

Comparative Effectiveness Research in the Era of Health Reform

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Although the provisions of the recently passed health reform bill (the Patient Protection and Affordable Care Act) addressing access to health insurance have received the most publicity, a critical component of the package of initiatives will certainly affect the way clinicians practice medicine, the way care will be organized, and potentially the way health care will be reimbursed. Many of these provisions are contained under the broad rubric of “comparative effectiveness research” (CER).

Comparative effectiveness research is nothing new. Clinicians have always compared treatments with each other. We want to provide our patients with the best treatments available, taking into account issues of convenience, relative benefits, relative harms, cost, and accessibility. The marked increase and interest in CER over the past several years is the result of several existing forces:

- The large increase in the number of treatments available. Providers and patients have more choices and they need assistance in determining which treatments or diagnostic tests are best.
- The rapid rise in health care costs and the marked variability in utilization of treatments across geographic areas have led to recognition for potential cost savings when less expensive treatments are available.
- Experience has demonstrated that research results conducted in tertiary care settings, often examining highly selected populations, may not be generalizable to the broader public which is much more diverse in age, demographics, and associated conditions.
- Broad recognition that effective treatments may be underutilized in the US and some ineffective or only marginally effective treatments may be overutilized. We may provide the wrong treatment to the wrong patient at the wrong time.

Comparative Effectiveness Research

While there are several published definitions of CER, the most accepted definition was provided by the Institute of Medicine of the National Academies in 2009: “Comparative effectiveness research is the generation and synthesis of

evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policymakers to make informed decisions that will improve health care at both the individual and population levels.”¹

While older literature on comparative effectiveness research focused on “drug A vs. drug B” comparisons as a major characteristic of comparative effectiveness, the above current definition is much broader.² Not just treatments will be examined; we can also compare different methods of

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preventing disease. For example, comparing the pros and cons of strategies of fecal occult blood tests vs. colonoscopy vs. virtual colonoscopy (a radiographic procedure) would be an example of a prevention-focused, not a treatment-focused, CER study. The question for such a study is not whether colorectal cancer screening prevents cancer or saves lives (that has been established) but rather which type of colorectal cancer screening strategy is the most effective. Similarly, monitoring a clinical condition in chronic disease or enhancing methods of care delivery are also potential CER topics. For example, we know that treatment of mental health disorders such as depression improves patient well-being, but issues of organizing that treatment in real-world settings of primary care are still unclear. Much of the recent literature has focused on systems of integrated or collaborative care in which a mental health professional practices very closely with, or sometimes in the same office as, the primary care

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provider in treating common mental health diagnoses. What method of care delivery is the most effective and efficient?³ CER can address such questions of more effectively and efficiently delivering care to patients. All too often there is a lag of many years between demonstrating that a treatment is effective and its implementation in practice.

Types of Comparative Effectiveness Research

Systematic Literature Review

Prior to embarking on expensive and time-consuming new data collection, it is critical to document what we already know about a clinical problem and its treatments. Fortunately, methods of systematic review and meta-analysis are now well-developed. The federal Agency for Healthcare Research and Quality (AHRQ) has, for almost 15 years, supported 14 Evidence-Based Practice Centers (EPCs) in North America. Two EPCs are in North Carolina: one at Duke University and another shared EPC between Research Triangle International and the University of North Carolina at Chapel Hill (RTI-UNC). These reviews address specific key questions, work within a theoretical framework, and generally take up to one year to complete. All products from these reviews are published both online and in peer-reviewed medical journals. Systematic review topics in CER range from the relatively narrow (comparing biologic treatments in rheumatoid arthritis) to reviews examining policy level interventions such as the above-mentioned use of integrated care in mental health.⁴ One of the most important components of such systematic review is identifying the research gaps identified from the review of the literature. What are the most important questions that need to be answered? What type of study design would be most appropriate? What are the main methods problems with the prior research? A challenge over the next several years will be speeding the cycle of research from literature review and identification of research gaps to new study implementation. If CER is to be one of the components of health reform implementation, then we must disseminate and implement its results more quickly.

