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# HOW WILL COMPARATIVE EFFECTIVENESS RESEARCH INFLUENCE CLINICAL DECISION MAKING?

Nicholas Zaorsky, MD and Timothy Showalter, MD

## Abstract

Most health care recommendations in the United States have come from trials designed to measure efficacy of medical interventions, with randomized controlled trials considered the gold standard for evidence-based medicine. Comparative effectiveness research has become an essential component of research to help define the benefits, risks, and effectiveness of different interventions for a particular illness. Comparative effectiveness research is informally defined as an assessment of all available options for a specific medical condition, with intent to estimate effectiveness in specific subpopulations. In this article, we contrast efficacy-based healthcare research and recommendations in the United States, under the model of evidence-based medicine, to the contemporary paradigm of comparative effectiveness research. We review the recent emphasis by the federal government on comparative effectiveness research. Finally, we review the limitations of effectiveness and efficiency.

### (I) What are the limitations behind current medical recommendations in the United States?

Currently, most healthcare recommendations in the United States are based on studies designed to evaluate efficacy, which measures whether one novel intervention could have an impact on outcomes under ideal conditions.<sup>1</sup> The gold standard of proving efficacy is a randomized controlled trial (RCT). Trials of efficacy have been crucial in the discovery of diagnostic tests, medications, surgical instruments, and systems of medical delivery.

However, medical recommendations based solely on efficacy are limited for a number of reasons.<sup>1-3</sup> The results of an efficacy trial are aimed to provide a therapy for a homogenous population of healthy participants under highly-controlled conditions, which may not reflect the population heterogeneity seen in community practice. Due to the long study periods of efficacy trials, published results may be lagging behind the latest scientific research and interventions, making trial results when an immediate medical decision is necessary. As level I evidence from RCTs does not always exist, recommendations are based rather on various reviews of differing objectives, outcome measures, and study qualities. In addition, testing for efficacy examines all potential interventions that may have incremental benefits when no proven therapy exists, thereby not aiding in practical medical decision making between already accepted treatment options. RCTs are usually limited to major academic institutions, which have established databases and scientists devoted to publication of the data. RCTs typically exclude smaller institutions and private practices, which may serve patient subpopulations. These patient subpopulations may not present to the large academic institutions and may respond differently to a recommended

therapy. The potential benefits at the clinical trial level do not always translate to real-world improvements as well, when other factors such as time and cost are factored in. Furthermore, efficacy-based trials simply may not accrue enough patients to answer a queried hypothesis. Finally, trials of efficacy are typically expensive, precluding testing of other potential interventions that may have incremental benefits. These limitations call for complementary research that is designed to better inform the clinical decision making process.

### (II) What is comparative effective research?

Comparative effectiveness research (CER) is separate from and complementary to research approaches that measure efficacy. CER is informally defined as an assessment of available options for treating specific medical conditions in selected groups of patients.<sup>4,5</sup> CER focuses on treatment effectiveness, i.e. whether the intervention makes an impact under “real-world” conditions, and efficiency, i.e. whether an intervention is worth the resources it consumes.<sup>1</sup> The contemporary concept of CER is to incorporate all available data to direct practitioners to optimal patient-specific treatment decisions. Studies in CER are recommended to: (1) influence clinical decision making by identifying the most effective health care options where clear options exist, (2) support the development of personalized or stratified medicine by examining the racial, ethnic, socioeconomic, and geographic variations in care that affect health outcomes, (3) find the clinical characteristics that predict which intervention would be most successful in an individual patients, (4) integrate outcome measures, including patient-reported quality of life and costs to patients and providers, and (5) link data from public and private entities.<sup>2,5-9</sup> Examples of CER studies are now present throughout medicine and include research designed to evaluate the effectiveness of medical interventions in cardiology, endocrinology, medical oncology, radiation oncology, and psychiatry.<sup>10-15</sup>

CER also focuses on targeting specific patient subpopulations through predictive biomarkers and companion diagnostics.<sup>16,17</sup> Predictive biomarkers are baseline characteristics that categorize patients by their likelihood of responding to a particular treatment, including favorable and unfavorable responses. Examples of predictive biomarkers include Apolipoprotein E4 (APOE4) status in Alzheimer’s patients and Human Epidermal growth factor Receptor 2 (HER2) overexpression in breast cancer patients.<sup>18,19</sup> Companion diagnostics are predictive biomarkers that are developed into commercially available diagnostic tests, such as Oncotype DX for breast cancer.<sup>17</sup>

Biomarker-specific therapeutic interventions are combined with companion diagnostics to target a patient subpopulation for treatment. The combination of one therapy with one biomarker

is the sine qua non of 'personalized' stratified medicine. By targeting patients on the basis of biomarkers, patient subpopulations that respond differently to treatment are identified, thereby generating more favorable benefit-risk profiles for the therapeutic. This is in contrast to the traditional empirical 'all-comers' approach of efficacy-based trials, where any patients with the disease of interest may be enrolled.<sup>20</sup> Estimates of treatment effect size that are limited to biomarker-expressing patient subpopulations may better reflect the impact of a candidate therapeutic agent. Moreover, trials limited to patient subpopulations avoid exposure of others to a drug since these individuals would lack the predictive biomarker. CER may therefore strengthen the ability to measure effect and improve patient safety.

