estimates of effect.<sup>34</sup> But some prominent journal editors claim that commercial interests are so likely to bias the outcomes and reporting of industry-sponsored studies that they all need to be reanalyzed by academic statisticians.<sup>35</sup>

This position completely ignores factors that may influence academic statisticians, such as the desire to create controversy and attract attention, which also can bias the outcomes and reporting of studies, regardless of their sponsorship. We see the position as shortsighted. The application of high-quality methods and principles is more important than a researcher's affiliation. Research findings must be analyzed through the traditional process of conjecture and refutation, in which hypotheses are developed, tested, refined, and then tested in new studies.<sup>36</sup>

## Conclusion

To make the best possible decisions about patient care, we need research that has met the highest possible standards in its conduct and reporting. We also need results from the full range of high-quality comparative effectiveness research, including randomized controlled trials, rigorous literature syntheses, meta-analyses, and observational studies.

Taking the best advantage of that variety of studies requires decision makers to determine in advance what types and levels of uncertainty they will accept, so they know what weight to give different pieces of evidence in their deliberations. Researchers should have a clear understanding of the strengths and limitations of the methods used in each type of study.

This paper provides insights and a framework to help accomplish these goals, and it highlights four key principles that must be kept in mind. First, the choice of methodologies for answering each important question will depend on the circumstances and the tolerance for being wrong; all existing methods may be useful.

Second, whichever methods are chosen, researchers should design and implement studies according to existing best practices. The resulting reports should include enough detail that any user can evaluate the methods and replicate the methodology in a different setting or patient group.

Third, given resource constraints that limit the

availability of head-to-head randomized controlled trials, high-quality observational methods can play a particularly important role in comparative effectiveness research because they can relatively quickly generate results that are

applicable to real-world situations.

Finally, the application of high-quality methods and principles in a study is more important than details of the study design or the affiliation of the researcher. ■

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Nancy Dreyer and coauthors write in this issue about a core topic: What types of studies and quality of clinical evidence should be required to judge the comparative effectiveness of clinical interventions? In addition to the gold standard of evidence from randomized clinical trials, they argue, data from so-called observational studies should also be included.

“After working in comparative effectiveness of safety for twenty-five years, I am a believer in examining how drugs and medical devices perform in real-world situations, which enables choices based on quantitative evaluations of benefits and risks,” says Dreyer, chief of scientific affairs and senior vice president at Outcome Sciences, in Cambridge,

Massachusetts. “The value of observational research is not well understood by my clinical colleagues, and I have been working to develop clear and well-accepted guidance documents to promote quality.”

Outcome Sciences is the leading provider of patient registries, studies, and technologies for evaluating real-world outcomes of health care. It also provides strategies for marketing drugs and medical devices. Dreyer, who is a pharmacoepidemiologist, leads a team of epidemiologists, outcomes researchers, and biostatisticians who conduct research on comparative effectiveness.

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