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.

TABLE 1 Attributes of Different Clinical Trial Designs

Clinical Study Design	Relative Cost	Design and Data Collection	Patient Population	Potential for Bias	Advantages and Disadvantages
Observational studies (including registry studies)	$	Can be retrospective or prospective in design; data quality is variable	Typically unselected population (e.g., Medicare)	Without randomization, comparative effectiveness studies cannot be performed	Large population; often many unmeasured variables or unexplained factors
Traditional RCTs	$$$$-$$$$$	Prospective design; data collection occurs at specialized study centers	Highly-selected patient population at study centers; may lead to results that are not generalizable	Randomization eliminates confounding bias	Current gold standard for comparative-effectiveness studies
Registry-based RCTs	$$-$$$	Prospective design; data collection often occurs at diverse clinical sites	Typically designed to study a specific patient population (e.g., those undergoing PCI)	Randomization eliminates confounding bias	Large number of outcomes; harnesses power of already-established clinical registry
Large, pragmatic clinical trials	$$-$$$$	Prospective design; data is collected ubiquitously as part of clinical care	Depending on electronic infrastructure, can be broad or selective; can incorporate enrichment criteria	Randomization eliminates confounding bias	Simple design; large number of outcomes; requires infrastructure that can facilitate easy and quick enrollment

PCI = percutaneous coronary intervention; RCT = randomized controlled trial.

which will be the loss of financial incentives for performing traditional clinical trials that support site investigators, site-based research, and clinical research organizations.

THE FUTURE OF INNOVATIVE CARDIOVASCULAR CLINICAL TRIALS

The push for innovative, pragmatic RCTs started with the need for less expensive, more generalizable answers to questions that occur in day-to-day clinical care settings and guide clinical practice. Characteristics of pragmatic RCTs include:

- Large sample sizes with representative populations fostered by simple inclusion criteria and few exclusion criteria
- Simplified operational approaches: limited site monitoring, safety reporting, trial-specific visits/assessments, and regulatory/compliance documentation
- Embedding the trial procedures within routine clinical care processes
- Avoiding complex drug storage and accountability procedures for investigational products
- Fewer restrictions on the use of concomitant therapies (i.e., allow patients to be treated according to the "standard of care" outside of the randomized comparison)
- Leveraging electronic health record (EHR) and observational data already collected in routine clinical practice or within ongoing observational registries to eliminate redundant data collection

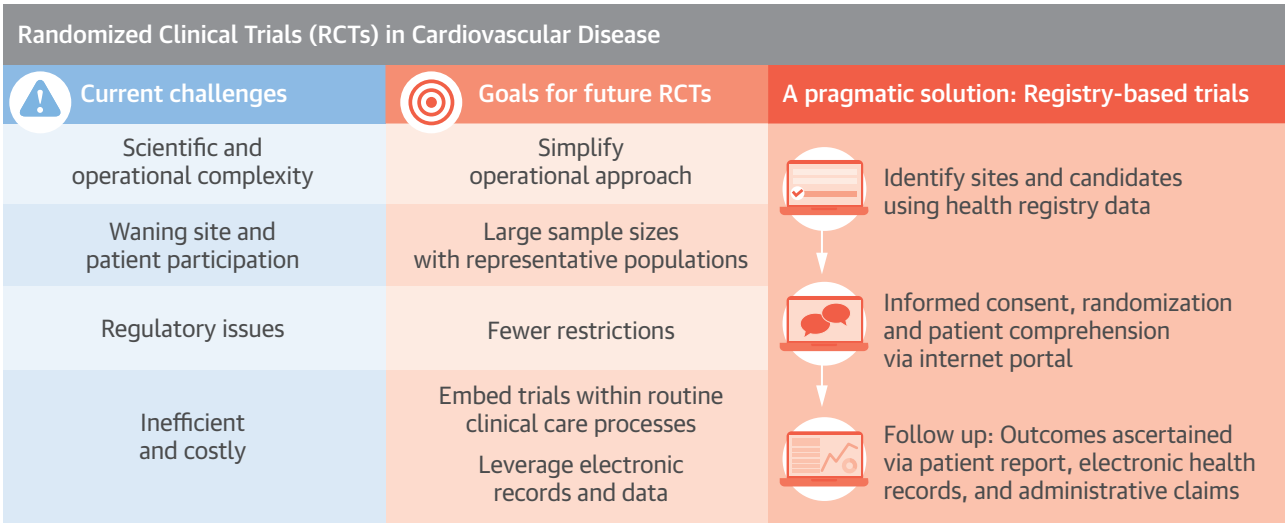
In 2015, the U.S. Department of Health and Human Services also announced proposed revisions to the Common Rule, a set of regulations that protects subjects who participate in research (24). These changes apply to all clinical sites that conduct research sponsored by a supporting agency of the U.S. government (including the NIH). The primary goals of the rule are to "modernize, simplify, and enhance the current system of oversight" (24). The proposed changes included simplified informed consent provisions; a requirement to use a single, central IRB in most clinical trials; and new data security and health information protection standards. Although some of these changes may facilitate clinical trial processes and others may hinder them, these regulations provide a foundation for changes in how RCTs are conducted in the United States.

