Using Science to Improve the Nation's Health System: NIH's Commitment to Comparative Effectiveness Research

Michael S. Lauer; Francis S. Collins

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NIH's Commitment to Comparative Effectiveness Research

Michael S. Lauer, MD
Francis S. Collins, MD, PhD

Since Barack Obama became the 44th president of the United States in January 2009, nearly all sectors of society have engaged in intense discussions about the best ways to stimulate the nation's economy and reform the US health care system. The National Institutes of Health (NIH) has been—and will continue to be—in the middle of such conversations, emphasizing the power of biomedical research to show what health interventions yield the greatest benefits.

Health reform and economic concerns may have moved comparative effectiveness research (CER) from relative obscurity into the public policy spotlight. However, CER is not a new concept to NIH, which has long recognized and supported the value of CER for providing evidence-based, well-validated approaches to medical care.

For instance, nearly 2 decades ago, NIH-supported researchers published results of the Cardiac Arrhythmia Suppression Trial (CAST).[1] To the surprise of many, 3 drugs that suppressed ventricular premature beats (encainide, flecainide, and moricizine) not only failed to reduce the risk of sudden cardiac death, but actually increased arrhythmic death rates. About 14 years later, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), a comparative effectiveness trial funded by NIH,[2] demonstrated that oral administration of the antiarrhythmic drug amiodarone proved no better than standard heart failure care (such as β-blockade), whereas implantation of an internal cardioverter defibrillator reduced mortality by 23%.

Despite the positive results of SCD-HeFT, only a subset of patients with heart failure derives benefit from implantable defibrillators. Consequently, NIH, the Agency for Healthcare Research and Quality (AHRQ), and the American College of Cardiology have joined together to support an observational CER study of 3500 patients receiving implantable cardioverter-defibrillators. The 3½-year study, launched in January 2010, should help clinicians better gauge whether a patient is likely to benefit from a defibrillator.

Other major CER efforts supported by NIH have compared antipsychotic drugs for the treatment of schizophrenia, strategies for preventing deaths from prostate cancer, antihypertensive medications, treatments for bullous emphysema, and approaches to preventing diabetes. A 2007 report by the Congressional Budget Office cited NIH's comparative effectiveness studies as prime examples of government-sponsored research that could directly inform clinical practice and public policy.[3]

Today, the biomedical research community has an unprecedented opportunity to build on this foundation. The United States urgently needs the evidence to design a system that offers health interventions that are both beneficial and cost-effective. The American Recovery and Reinvestment Act (ARRA) of 2009 appropriated $1.1 billion for CER, with $400 million of that funding allocated to NIH and the remainder to AHRQ and the Office of the Secretary of the Department of Health and Human Services.

While the ARRA-mandated report of the Federal Coordinating Council acknowledged that NIH historically has been the largest source of federal support for CER,[4] NIH has important partners in other government agencies, particularly AHRQ. NIH generally contributes to CER by supporting primary research, including both observational studies and randomized control trials. AHRQ's strength is in conducting secondary comprehensive meta-analyses of multiple studies, seeking to identify overarching conclusions and propose practice guidelines.

By the end of September 2009, NIH had committed most of its $400 million ARRA allocation for CER through a variety of mechanisms, including Challenge grants, larger-scale Grand Opportunity grants, pay line expansions, competitive revisions, and administrative supplements. To prioritize these spending decisions, a high-level, trans-NIH committee considered a variety of criteria that met the Federal Coordinating Council's definition of CER.[4] These criteria included potential public health benefit, variability in practice, low probability for support by nongovernmental sectors, potential for multiplicative effect, focus on diverse populations and subgroups, engagement of communities in research, and application to the stated priorities of the Medicare Modernization Act and the Institute of Medicine (IOM).[5]

In addition to providing a much-needed funding boost for CER, ARRA-related activities helped delineate 5 important challenges facing NIH as it considers how to use science to benefit health care reform.

