The Confirmatory Trial in Comparative-Effectiveness Research

Alan M. Garber, M.D., Ph.D., and Mark A. Hlatky, M.D.

Despite the infusion of more than $1 billion through the American Recovery and Reinvestment Act of 2009 and the potential commitment of much more money, there will never be enough funding to perform all the comparative-effectiveness studies that we want. The depth of interest in such studies became apparent when the Committee on Comparative Effectiveness Research Prioritization of the Institute of Medicine received more than 1200 nominations of distinct topics to be among the first supported under the act. Thus, a critical question is how to choose the studies that will be supported with substantial, but not unlimited, funds. How much should go to large database analyses, how much to medical-literature reviews, and how much to large, rigorously designed, randomized clinical trials? And what questions should such studies address?

Seldom would confirmatory randomized trials rise to the top of a list of comparative-effectiveness research priorities, especially if previous studies have produced negative results. Research should be pursued only if the value of the information that it can be expected to reveal is great enough to justify the costs. The very term “confirmatory” implies that such studies are not expected to produce dramatic new insights. Furthermore, randomized trials can be expensive. Comparative-effectiveness trials involve the usual challenges of screening and recruiting study subjects, following them for many months — if not years — and ascertaining outcomes. In addition, many such trials must be large enough to detect small differences in clinical outcomes, since a defining feature of such studies is a comparison with one or more “best,” often highly effective, alternatives, rather than with placebo alone.

The Immediate Risk-Stratification Improves Survival (IRIS) trial of the early use of an implantable cardioverter–defibrillator (ICD) after myocardial infarction, reported on by Steinbeck and colleagues in this issue of the Journal, is such a confirmatory trial. The clinical hypothesis that it tested is an important one. In the first few months after hospital discharge for an acute myocardial infarction, patients are at higher risk for sudden cardiac death, a condition that ICDs treat effectively in other patient groups. However, the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) had previously shown that patients who were randomly assigned to an ICD early after an acute myocardial infarction did not live longer than controls, because the substantial reduction in the number of sudden cardiac deaths was offset by an excess of nonsudden cardiac deaths. This result stands in striking contrast to the mortality benefits of ICDs seen in other populations. Although DINAMIT might have been a “false negative” trial, crippled by a small sample size or design flaws, it is also possible that ICDs are ineffective immediately after an acute myocardial infarction, when recurrent ischemia may be more likely than a primary arrhythmia to cause sudden death. Distinguishing between these possibilities required additional evidence from other randomized trials.

Just as in the DINAMIT trial, the IRIS trial showed no difference in overall mortality between patients who were randomly assigned to an ICD and patients who received conventional therapy early after an acute myocardial infarction. And, in IRIS, as in DINAMIT, the lower rate of sudden cardiac death among patients with an ICD was counterbalanced by a higher rate of nonsudden death. IRIS confirmed that ICD ther-
apy is not effective early after an acute myocardial infarction, notwithstanding the high risk of sudden death among such patients. This result is consistent with other data that show that the effectiveness of ICDs increases with the time since an acute myocardial infarction and that patients may die despite receiving appropriate ICD shocks.

Few, if any, medical interventions work in every patient for the conditions they are designed to treat. As it determines which treatment is more effective, comparative-effectiveness research addresses the question: “In which patients?” Evidence that an intervention is effective in one population does not ensure that it will also be effective in other populations, yet therapies proved to work in narrowly defined clinical situations are often applied more broadly in practice (as “indication creep” or “off-label use”). Such therapies are sometimes extended to patients for whom the treatment is ineffective or harmful. By establishing the boundaries between the effective and ineffective applications of a treatment, comparative studies such as IRIS can improve health outcomes.

It could be argued that IRIS and other confirmatory trials will not change practice. Indeed, without this trial, it is unlikely that many patients would receive ICDs within 40 days after an acute myocardial infarction, since the previous randomized trial did not show a trend toward efficacy and current clinical guidelines do not recommend it. Furthermore, if the goal of comparative-effectiveness research were to reduce health expenditures, in this case a new trial could have the opposite effect; that is, a positive result might lead to the increased adoption of an expensive intervention, whereas a negative result would only reinforce existing practice. However, to focus only on the budgetary impact would be to miss the point of comparative-effectiveness research. Such studies are designed to improve the safety and effectiveness of medical practices, not to show that the less expensive approaches to a clinical problem are always superior. Furthermore, although the results of these studies can guide payment reforms and other policies to improve the effectiveness and quality of care, a more efficient health care system does not always mean lower expenditures. If IRIS had established that ICDs are highly effective in this patient population, even this expensive intervention might have offered great value. That possibility is a strong reason to consider carrying out a new randomized trial, even after a negative study.

ICDs benefit selected patients, but the IRIS trial confirmed that they do not benefit all patients at high risk for sudden cardiac death. This result is worth knowing. It can direct efforts away from an expensive yet ineffective procedure toward either new or established alternatives. Confirmatory studies such as this one have a circumscribed but important role in comparative-effectiveness research.

Dr. Garber reports serving on the Committee on Comparative Effectiveness Research Prioritization of the Institute of Medicine; and Dr. Hlatky, receiving consulting fees from GE Healthcare.

From the Veterans Affairs Palo Alto Health Care System (A.M.G.) and Stanford University (A.M.G, M.A.H.) — both in Palo Alto, CA.


