JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 68, NO. 17, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.07.781

THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

The Changing Landscape of Randomized Clinical Trials in Cardiovascular Disease

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ABSTRACT

Large randomized clinical trials in cardiovascular disease have proliferated over the past 3 decades, with results that have influenced every aspect of cardiology practice. Despite these advances, there remains a substantial need for more high-quality evidence to inform cardiovascular clinical practice, given the increasing prevalence of cardiovascular disease around the world. Traditional clinical trials are increasingly challenging due to rising costs, increasing complexity and length, and burdensome institutional and regulatory requirements. This review will examine the current landscape of cardiovascular clinical trials in the United States, highlight recently conducted registry-based clinical trials, and discuss the potential attributes of the recently launched pragmatic clinical trial by the Patient-Centered Outcomes Research Institute's National Patient-Centered Clinical Research Network, called the ADAPTABLE (Aspirin Dosing: A Patient-centric Trial Assessing the Benefits and Long-term Effectiveness) trial. (J Am Coll Cardiol 2016;68:1898–907)

Since the 1980s, with the conduct of ISIS-1 and -2 (the First and Second International Study of Infarct Survival) (1,2), large clinical outcomes trials in cardiovascular disease have proliferated, and the involvement of a broad range of stakeholders (clinicians, research organizations, professional societies, patients, and the pharmaceutical and device industries) has deepened over time.

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Evidence generated from clinical trials has substantially influenced the diagnosis and treatment of cardiovascular diseases, including acute myocardial infarction (MI), heart failure, arrhythmias, coronary revascularization, and chronic coronary artery disease (3–6). Despite the large number of clinical trials and depth of evidence in cardiovascular medicine, a surprisingly large proportion of recommendations in the American College of Cardiology (ACC)/American Heart Association clinical practice guidelines are on the basis of lower-quality evidence (7). As the burden of cardiovascular disease continues to grow worldwide and treatment options proliferate (8,9), the need to understand the comparative effectiveness and safety of new or established drugs, biologics, devices, and treatment strategies for patients with cardiovascular disease remains a clear priority. Although many forms of evidence (including high-quality observational studies) exist to study these therapies, randomized controlled trials (RCTs) remain the standard to establish therapeutic efficacy and safety (10). However, because of the growing complexity of RCTs, the traditional approach to conducting clinical trials will be inadequate to keep pace with the need for evidence. Innovations in trial design and conduct, such as the use of existing registries as the basis for patient enrollment and data collection, and pragmatic trial designs represent a paradigm shift that will contribute to addressing the growing need for high-quality clinical evidence (**Table 1**).

The cardiovascular community is uniquely positioned to lead in the future conduct of RCTs, especially if the experience of its investigators/sites and the presence of clinical registries and key areas of research infrastructure can be used. As with other areas of medicine, there is always a need to further develop the evidence base in cardiology, and future RCTs will add to already-existing clinical guidelines and appropriate use criteria (11–15). There is no doubt that cardiologists should lead as large, pragmatic studies are implemented by engaging our patients and clinicians alike, by designing simple studies that address key patient-centered clinical questions, and by working with professional societies and regulatory and funding agencies to do so in a timely and efficient manner.

CURRENT CHALLENGES WITH TRADITIONAL CLINICAL TRIALS

Many characteristics of traditional clinical trials introduce inefficiencies and delays. These characteristics include waning site/patient participation, increasing scientific/operational complexity and cost, and regulatory issues, both at the sites and with national and international agencies. Many of these challenges have been detailed in published perspectives and reviews, with warnings that an overhaul of the clinical trial systems in the United States is imperative (16–21). Subsequently, many clinical trials, even those funded by the U.S. National Institutes of Health (NIH), have relied on enrollment outside of the United States due to rising costs; poor screening to enrollment ratios; and lack of engagement of patients, clinicians, and investigators within our country (19). Furthermore, the increasing complexity of trial protocols; long timelines for budget negotiations, contracting, and institutional review board (IRB) approval; and other logistical difficulties have created an atmosphere of obstruction, rather than facilitation, of clinical research in the United States (22). Given these challenges, many stakeholders, including professional societies, academic research organizations, industry sponsors, regulatory agencies, and funding agencies, have placed a significant focus on developing and refining methods to conduct more pragmatic trials (23). Although much that has been learned over the past decades in the conduct of traditional clinical trials is applicable to the transformation of trial design and conduct, it is also clear that different skills and approaches will be required to carry out pragmatic trials. Furthermore, there will be obstacles and arguments to address as the pragmatic trials are implemented, not the least of

ABBREVIATIONS AND ACRONYMS

CDRN = clinical data research network

EHR = electronic health record

IRB = institutional review board

MI = myocardial infarction

NCDR = National Cardiovascular Data Registry

PCI = percutaneous coronary intervention

PCORI = Patient-Centered Outcomes Research Institute

PCORnet = Patient-Centered Outcomes Research Institute's National Patient-Centered Clinical Research Network

RCT = randomized controlled trial

Boston Scientific, Epi-EP, Medtronic, Micelle Technologies Inc., OrbusNeich, St. Jude Medical, Terumo, and Volcano/Philips. Dr. Curtis has received research grants from GlaxoSmithKline, Novartis, Amgen, Boston Scientific, and Gilead. Dr. Hernandez has received research grants from the NIH, PCORI, Agency for Healthcare Research and Quality, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Merck, Novartis, and Portola Pharmaceuticals; and has served as a consultant for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck, and Novartis. Dr. Masoudi has received grants/research support from the NHLBI, ACC, PCORI, and the John. A. Hartford Foundation; and serves as an ACC Chief Science Officer (National Cardiovascular Data Registries) and member of the Board of Trustees. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 15, 2016; revised manuscript received July 10, 2016, accepted July 12, 2016.