In parallel, data collection for clinical research must also become more embedded in routine clinical practice to engage more patients, clinicians, and sites, and create a learning health system that reinforces high-quality health care. In doing so, costs and complexity can be reduced and timelines can be compressed if patient enrollment and data collection/entry can be streamlined into day-to-day clinical care, a practice that has become more common in cardiology, through carefully designed registries, EHRs, and/or administrative claims datasets. Thus, registry-based RCTs have been designed and initially conducted in Scandinavia, New Zealand, and the United States, and large, pragmatic RCTs have been designed and are being implemented across the world. These innovative trials provide a glimpse into the conduct of future cardiovascular clinical trials (**Central Illustration**) (25).

REGISTRY-BASED CLINICAL TRIALS

The TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) and the SAFE-PCI (Study of Access Site for Enhancement of

CENTRAL ILLUSTRATION **U.S. Landscape of Randomized Clinical Trials in Cardiovascular Disease**



Jones, W.S. et al. J Am Coll Cardiol. 2016;68(17):1898–907.

Pictured is a representation of how data will be collected in the ADAPTABLE (Aspirin Dosing: A Patient-centric Trial Assessing the Benefits and Long-term Effectiveness) trial. This proposed data collection system involves direct patient data entry, patient completion of informed consent, and electronic identification of patients and follow-up during the course of the study.

PCI) for Women trials in the United States are among the first registry-based RCTs (**Table 2**) (26,27). The TASTE trial was conducted within the SCAAR (Swedish Coronary Angiography and Angioplasty Registry), and it enrolled patients at all 29 percutaneous coronary intervention (PCI) centers in Sweden, 1 center in Iceland, and 1 center in Denmark. Patients with acute ST-segment elevation MI initially provided oral informed consent during the procedural consent process, and then later provided written consent after hospital admission and recovery from the acute event. This approach to informed consent, a controversial aspect of the study, facilitated the enrollment of over 7,000 patients, representing 61% of all patients screened undergoing primary PCI during the enrollment period in just over 2 years. Patients were randomly assigned via the online registry portal to thrombus aspiration followed by PCI or to PCI alone in open-label fashion. Data entry occurred at the point of clinical care within the registry, further reducing site effort and burden.