Clinical Trials

Clinical trials for Federal Drug Administration (FDA) approval of a new medication in the US generally compare a new pharmaceutical with a placebo or inactive treatment. In comparative effectiveness research, the comparison study is between two different *active* treatments. Such CER trials may be quite large since the differences in treatment effect between the two active treatments may be relatively modest. Careful issues of study design, appropriate outcome measure used, and study setting characterize CER trials. The outcomes measured should be patient-oriented outcomes such as functioning, avoidance of hospitalization, or longevity. Biologic measures such as variation in a blood test may not correlate with patient-oriented outcomes and may not be appropriate as primary outcomes. For example, studies in diabetes which address only blood glucose control, which

may not correlate with patient-oriented outcomes such as feelings of well-being or heart attack rates. These would not be considered comparative effectiveness trials. Similarly, study setting and population matter. Study settings should involve practices and populations which reflect individuals affected by the disease in terms of their demographics and comorbidities. In addition, the setting should reflect where patients are usually seen with the disease (often in primary care settings). Specialty-oriented conditions such as transplants may only be seen in tertiary settings. Finally, the study should be conducted over a sufficient period of time so that the patient-oriented outcome will appear. An example of a CER trial is the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) which compared different types of antipsychotic medications for the treatment of schizophrenia.⁵

Observational Studies

While the randomized clinical trial (RCT) remains the optimal method of demonstrating the efficacy, and sometimes the effectiveness, of an intervention, not all patient-oriented or policy questions can or should be addressed by RCTs. Trials may not enroll broadly generalizable populations and are often not large enough to detect some treatment effects or harms. Observational studies can also be used to evaluate strategies of care as opposed to changes in isolated care components. In the past, observational studies in CER have been hindered through almost sole reliance on administrative or pharmaceutical claims data. Analytic techniques to evaluate these data have markedly improved over the past five years.⁶ Since patients are, by definition, not randomized in observational studies, statistical techniques may be used to partially adjust for the lack of randomization. While observational studies should not be used as a substitute for appropriate randomized trials, they are a useful adjunct. The rapid rise in the use of electronic health records (EHRs) will be an important addition to observational studies.⁷ The availability of generalizable laboratory and clinical data will substantially assist clinicians in evaluating the effectiveness and harms of treatments in everyday practice. The technical challenges of linking across multiple EHR platforms and of linking EHR information with administrative claims data are substantial, but the gain in terms of assessing clinical outcomes more rapidly would be of tremendous public health value.

Dissemination: The Missing Link

While the research outlined above is substantial and exciting, its value to providers and patients will be minimal unless it is disseminated and utilized in practice. An anecdote may help to illustrate the costs of not conducting timely CER studies. Vertebral compression fractures are a common and disabling disorder in the elderly; they are closely related to osteoporosis. Over 10 years ago, a technique called vertebroplasty was

Spending Limited Health Care Dollars on What Works Best:

The Promise of Comparative Effectiveness Research

Senator Josh Stein

Imagine sitting in your doctor's office. Your chest is tight again. The pain you feel is exceeded only by your fear: Will you survive? What will happen to your family if you don't? Your doctor talks to you about the two main options for treating your chronic chest pain—angioplasty or bypass surgery—and then makes a recommendation. What did your doctor recommend?

Surprisingly, the answer may depend on the location of your doctor's office, not the cost or effectiveness of the treatments themselves. If you live in Morganton, you are much more likely to get bypass surgery than if you resided just down NC Highway 64 in Rutherfordton.

According to a recent analysis of Medicare data by the North Carolina Health Access Coalition, Medicare patients in Morganton were more than twice as likely to receive a cardiac bypass as Medicare patients in Rutherfordton (6.24 per 1,000 Medicare patients in Morganton vs. 2.87 per 1,000 patients in Rutherfordton).¹ These findings indicate widely divergent treatment practices for chronic chest pain across neighboring counties in North Carolina.