Author Affiliations: Office of the Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland (Dr Lauer); and Office of the Director, National Institutes of Health (Dr Collins).
Corresponding Author: Francis S. Collins, MD, PhD, Office of the Director, National Institutes of Health, Bethesda, MD 20892 (collinsf@mail.nih.gov).

First, a major challenge for any federal science agency is how best to interact with many stakeholders when setting research priorities. The ARRA mandated an IOM report[5] to identify 100 top national priorities for CER. After the report was released, NIH determined that substantial NIH-funded CER efforts were already under way for 88 of the stated priorities. To help close the remaining gaps, NIH has used ARRA funding to support a variety of new CER research and training efforts. Under the provisions of the historic health care reform law enacted March 23, 2010, NIH will serve on the Board of Governors of a Patient-Centered Outcomes Research Institute, which is eventually projected to have an annual budget of approximately $600 million. Among the board's likely responsibilities will be to establish priorities for CER.

The second challenge for NIH is how to shape and support the next generation of CER studies. This new breed of CER may feature substantially different trial designs, very large sample sizes, high-throughput technologies, routine utilization of electronic medical records, and adaptations that reflect the infrastructures of integrated health care systems. New approaches and strategies are needed to transform the clinical trial enterprise, as well as to take maximum advantage of other existing and newly formed resources for CER.[6]

A third issue is how to help researchers effectively use nonexperimental observational methods that are inherently limited by serious selection and confounding biases. Experiences with antiarrhythmic drugs[1] and postmenopausal hormone therapy[7] serve as potent reminders that clinical trials must remain the gold standard for identifying effective strategies for promoting health and managing disease. Nonetheless, large-scale observational studies have value in a number of respects, such as generating viable hypotheses, confirming results of randomized trials in understudied patient subsets, learning about rare events, and gaining insight into processes of care delivery.

Fourth, the principles of CER must be extended beyond patient-oriented clinical science to systems-oriented implementation science. It is imperative that NIH tackle this tough issue if CER discoveries are to be disseminated and adopted in a manner that expeditiously improves health. All too often, important CER discoveries are slow to be adopted into practice. At other times, the opposite occurs: strategies that lack an evidence base are nonetheless rapidly adopted. There is increasing recognition that the processes of dissemination and implementation are legitimate targets for rigorous scientific evaluation.[8] For example, a cluster randomized trial funded by NIH recently demonstrated that quality improvement strategies could lead to better outcomes among women in labor.[9]

A fifth challenge for NIH is how to leverage its multidisciplinary expertise in high-throughput technologies so that CER complements rather than conflicts with the promise of personalized medicine. Just as the disciplines of epidemiology and genetics have informed each other to make possible previously unimagined discoveries, the disciplines of CER and high-throughput biomedicine are positioned to enable major transformations in the delivery of high-quality, super-efficient health care.

One concern is whether in the process of conducting CER, the importance of individual responses to health interventions will be overlooked or minimized. Genomic sequencing, gene expression analysis, epigenetics, advanced proteomics, and other high-throughput technologies will give CER investigators the power to analyze effectiveness data at many different levels of resolution—ranging from the individual to subsets of patients to very large populations. Large-scale, randomized CER studies are needed to obtain well-validated answers about which interventions work best. But such studies must include assessment of individual differences in genetic risk factors and environmental exposures, or run the risk that subsets of individuals may have significantly different responses to an intervention than the group as a whole. Analyses of CER data sets must take these individual differences into account. Both CER and personalized medicine are essential parts of the equation for using science to improve health care.

Science cannot operate in a vacuum, especially at this critical juncture in the nation's history. The monumental effort to overhaul the US health system will require the knowledge and dedication of many constituencies, including NIH-funded biomedical researchers.[10] By recognizing NIH's past contributions to CER and including NIH in the conversation about CER's future direction, the nation's leaders have put the many disciplines of biomedical science in a strong position to forge major improvements in the nation's health. It is time to move forward together.

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Editor's Note: In 2012, *JAMA* and the Archives journals will publish theme issues on comparative effectiveness research.

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