The SAFE-PCI for Women trial was conducted within a network of U.S. investigators called the National Cardiovascular Research Infrastructure and involved a collaboration between industry, the National Cardiovascular Data Registry's (NCDR's) CathPCI Registry, the ACC/Society for Cardiovascular Angiography and Intervention, the U.S. Food and Drug Administration (FDA) Office of Women's Health, and The Duke Clinical Research Institute (**Figure 1**) (28). In total, 1,787 women at 60 sites undergoing urgent or elective PCI or diagnostic cardiac catheterization were randomized to either radial or femoral arterial access. Informed consent and randomization were performed according to standard procedures for traditional clinical trials, but were synchronized with the procedural consent. Although research coordinator effort was substantially reduced, data entry into NCDR CathPCI was often performed after the PCI, a limitation compounded by the fact that administrative personnel, and not clinicians, most often entered data into the registry. Additionally, trial data beyond those data collected by the registry were required because long-term clinical outcomes and follow-up were not available via NCDR CathPCI. However, 1 advantage of the final trial analytic database was that it was compliant with FDA regulatory submission standards for approval-based trials.

These early experiences have generated interest in further use of existing registries as the foundation for RCTs. The use of registry data should streamline the identification of participating sites, facilitate patient identification, and simplify data collection. However, opportunities exist to improve the electronic identification and point-of-care enrollment of potential trial participants in registry-based RCTs within and

TABLE 2 Similarities and Differences Between TASTE and SAFE-PCI for Women

	TASTE	SAFE PCI for Women
Sample size	7,244 patients undergoing PCI for STEMI 61% of all STEMI patients during the study period	1,787 women undergoing catheterization (690 undergoing PCI)
Enrollment time	28 months	22 months
Enrollment source	SCAAR	Investigator network in NCRI
Sites	29 Swedish, 1 Icelandic, and 1 Danish center	60 sites in the United States
Randomization	1:1 randomization to thrombus aspiration + PCI vs. PCI alone; occurred via online module within registry	1:1 randomization to radial vs. femoral arterial access; occurred via online module in trial database
Adherence to randomized allocation	93.9% underwent assigned treatment	Access site crossover occurred in 27 patients
Design	Open-label RCT	Open-label RCT
Informed consent	Oral consent prior to PCI; written consent within 24 h of PCI	Written, informed consent prior to catheterization or PCI
Data collection	Direct, web-based data entry (for baseline and procedural data)	Data routinely entered into NCDR, then transferred electronically to case report form
Primary endpoint	All-cause mortality at 30 days	Bleeding or vascular complications within 72 h of PCI or hospital discharge
Follow-up	100% complete	99.9% complete
Trial maintenance	Steering committee increased sample size due to lower than expected primary endpoint rate	Data safety monitoring committee recommended termination of study when 446 of 1,800 planned PCI patients were enrolled

NCDR = National Cardiovascular Data Registry; NCRI = National Cardiovascular Research Infrastructure; SAFE-PCI = Study of Access Site for Enhancement of PCI; SCAAR = Swedish Coronary Angiography and Angioplasty Registry; STEMI = ST-segment elevation myocardial infarction; TASTE = Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia; other abbreviations as in Table 1.

outside of procedural-based registries like SCAAR and NCDR CathPCI. Furthermore, clinical outcomes after hospital discharge can be recorded in registries conducted in countries with integrated national health systems encompassing both inpatient and outpatient care. In the United States, however, longitudinal follow-up is being pursued in some cardiovascular registries, but will need to become more widespread before registry-based trials will truly be feasible on a larger and less-expensive scale. Nonetheless, registry-based trials for cardiovascular disease are currently ongoing in several European countries and New Zealand, so this option for conducting pragmatic trials will continue to evolve (29).

WHAT IS NEEDED TO CONDUCT PRAGMATIC TRIALS

Efforts to innovate and develop registry-based RCTs and pragmatic RCTs will continue to require creative approaches to common challenges including:

- Facilitating EHR-based enrollment/recruitment;
- Developing streamlined, informed consent processes that still maintain the protection of participants;
- Leveraging existing data collection forms of registries that may not align with data needed for an RCT, especially longitudinal follow-up;
- Creating relatively fixed data infrastructure apparatus for clinical trials;
- Ensuring robust data security processes that ensure the protection of private health information;
- Defining minimal risk more clearly (especially as it applies to inclusion/exclusion criteria and IRB approval);
- Determining whether randomization into pragmatic trials in itself introduces risk, and how this should be handled by an IRB;
- Completing and validating endpoint ascertainment using administrative claims, participant-reported outcomes, and EHRs.

