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Methodological Issues in Comparative Effectiveness Research: Clinical Trials

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ABSTRACT

The US Department of Veterans Affairs (VA) Cooperative Studies Program has been conducting comparative effectiveness clinical trials for nearly 4 decades in many disease areas, including cardiovascular disease/surgery, diabetes mellitus, mental health, neurologic disorders, cancer, infectious diseases, and rheumatoid arthritis. The features that have made this program advantageous for conducting comparative effectiveness clinical trials are described along with methodological considerations for future trials based on lessons learned from its experience conducting these types of studies. Some of the lessons learned involve managing risk factors, clinical equipoise, patient preferences, evolving technology, the use of usual care as a comparator and pharmaceutical issues related to study drug blinding. These issues are not unique to the VA but can play an important role in enabling valid comparisons between treatments that may have differences in delivery or mechanisms of action and could affect the execution and feasibility of conducting a clinical trial with a comparative effectiveness aim. We also outline some future directions for comparative effectiveness clinical trials.

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Comparative effectiveness clinical trials are randomized comparisons of treatments designed to determine which treatment options are superior in order to help better inform decision makers. Treatment options could be similar, such as a comparison of different drugs or surgical techniques, or could be very different such as comparisons of drugs versus surgery, surgery versus a device, watchful waiting versus an immediate intervention, and behavioral therapy versus pharmacologic therapy. The Department of Veterans Affairs (VA) Cooperative Studies Program (CSP) has been conducting these types of studies for nearly 4 decades. An early example of a comparative effectiveness clinical trial conducted by the CSP was the VA Randomized Trial of Coronary Artery Bypass Surgery for Stable Angina.[1,2] This trial was conducted soon after the development of the bypass surgery procedure. The objective was to compare the emerging new procedure with standard medical therapy in patients with coronary artery disease who had stable angina. The trial showed that only a small group of high-risk patients benefited from the procedure and that most patients could be treated safely with medications until symptoms or severity of the disease progressed toward warranting surgical intervention. The trial led to an immediate reduction in bypass surgery procedures within the Veterans Health Administration.

Comparative effectiveness studies have a long history in clinical trials. In their seminal report, Schwartz and Lellouch[3] made the distinction between pragmatic and explan-

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atory trials. The former are conducted in "real-world" situations to compare the *effectiveness* of several treatments or treatment strategies (e.g., combinations of drugs), whereas the latter are conducted under idealized conditions to compare the *efficacy* of several treatments (e.g., placebo-controlled drug trials typically conducted by pharmaceutical companies). The distinction between effectiveness and efficacy is not always clear. Many trials include components of both types of studies. As a brief overview, the traditional efficacy trial often uses a placebo control and is conducted under ideal conditions for obtaining explanatory results. Some of these conditions include homogeneous inclusion criteria, academic or specialized medical centers, and surrogate or intermediate types of outcomes (e.g., lung function, ejection fraction, and biomarker levels). In contrast, effectiveness studies are conducted under real-world conditions so that the results are more applicable to the general population of patients with the disease. These studies may include community hospitals, heterogeneous or broad inclusion criteria, and patient-centered outcomes (e.g., morbidity, mortality and quality of life). Thorpe and colleagues[4] have published a comprehensive review of the distinctions between efficacy and effectiveness clinical trials.

In this review, we (1) present features of the VA CSP program that have made it advantageous for conducting comparative effectiveness clinical trials, (2) describe some methodological considerations for future trials based on lessons learned from our experience with these types of studies, and (3) outline some future directions for comparative effectiveness clinical trials.

ENVIRONMENT OF THE DEPARTMENT OF VETERANS AFFAIRS

The VA has created a favorable environment for conducting comparative effectiveness clinical trials. Its inherent features include a clear mission, an integrated healthcare system, a stable patient population, national databases, electronic medical records, and a recently instituted central institutional review board. The Veterans Health Administration is the largest integrated healthcare system in the United States that provides comprehensive medical care to >5.5 million veterans each year. The VA also has numerous national databases that record all VA hospitalizations (patient treatment file), clinic visits (outpatient clinic file), and deaths (beneficiary identification and records locator system) that are available to researchers for tracking patients and their medical information. In addition, the VA maintains an electronic medical records system (centralized patient records system) that provides longitudinal clinical information about the treatment of veterans. Taken together these databases provide a wealth of data for use in conducting comparative effectiveness research (CER) studies.

Another important feature of the VA is that it funds core infrastructure for research. Its CSP funds statistical and epidemiology coordinating centers for the conduct of both multisite clinical trials and observational studies, as well as centers to coordinate pharmaceutical and health economics activities. The VA CSP also funds the planning of studies, bringing together clinical and methodological expertise to determine the right question and appropriate study design. This expertise includes biostatisticians, epidemiologists, clinicians, geneticists, pharmacists, and health economists who collaborate on the planning of studies alongside clinical investigators. More recently, within its network of statistical centers, the CSP has begun developing a methodology core that supports researchers conducting biostatistical and epidemiologic research relevant to the design, conduct, and analysis of VA cooperative studies.

METHODOLOGICAL CONSIDERATIONS

The VA CSP has had a long history of conducting comparative effectiveness clinical trials. Although its origins date to the 1940s with the seminal studies of treatments for tuberculosis,[5] the program was officially organized in 1972, and since that time it has conducted >175 studies. Many of these efforts can help to inform future studies by highlighting key considerations for making valid treatment comparisons and by identifying execution and feasibility issues for potentially complex comparative trials that lead toward more robust findings. Some of these considerations relate to the management of risk factors, maintaining studywide clinical equipoise, accounting for patient preferences, accommodating evolving technology, the use of usual care as a comparator, and pharmaceutical issues related to study drug blinding. We illustrate issues related to these areas from the following 8 studies conducted by the VA CSP: the VA Trial of Coronary Artery Bypass Graft Surgery,[1,2] Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE),[6,7] VA Diabetes Trial (VADT),[8,9] Options in Management with Anti-Retrovirals (OPTIMA),[10] Homocysteinemia in Kidney and End Stage Renal Disease (HOST),[11] Open versus Endovascular Repair (OVER),[12] VA Robotics in Chronic Stroke (VA ROBOTICS),[13,14] Rheumatoid Arthritis: Comparison of Active Therapies in Patients with Active Disease Despite Methotrexate Therapy (RACAT),[15] and Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy (VA NEPHRON-D).[16] A brief summary of the key design features of these studies is presented in Table 1. These studies were selected because they illustrate methodological considerations that can arise in comparative effectiveness clinical trials and are not unique to VA CSP.

Management of Risk Factors

In designing clinical trials there is often a "single-disease" mentality that focuses mainly on the disease under study. However, in studies of patients with multiple comorbidities, as is often the case in the elderly, medical conditions other than the one under investigation also must be properly managed medically to avoid spurious treatment effects. As an example, the COURAGE trial was designed to determine the best strategy to treat patients with stable chronic isch-