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Review

Innovative designs of point-of-care comparative effectiveness trials

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ABSTRACT

One of the provisions of the health care reform legislation in 2010 was for funding pragmatic clinical trials or large observational studies for comparing the effectiveness of different approved medical treatments, involving broadly representative patient populations. After reviewing pragmatic clinical trials and the issues and challenges that have made them just a small fraction of comparative effectiveness research (CER), we focus on a recent development that uses point-of-care (POC) clinical trials to address the issue of "knowledge-action gap" in pragmatic CER trials. We give illustrative examples of POC-CER trials and describe a trial that we are currently planning to compare the effectiveness of newly approved oral anticoagulants. We also develop novel stage-wise designs of information-rich POC-CER trials under competitive budget constraints, by using recent advances in adaptive designs and other statistical methodologies.

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1. Introduction

The past five years witness the beginning of a new era in the US health care system, following the health care reform legislation in March 2010. One of the provisions of the Patient Protection and Affordable Care Act (PPACA) is the establishment of a non-profit Patient-Centered Outcome

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Research Institute (PCORI) to undertake comparative effectiveness research (CER), examining the "relative health outcomes, clinical effectiveness, and appropriateness" of different medical treatments. PCORI provides funding for selected pragmatic clinical trials or large simple trials, or large-scale observational studies, involving broadly representative patient populations for CER. Observational studies are often used to provide data for CER; an example is Stukel et al. [1] that describes statistical analysis of large Medicare claims databases to compare survival rates after medical and surgical treatments for acute cardiovascular disease. The key problem with observational approaches involves 'confounding by indication', the tendency for freely choosing clinicians and patients to choose treatments with their anticipated effects in mind. Careful design of observational studies and adjustments for bias together with sensitivity analysis methods have been developed to mitigate overt biases and address uncertainties about latent biases in observational data; see [2,3]. A more definitive way to remove these biases is to use randomization, leading to CER clinical trials. However, the cost, complexity and potential lack of impact of CER clinical trials compare unfavorably with the relative ease of observational studies. In Section 2 we give an overview of these large simple trials and the more general pragmatic trials and the issues and challenges that have made them just a small fraction of the totality of CER studies. Lai and Lavori [4] describe three methods, two of which are briefly reviewed in Section 2, to address these issues.

In Section 3 we focus on the remaining one of the methods, namely using point-of-care (POC) clinical trials to close the "knowledge-action gap" described in Section 2.1. In particular, we review recent developments, after the publication of [4] in 2011, in both informatics and methodological advances for POC-CER trials. We also give illustrative examples of these trials. We begin Section 4 by describing one such trial planned at the Department of Veterans Affairs (VA) to compare the effectiveness of three oral anticoagulants that were approved in the US and many other countries in the last five years. Practical issues that arose during planning led us to develop a novel class of stage-wise POC-CER trials in a general framework. The stage-wise designs are information-rich and cost-effective in producing evidence-based answers to questions which evolve sequentially about the treatments. These questions not only arise endogenously during the course of the trial but also exogenously from other studies and the changing landscape of medical knowledge and practice.

As Section 4.1 shows, traditional clinical trial designs for POC-CER trials cannot handle problems of such complexity and yet require very large sample sizes and upfront commitment of a corresponding large amount of funding. Novel designs are therefore needed. Chapter 7 of [5] lists adaptive designs and "using point-of-care clinical trials to create a learning health care system" as two important innovations in clinical trial designs, and discusses their advantages and challenges. The paper [6] in this tenth anniversary issue gives an overview of the major developments and issues in adaptive designs of confirmatory trials to test new treatments in the past decade. Not only does the present paper address the other class of innovations in clinical trial designs, namely POC trials, but more importantly it also modifies some important ideas underlying the advances in adaptive designs described in [6] to resolve the difficulties and circumvent the hurdles currently facing POC-CER trials. As Section 4 shows, a major difference between the adaptive designs of confirmatory clinical trials to test new treatments and POC trial designs is that the latter do not require blinding as they involve approved treatments and blinding may even be infeasible. The stage-wise designs developed in Section 4 capitalize on their unblinded feature to allow more efficient use of accumulated information during the course of the trial. Section 5 gives further discussion of this approach and some concluding remarks.