The initial registry-based trials, such as TASTE and SAFE PCI for Women, implemented novel approaches that will need refinement with support from stakeholders, such as patients, investigators, clinical research organizations, professional societies, and funding entities (e.g., industry, government), to determine how registry-based RCTs and large, pragmatic RCTs are designed and executed in the future. Many of these refinements have been discussed in a recent European Society of Cardiology Task Force communication on drug development (30). Examples of ongoing work on this topic include multiple NIH initiatives (Recruitment Innovation Centers, Trial Innovation Centers, IRB-reliance tools), the Clinical Trials Transformation Initiative, and a living textbook and multiple experiences from the NIH Collaboratory (31–33). Additionally, the Veterans Affairs health care system has recently introduced the capability to randomize patients in its EHR, called the Computerized Patient Record System. Two ongoing trials are enrolling patients and conducting follow-up via the Computerized Patient Record System, and another trial is planned for the near future (34). The Patient-Centered Outcomes Research Institute (PCORI) is also uniquely suited to address these issues, because all stakeholders are engaged and a clinical informatics infrastructure has been established.

PCORI ESTABLISHED A NETWORK OF NETWORKS

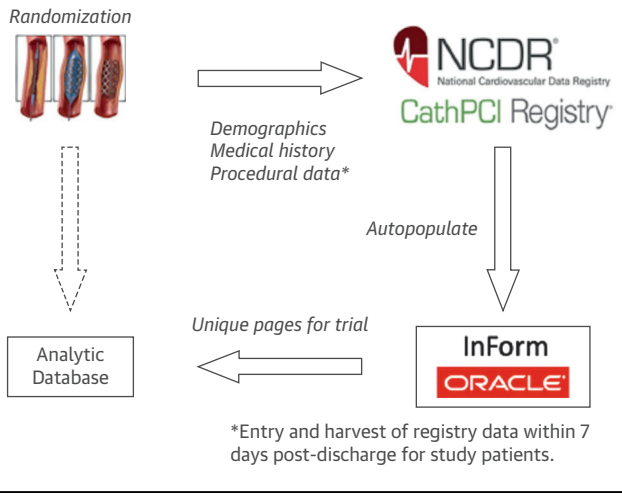
In December 2013, PCORI created a national clinical research network (Patient-Centered Outcomes Research Institute's National Patient-Centered Clinical Research Network [PCORnet]) comprised of 20

patient-powered research networks and 13 clinical data research networks (CDRNs), with engagement of health systems, hospitals, and ambulatory sites across the United States (35). The objective of PCORnet is to create a national research infrastructure that engages patients, clinicians, and health systems, and which leverages EHRs, administrative claims data, and data directly from patients to more efficiently conduct high-quality clinical research. Ultimately, the vision for PCORnet is to conduct widely generalizable observational studies and to support clinical trials at relatively low cost. By implementing available clinical data generated during routine care and ascertaining clinical endpoints via administrative claims data, patient reports, and EHRs, large groups of patients can be recruited quickly and followed over time, across health systems and networks.