I am not a doctor or a health researcher so I do not know which treatment is more appropriate under which circumstances, but dramatic disparities like these indicate that too often in our health care system, treatment decisions are based on reasons other than empirical evidence.

As a society, we want patients to receive the most effective tests and treatments in the most appropriate settings: we want medical care that improves patient health and contains costs. In other words, we want cost effective medical care that works.

Unfortunately, too often in North Carolina and across the country, what happens in health care is underuse of proven medical tests and treatments and overuse of unproven medical tests and treatments that don't help the patient and, even worse, sometimes harm the patient.

As a result, nationally, we are spending billions of dollars in wasted treatments. Recent studies indicate that as much as 30% of all expenditures in Medicare are wasted on unnecessary tests, treatments, and procedures that do not improve health outcomes.²

Last summer, the *New Yorker* published an article that explored why McAllen, Texas is the second most expensive health care market in the nation.³ Medicare spent \$15,000 per enrollee in McAllen, almost twice the national average and twice the rate of El Paso, Texas, which is demographically and economically similar to McAllen. Yet even with the extra spending, Medicare enrollees in McAllen did not see any benefit in health outcomes compared to those in El Paso. The cause for this disparity was simply across-the-board overuse of medicine in McAllen.

Other national studies have confirmed that, as a nation, we are spending health care dollars unwisely. A 2003 study by Dartmouth researchers concluded that patients in higher-spending regions received 60% more care than elsewhere, but did no better than the patients in the lower-spending regions in terms of survival, ability to function, or satisfaction.⁴ If anything, they fared worse. Another Dartmouth study found that the more money Medicare spent per person in a given state, the lower the state's quality ranking tended to be.⁵

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developed, which involved strengthening the compressed bone through injection of cement. Case series studies that were restricted to a before-after comparison of patient outcomes demonstrated that they felt much better after the injection. Over 1,000 patients per year received this treatment in North Carolina. It was not until the summer of 2009 that randomized trials demonstrated that the level of improvement in patient well-being was similar whether they received the cement injection or a sham injection of lidocaine.⁸ There is still a great deal that we don't know about vertebroplasty. It remains possible that some subsets of patients may benefit from the treatment, but lack of information for almost a decade exposed many patients to a treatment of essentially unknown efficacy that also carries some risk. Well-conducted trials 10 years ago might have led to much better current information about treatment options for patients and providers.

How are we to avoid the fate of CER studies winding up on a shelf or in a library? Physicians are exposed to hundreds of research articles each week. Dissemination of the highest quality information in an unbiased fashion will be critical if CER is to positively affect care patterns in the US. Past federal efforts have been on a relatively small scale and dissemination efforts have been disappointing to date. However, funding from the American Recovery and Reinvestment Act (ARRA) stimulus bill and especially the new health reform legislation will significantly increase the visibility of CER. This will include not only peer-reviewed journal articles but also direct dissemination of results to providers and patients.

Combining CER information with electronic health records is an obvious extension of these joint efforts. The challenge of providing information to physicians and patients in a convenient format, at a time close to the provision of

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When making treatment decisions, we need to do what is best for the patient, not just order up more care that does not improve health. But how do we know what works best?

Comparative effectiveness research (CER) promises to provide us with this information. Comparative effectiveness is an approach that analyzes how health care is provided across broad populations and identifies those procedures, medications, and treatments that are most effective for a given situation. CER asks not whether a certain procedure or pharmaceutical is better than a placebo (doing nothing), but whether it is better than alternative procedures or pharmaceuticals—in other words, which treatment works best.

The federal government has prioritized CER. As part of the Recovery and Reinvestment Act of 2009, the federal government is investing more than \$1 billion in CER through the US Department of Health and Human Services, the Agency for Healthcare Research and Quality, and the National Institutes for Health.

We are fortunate here in North Carolina because we are home to some of the most respected and active CER researchers in the nation. A conservative figure for the amount of federal funds already awarded to in-state institutions for CER training, studies, and clinical trials taking place over the next three years totals roughly \$40 million. This number is almost certain to rise because additional funding for this field is anticipated to grow substantially in the coming years.

