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The Role of Comparative Effectiveness Research in Medicine and Health

Aisling R. Caffrey, PhD, MS

TODAY, MORE THAN EVER, HEALTHCARE systems need to do more with less. Clinicians, decision-makers, and other stakeholders are seeking evidence-based healthcare practices that control expenditures while improving patient care. Of particular concern is the paucity of supportive clinical data related to alternative therapeutic options for the treatment of acute and chronic conditions. The demand for high-quality pharmacoepidemiologic and pharmaco-economic research is at unprecedented levels, with government agencies, foundations, and private industry collectively committing billions of dollars in funding for studies examining the beneficial and unintended effects of medications.^{1,2} Pharmacoepidemiology provides vital insights into effectiveness and safety, while pharmaco-economics addresses value and costs given limited healthcare resources.

WHAT IS COMPARATIVE EFFECTIVENESS RESEARCH?

Often, the selection of the most appropriate treatment is complicated by limited efficacy, effectiveness, and safety data. In efficacy trials, the capability to produce the planned effect under ideal conditions is typically assessed in an active study drug compared to a placebo comparator. Alternatively, comparative effectiveness focuses on head-to-head comparisons between two or more active treatments in the real-world clinical setting. While randomized controlled trials provide evidence for the drug approval process, there is a lack of comparative data on which agents produce the most favorable clinical outcomes with the fewest side effects in various real-world clinical populations. Realizing the need for evidence supporting prescribing decisions and the importance of comparative effectiveness research, programs developed under the 2009 American Reinvestment and Recovery Act and 2010 Patient Protection and Affordable Care Act, as well as initiatives from other public and private agencies, have sought to fill critical gaps in knowledge regarding best treatment practices.

STUDY DESIGNS AND CAUTIONS OF COMPARATIVE EFFECTIVENESS RESEARCH

Comparative effectiveness research can be carried out with various study designs including clinical trials and observational studies, as well as meta-analyses and systematic reviews. Study design selection depends on the research question, exposure prevalence, primary and secondary outcomes, data availability, existing knowledge, costs, and limitations of each design. One of the greatest challenges for comparative effectiveness clinical trials and observational studies relates to the comparability of patients in different treatment groups. Confounding by indication is a primary concern in comparative effectiveness research. The likelihood of receiving different drugs directly relates to the indication for treatment, patient characteristics, provider characteristics, and facility characteristics which can confound the observed relationship between exposure and outcome.³ Further, it is often difficult to conceptualize and define these potential external influences.

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Clinical trials rely on randomization to balance baseline patient characteristics between study drugs. Whereas observational studies use analytic techniques and other study design approaches to mitigate the impact of confounding by evenly distributing significant variables associated with the exposure and outcome.³ Randomization is considered the gold

standard approach to balancing patient characteristics, including both measured and, more importantly, unmeasured confounders, in order to evaluate the impact of treatment on the study endpoints. However, residual confounding can occur through the omission of a key confounder analytically or in cases of randomization failure. Indeed, subgroup analyses are highly criticized as the effects of randomization may have failed in the subgroups assessed, resulting in analyses of nonrandomized data.

Imbalance in clinically significant variables can bias the results of both clinical trials and observational studies. Usually it is difficult to assess whether these variations were due to chance or selection bias, particularly when statistically significant differences remain after randomization in clinical trials or analytic adjustment in observational studies. Such variations may indicate residual confounding, for example, if additional differences existed between treatment groups in variables that were not assessed (unmeasured confounders), or may even indicate effect modification. When significant baseline imbalances are observed between treatment groups, regardless of study design, assessments of residual confounding should be completed.

In general, the resources required for large clinical trials, particularly those powered to detect superiority, are cost prohibitive and patient enrollment can be slow. Additionally, non-inferiority is easier to detect than superiority. Due to these limitations, there may be reluctance to fund head-to-head active comparator trials. A major strength of observational comparative effectiveness research is that it uses existing data to discern important real-world differences in effectiveness and safety. To improve the efficiency of comparative effectiveness clinical trials, observational research can be used to guide the development and design of randomized trials.

COMPONENTS OF A SUCCESSFUL COMPARATIVE EFFECTIVENESS RESEARCH PROGRAM

Properly designed, conducted, and interpreted comparative effectiveness research can provide evidence-based knowledge for clinical decision-making that optimizes patient outcomes. As researchers and consumers of healthcare research, the best resources for comparative effectiveness technical reports and methods guides include the Agency for Healthcare Research and Quality Effective Healthcare Program, the Institutes of Medicine, the Patient-Centered Outcomes Research Institute, and the National Information Center on Health Services Research and Health Care Technology. Other resources that assist in the critical evaluation of the literature include the GRACE principles, Good Research Practices for Comparative Effectiveness Research from the International Society for Pharmacoeconomics and Outcomes, and the Guidelines for Good Pharmacoepidemiology Practices from the International Society for Pharmacoepidemiology.⁴⁻⁶

For comparative effectiveness research, a strong, interdisciplinary research team is needed, and core contributors should include physicians, pharmacists, and pharmacoepidemiologists. Also, patients are increasingly recognized as

key stakeholders in designing clinical research.² With the tremendous growth in health outcomes and health economics, there is record demand for trained professionals in these fields, though few universities in the country offer such programs. The Program in Pharmacoepidemiology and Pharmacoeconomics of the University of Rhode Island College of Pharmacy engages in the focused, interdisciplinary training of the next generation of pharmacoepidemiologists and pharmacoeconomists.

My research program has focused on the comparative effectiveness of antimicrobials for the treatment of infectious diseases.⁷ The goal of this research is to provide insight into the optimal treatments for invasive infections, enhancing patient safety by reducing treatment failures and adverse outcomes, through the use of rich data sources and sophisticated analytical techniques.^{8,9} To address potential biases, the most accurate sources available for defining exposures, outcomes, and potential confounders are used, including pharmacy data, microbiology data, laboratory results, and records of inpatient and outpatient care from electronic medical records. Further, we utilize advanced statistical methods, including propensity scoring, calibration, and assessments of residual confounding, to mitigate confounding and achieve balance between treatment groups.

In summary, with the proper study team, study design, study methods, and resources, comparative effectiveness research plays an important role in evidence-based medicine. Evidence-based pharmacotherapy is necessary for maximizing positive clinical outcomes and minimizing negative effects to better inform and improve clinical practice.

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Disclosure of Financial Interests

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