### (III) Quantifying the success of comparative effectiveness research

The expected net present value (eNPV) has been used to estimate the potential success of medical studies including comparative effectiveness trials.<sup>20,21</sup> The eNPV is the risk-adjusted sum of the value of an investment or project. It integrates the costs necessary to undertake a potential project (e.g. cost to develop a clinical test, timing of development and approval, time to physician adoption) to the potential monetary benefits (e.g. the sales and lifetime gross profit of a test).<sup>21</sup> Companies tend to fund projects that have a positive eNPV because it indicates a value-adding investment.<sup>20,22</sup> With substantial prior confidence in predictive biomarkers, a stratified medicine development strategy often generates a higher eNPV than an 'all-comers' approach.

The eNPV has been used to estimate the potential success of medical studies.<sup>20</sup> For example, in oncology, eNPV modeling studies for HER2, the biomarker used for response to the drug trastuzumab, mirrored the actual benefits of trastuzumab in clinical trials that included patients expressing HER2.<sup>16,23, 24</sup> In neurology, eNPV modeling studies have shown that prospective stratified medicine approaches that identify patients positive for APOE4, the candidate biomarker for bapineuzumab, created a six-time greater eNPV value than the traditional approach of using bapineuzumab on all Alzheimer's patients.<sup>16</sup> In these eNPV modeling studies, patient subpopulations that would respond best to a therapy were identified. The eNPV of conducting trials for therapies aimed directly at the subpopulations mirrored the actual successes of the trials.

### (IV) The impetus behind comparative effectiveness research in the United States

CER is not a novel idea, but the United States government has recently provided a new push for CE.<sup>25</sup> In recognition of the value in CER research, the American Recovery and Reinvestment Act of 2009 allocated \$1.1 billion to toward CER and the Patient Protection and Affordable Care Act of 2010 created the Patient Centered Outcomes Research Institute (PCORI) with an estimated \$600 million yearly funding to pursue CER.<sup>26</sup>

Both PCORI and the Agency for Healthcare Research and Quality (AHRQ) define CER as research "designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options. The evidence is generated from research studies that compare drugs, medical devices, tests, surgeries, or ways to deliver health care."<sup>27</sup>

Controversy persists on whether costs of care should be included as a component of CER. Based on the guidelines of PCORI and the Centers for Medicare and Medicaid Services, cost will not be considered in reimbursement or in investigations of CER, and cost per quality adjusted life years analyses are specifically prohibited. However, in the current budget climate and limited medical resources, cost has become an important consideration, if not officially sanctioned. Unofficially, CER studies include analyses of the economic impact of potential interventions with cost-effective and cost-benefit analyses.<sup>28,29</sup>

### (V) CER follows studies that establish efficacy

CER will be crucial for the treatment of patients with known biomarkers and multiple modalities of therapy available. Nonetheless, dynamic interactions exist among the prevalence of predictive biomarkers, the clinical performance of the companion diagnostic, and the effect of a therapy.<sup>16</sup> First, if a therapy has a rapid efficacy onset and acceptable safety profile, the predictive biomarkers may not be necessary since a physician may rapidly determine therapeutic response.<sup>20</sup> Second, if the companion diagnostic is not widely distributed, then it will be impossible to screen for a biomarker. Third, the need to screen more patients with a companion diagnostic may lengthen the duration of a study. Prospective RCTs will still be necessary to validate the companion diagnostic and establish the predictive value, which would increase the cost of development and negate potential savings. Fourth, treatment response of a biomarker-specific therapy may not correlate strongly with biomarker expression, as was the case with EGFR expression and cetuximab, where the expression of EGFR did not correlate with the expected benefit in progression-free or overall survival.<sup>30</sup> If a companion diagnostic does not already exist for a disorder, its development adds to the risk of failure and a negative eNPV. Further, information regarding the prevalence of a biomarker may not be available in a large database of patients, precluding the use of that therapy. Finally, biomarker-specific therapies face restricted pricing flexibility for their use in a smaller patient population.<sup>16</sup> If there are fewer people who could benefit from the drug, the company providing the drug must tailor the price for these individuals. Thus, studies of effectiveness or efficiency are not always feasible, while studies of efficacy continue to be important in innovation and population medicine.

### Conclusion

Current health care recommendations in the United States have mostly come from trials of efficacy, which ask if a therapy

could work in an ideal situation. In contrast, CER focuses on whether an intervention makes an impact under “real-world” conditions (its effectiveness) and if an intervention is worth the resources it consumes (its efficiency). CER integrates the use of predictive biomarkers and companion diagnostics to predict which intervention would be most successful in an individual patient. The eNPV of such studies is higher than that of efficacy-based RCTs, and the US government has recently provided a financial impetus for increasing CER. Nonetheless, CER has elicited concerns for a variety of reasons, including methodological challenges, choice of appropriate comparator, lack of biomarker data in large databases, and lack of existing efficacy trials. The push toward CER represents an extension of research resources beyond the traditional biomedical research model of evidence-based medicine, in which carefully-designed RCTs to measure efficacy reign supreme. Future health care recommendations will come from studies of effectiveness and efficiency.

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### “Red Panda”

Photography by Dan Roan, MD