This past legislative session, recognizing the emerging importance of this research, the North Carolina General Assembly created the Comparative Effectiveness Study Commission. Representative Bob England and I are co-chairing this Commission, which is comprised of other legislators and includes an advisory board made up of researchers, third party payers, medical providers, and others.

The Commission is tackling a number of questions, including the following:

- How can we position North Carolina to benefit economically from increased federal investment in this type of research?
- How can we enhance researchers' access to broad ranges of health care data to advance this important research while guaranteeing patient privacy?
- How can we improve dissemination of CER to health care providers?
- How can we ensure that the state's health care dollars are spent wisely?

Our fundamental objective, however, is to identify ways to improve the health of the people of the state. As the Commission continues its deliberations, Representative England and I would welcome hearing your ideas to promote this most basic and most critical of goals.

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care, and in a way that not does significantly slow down the process of care will require significant testing and process of care modification. We have a lot of work to do.

How is This All Going to Get Done?

The US has significant resources in CER. Fortunately, the ARRA stimulus bill and the health reform legislation have substantial training funds to increase the pool of researchers to conduct this work. Significant work is occurring in North Carolina including randomized trials through industry and at all of the state's academic health centers. Duke University, Research Triangle International, and the University of North Carolina at Chapel Hill all have significant ongoing activities

through AHRQ, which to date has been the major federal agency engaged in CER. Both of North Carolina's Clinical and Translational Science Award (CTSA) centers at UNC and Duke (funded by NIH) have significant engagement with CER.

The health reform legislation establishes a new entity, the Patient Centered Outcome Research Institute, which will "assist patients, clinicians, purchasers, and policymakers in making informed health decisions by advancing the quality and relevance of the evidence concerning the manner in which diseases, disorders, and other health conditions can effectively and appropriately be prevented, diagnosed, treated, monitored, and managed through

research and evidence synthesis that considers variations in patient subpopulations, and the dissemination of research findings with respect to relative health outcomes, clinical effectiveness, and appropriateness of medical treatment...."⁹ This new Institute will be governed by a board of governors from public and private entities including representation from federal agencies, the practice community, industry, and payers. Funding for this research will be substantial, probably over \$350 million per year, but there is likely to be a period of considerable uncertainty as the new Institute starts up, develops relationships with other federal agencies, and devises its own internal policies. In the interim, providers should expect significantly more activity and collaboration across payers in order to improve care patterns. While CER has often been described as a means of decreasing health care costs by reducing utilization of relatively expensive treatments, some findings of CER have demonstrated underutilization of treatments. Once such underutilization is identified, short-term health care costs may rise, although long-term costs may be ameliorated through reduction in future hospitalizations.

Ongoing engagement from clinicians, policymakers, and payers will be needed to assure that the information and dissemination materials are relevant to practicing clinicians and their patients. How payers will respond to this new information is not yet clear. Federal legislation has mandated

that CER research should not be used as a tool to deny care to patients, reflecting the heterogeneity and the complexity of clinical care. However, CER can and should be used as one component of decision-making processes around the structure and function of the health care system. Treatments that are harmful or have no benefit over alternatives which may be less invasive or less expensive should obviously be discouraged. Study designs can be adapted so that they can be conducted much earlier in the development of technology using techniques such as "coverage with evidence development" which would expand the information gathered from patients when they receive a new procedure or technology.¹⁰ This would allow treatments to be used for patients in need, but would also provide significantly more information to providers and policymakers. Finally, the availability of additional information on treatment effectiveness in populations who are relatively understudied in the current health care system, such as the elderly over age 75 and certain minority populations, is greatly needed.

Comparative effectiveness research is not new, but its utilization to date has been modest. The increased emphasis on CER in both the public and private sectors has the potential to assist patients and providers in making better choices regarding diagnostic tests and treatments. Over the next four to five years, we will need to make sure that this potential is realized. **NCMJ**

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