ADAPTABLE: A PCORnet PRAGMATIC CLINICAL TRIAL

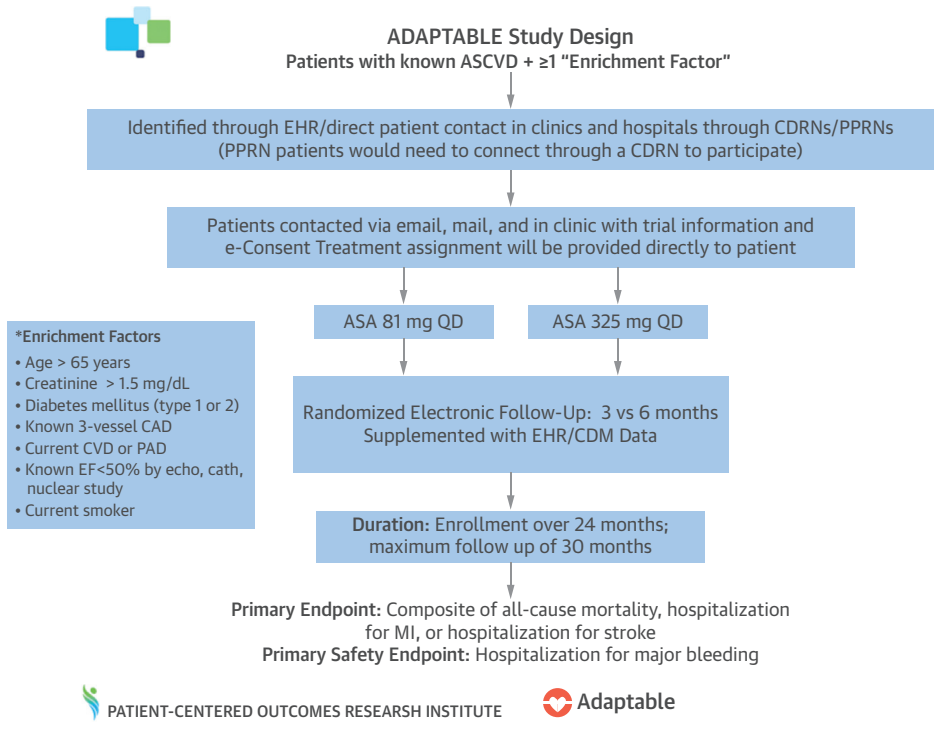
The first pragmatic RCT that will be conducted using the PCORnet infrastructure is called ADAPTABLE (Aspirin Dosing: A Patient-centric Trial Assessing the Benefits and Long-term Effectiveness) (**Figure 2**) (36–38). A patient leadership group, the Adaptors, were involved in the protocol design, and serve as members of the trial steering and executive committees. The study will enroll 20,000 subjects with established coronary heart disease, who will be randomly assigned to low-dose (81 mg daily) or high-dose (325 mg daily) aspirin therapy; relatively few exclusion criteria are applied to increase generalizability. PCORnet created a structured data platform (the PCORnet Common Data Model) that ADAPTABLE will use to organize data from the various hospitals and health systems into a consistent and usable format. This data infrastructure enables rapid queries of large datasets to answer research-related questions. Each CDRN in ADAPTABLE will query data from the Common Data Model in each of its health systems as a means of screening for potential participants using a combination of administrative claims codes and clinical documentation of atherosclerotic cardiovascular disease (e.g., prior MI, prior PCI, prior coronary artery bypass graft surgery, and presence of ≥70% epicardial coronary artery stenosis). Potential candidates for enrollment will be identified and will then be approached through multiple conventional (i.e., contact during clinic visits) and electronic (i.e., e-mails to patients or contact via the EHR system) means. Informed consent, randomization, and assessments of patient comprehension will occur via direct patient interaction and completion on an online portal (**Figure 3**). Follow-up will not occur via traditional means; rather, patients will receive electronic reminders to complete case report forms in the portal. Those unable to participate electronically or who miss 2 consecutive electronic visits will be contacted by telephone by the Duke Clinical Research Institute call center. During the course of the study, patients will be randomized to follow-up every 3 months versus every 6 months, and they will be asked to record the dosage of study medication, concomitant medications, and any hospitalizations that have occurred since the last interaction. Ascertainment of clinical endpoints will occur by: 1) direct patient entry of endpoints and hospitalizations on the internet portal; 2) queries of administrative and clinical data within each CDRN for cause-specific hospitalizations with International Classification of Diseases, 10th Revision codes for nonfatal endpoints, such as MI, stroke, and major bleeding using the Common Data Model; 3) queries of linked administrative claims data from Medicare and private health plans for cause-specific hospitalizations with International Classification of Diseases, 10th Revision codes for nonfatal endpoints, such as MI, stroke, and major bleeding; and additionally, 4) the Social Security Administration and National Death Index to