2. Overview of pragmatic and large simple trials for CER

2.1. Pragmatic trials as opposed to explanatory trials

About fifty years ago, Schwartz and Lellouch [7] distinguished "pragmatic trials" from clinical trials, called "explanatory trials", that aim at studying treatment effects in the presence of inter-subject variability in response. Whereas explanatory trials are exemplified by Phase I, II and III trials in the development of a new drug to build a clinical data package for regulatory approval of the drug, pragmatic trials involve approved drugs or treatments and aim at answering the question about which treatment should be used in practice. A pragmatic trial, therefore, should be conducted under "real world" conditions, in which blinding to treatment assignment is not required and clinical outcomes are measured directly rather than through surrogate endpoints that are often used to speed up explanatory trials. Hence it is also called a "naturalistic trial".

Large simple trials, which attracted much attention in the 1980s beginning with [8], are basically large pragmatic trials that aim at answering important health care questions, or confirming conclusions from meta-analyses of small trials, or identifying small but still worthwhile improvements in treatment outcomes for common diseases. One such trial was ISIS (International Studies of Infarct Survival), an RCT of IV atenolol versus placebo following myocardial infarction (MI) which involved 16,000 subjects and showed 15% reduction in mortality by day 7 [9]. A subsequent study involved 58,050 subjects from 1086 hospitals and used a $2 \times 2 \times 2$ factorial design to test oral captopril, oral mononitrate, and an IV magnesium sulphate in an immediate post-MI period. It found significant reduction in mortality for captopril, but not for the other two treatments [10].

Another large pragmatic trial was ALLHAT (the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), a randomized, double-blind, multi-center clinical trial sponsored by the National Heart Lung and Blood Institute in conjunction with the VA. It recruited more than 42,000 patients from 623 primary care clinics and its aim was to determine if the combined incidence of fatal coronary heart disease and non-fatal myocardial infarction differs between diuretic (chlorthalidone) treatment and each of three alternative antihypertensive pharmacologic treatments: a calcium antagonist (amlodipine), an ACE inhibitor (lisinopril), and an alpha adrenergic blocker (doxazosin). A lipid-lowering subtrial (≥10,000 patients) was designed to determine whether lowering cholesterol with an HMG Co-A reductase inhibitor (pravastatin), in comparison with usual care, reduced mortality in a moderately hypercholesterolemic subset of participants. ALLHAT was the largest antihypertensive trial ever conducted, and the second largest lipid-lowering trial. The study was conducted between 1994 and 2002 largely in community practice settings. Hypertensive patients were randomly assigned to receive one of four drugs in a double-blind design, and a limited choice of second-step agents was provided for patients not controlled on first-line medication. Patients were followed every three months for the first year and every four months thereafter for an average of six years of follow-up. This landmark study cost over $100 million, the final results were presented in 2002 [11], and [12] anticipated the results of this trial would translate into clinical practice. Yet, six years later, *The New York Times* article under the headline The Minimal Impact of a Big Hypertension Study on November 28, 2008 quoted C. Furberg, chair of ALLHAT, as saying "The impact was disappointing." The reasons cited for this "blunted impact" include the difficulty of persuading doctors to change, scientific disagreement about the government's interpretation of the results, heavy marketing by pharmaceutical companies of their own drugs, paying speakers to "publicly interpret the ALLHAT results in ways that made their products look better", and newer treatment options not included in the study.

The ALLHAT study is an example showing that a pragmatic clinical trial, when conducted in the traditional research mode, can be very expensive and time-consuming and there could still be a gap between the knowledge generated from the trial and actions taken in clinical care even if the results are definitive. This is called the "implementation gap" in discussions of CER and evidence-based medicine.