FIGURE 1 SAFE-PCI for Women Data Workflow



The data workflow in the SAFE-PCI (Study of Access Site for Enhancement of PCI) for Women study included autopopulation of the electronic case report forms (e.g., demographic, medical history, and procedural characteristics) in Inform (Oracle Corporation, Redwood City, California) using CathPCI registry data. Additional, trial-specific electronic case report forms were then entered directly into Inform, and this was integrated along with the CathPCI registry into the trial analytic database. NCDR = National Cardiovascular Data Registry.

FIGURE 2 ADAPTABLE Study Design

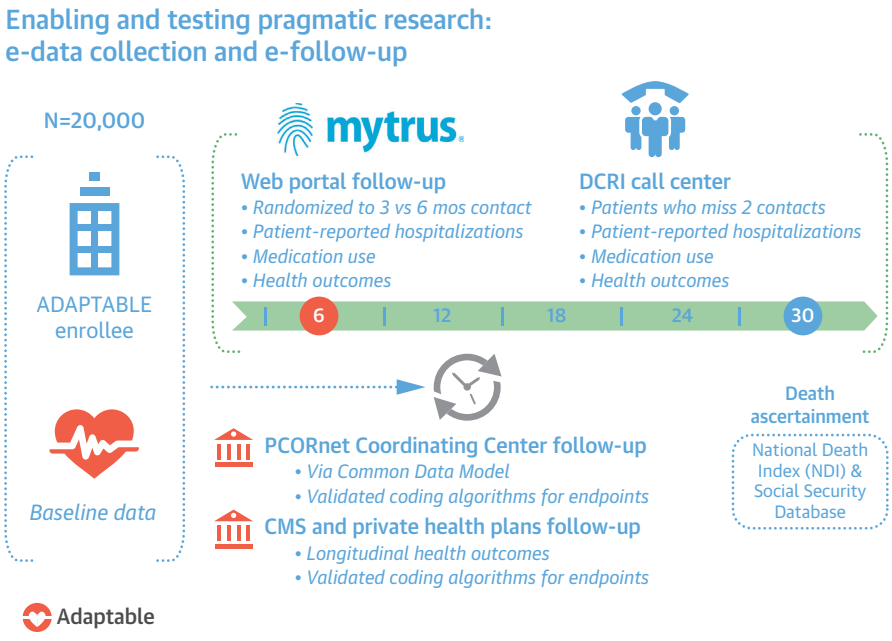


Pictured is the main ADAPTABLE (Aspirin Dosing: A Patient-centric Trial Assessing the Benefits and Long-term Effectiveness) study design, depicting the inclusion and exclusion criteria for the ADAPTABLE trial. A total of 20,000 patients with known atherosclerotic cardiovascular disease and ≥1 enrichment criteria will be identified via electronic and traditional means. Patients are randomized into the study via the electronic patient portal, and treatment assignment is provided directly to the patients that qualify for randomization. The primary efficacy endpoints and the primary safety endpoint are listed at the **bottom of the figure**. ASA = acetylsalicylic acid; ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; cath = catheterization; CDM = Common Data Model; CDRN = clinical data research network; CVD = cardiovascular disease; echo = echocardiography; EF = ejection fraction; EHR = electronic health record; MI = myocardial infarction; PAD = peripheral artery disease; PPRN = patient-powered research network; QD = daily.

ascertain deaths. Patient-reported hospitalizations will then be linked with hospitalizations from the Common Data Model and administrative claims data sources; those patient-reported hospitalizations that do not correlate with hospitalizations from these sources will be further investigated by the Duke Clinical Research Institute call center for source documents and clinical details. Few prior reports describe ascertainment of endpoints via these clinical- and claims-based analytic algorithms (39-41). As such, a validation plan to adjudicate a random sample of nonfatal endpoints in a blinded manner will evaluate the concordance of endpoint identification (via the methods used) and traditional adjudication using review of source documents by expert reviewers.

In performing ADAPTABLE, PCORnet and its partners will implement novel approaches to clinical research and will concurrently measure if and how each approach works. Whether these approaches (e.g., patient identification via the Common Data Model, direct entry of patient-reported outcomes, and endpoint ascertainment via queries of Common Data Model and administrative claims datasets) will be comparable to methods used for traditional trials will remain in constant focus during ADAPTABLE. Data completeness, data quality, and patient withdrawal will be measured and compared with large traditional clinical trials. Given the equipoise that exists regarding the dosage of aspirin for secondary prevention and the extreme variation in dosing that has recently been observed in clinical practice, it is an opportune time to answer this routine but important clinical question (42,43). The commitment from PCORI to perform this demonstration project of aspirin dosing and to test the capacity of the PCORnet infrastructure and engagement of patients, clinicians, and health systems to provide evidence indicates that the world is ready to move into this new era of clinical trials.

FIGURE 3 **ADAPTABLE Data Flow and Follow-Up**



The figure depicts how patients will be engaged throughout the study. Patients will directly log into the patient internet portal or be contacted by the Duke Clinical Research Institute (DCRI) call center at intervals of 3 or 6 months. During these encounters, patients will be asked about prior hospitalizations, health status, and concomitant medication use (including dosage of study medication). Ascertainment of cause-specific hospitalizations with International Classification of Diseases, 10th Revision codes for nonfatal endpoints, such as MI, stroke, and major bleeding, will be performed via queries of administrative and clinical data (i.e., the CDM) within each CDRN, and linked administrative claims data from Medicare and private health plans. Death status will be ascertained by routine queries of the Social Security Administration and National Death Index. CMS = Centers for Medicare & Medicaid Services; PCORnet = Patient-Centered Outcomes Research Institute's National Patient-Centered Clinical Research Network; other abbreviations as in **Figure 2**.

THE PATH FORWARD

Technical advances create both opportunities and responsibilities for cardiologists and cardiovascular professional societies to transform the culture of clinical trials in the United States. Innovations such as the use of registry-based trials and development of national research networks create an increasingly sound foundation for pragmatic trials and allow for refinement and adaptability, as lessons are learned and processes are developed. Registry-based trials, such as TASTE and SAFE-PCI for Women, and large, pragmatic trials, such as ADAPTABLE, have demonstrated that many barriers to trial conduct can be addressed. However, implementing the upcoming changes to the Common Rule into clinical research practice (e.g., improving patient comprehension of informed consent, and using a single, central IRB instead of multiple, independent IRBs), and achieving other critical goals (e.g., engaging patients and investigators, maintaining high levels of patient follow-up, and reducing costs) remains an important challenge. In addition to these challenges, regulatory agencies, such as the FDA, have consistently asked for more data and absolute precision in trial conduct, and it remains to be seen whether large, pragmatic trials will be accepted in regulatory submissions for pharmaceutical and device approval. Putative concerns for large, pragmatic trials that use EHR data include: 1) a high rate of patients lost to follow-up and/or incomplete endpoint ascertainment; 2) inaccurate and/or incomplete data collection from the patient portal; and 3) a potentially higher occurrence of protocol violations (e.g., patients being incorrectly identified by the computable phenotype and included in the study).

As has been discussed in this review, developing the capacity to conduct large, efficient pragmatic trials will require all stakeholders to understand the importance of this transformation and its potential positive effect on the routine practice of medicine in the coming decades. Given the rich tradition of

randomized trials in cardiology, cardiovascular specialists are uniquely positioned to provide leadership and build relationships among the broad range of stakeholders to achieve this transformative objective.

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KEY WORDS aspirin, coronary artery disease, Patient-Centered Outcomes Research Institute, pragmatic clinical trial