Circulation: Cardiovascular Quality and Outcomes

FRONTIERS IN CARDIOVASCULAR QUALITY AND OUTCOMES

Improving Cardiovascular Drug and Device Development and Evidence Through Patient-Centered Research and Clinical Trials

A Call to Action From the Value in Healthcare Initiative's Partnering With Regulators Learning Collaborative

ABSTRACT: The pipeline of new cardiovascular drugs is relatively limited compared with many other clinical areas. Challenges causing lagging drug innovation include the duration and expense of cardiovascular clinical trials needed for regulatory evaluation and approvals, which generally must demonstrate noninferiority to existing standards of care and measure longer-term outcomes. By comparison, there has been substantial progress in cardiovascular device innovation. There has also been progress in cardiovascular trial participation equity in recent years, especially among women, due in part to important efforts by Food and Drug Administration, National Institutes of Health, American Heart Association, and others. Yet women and especially racial and ethnic minority populations remain underrepresented in cardiovascular trials, indicating much work ahead to continue recent success. Given these challenges and opportunities, the multistakeholder Partnering with Regulators Learning Collaborative of the Value in Healthcare Initiative, a collaboration of the American Heart Association and the Robert J. Margolis, MD, Center for Health Policy at Duke University, identified how to improve the evidence generation process for cardiovascular drugs and devices. Drawing on a series of meetings, literature reviews, and analyses of regulatory options, the Collaborative makes recommendations across four identified areas for improvement. First, we offer strategies to enhance patient engagement in trial design, convenient participation, and meaningful end points and outcomes to improve patient recruitment and retention (major expenses in clinical trials). Second, new digital technologies expand the potential for real-world evidence to streamline data collection and reduce cost and time of trials. However, technical challenges must be overcome to routinely leverage real-world data, including standardizing data, managing data quality, understanding data comparability, and ensuring real-world evidence does not worsen inequities. Third, as trials are driven by evidence needs of regulators and payers, we recommend ways to improve their collaboration in trial design to streamline and standardize efficient and innovative trials, reducing costs and delays. Finally, we discuss creative ways to expand the minuscule proportion of sites involved in cardiovascular evidence generation and medical product development. These actions, paired with continued policy research into better ways to pay for and equitably develop therapies, will help reduce the cost and complexity of drug and device research, development, and trials.

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Biomedical innovation in cardiovascular care is important given the significant burden of cardiovascular diseases (CVDs) in America. Over 18 million people have CVD; CVDs cause roughly a quarter of deaths nationally,[1,2] and unmet need remains in CVD care (especially risk reduction[3]). Furthermore, there are significant sociodemographic inequities, with older adults, those with lower education, racial or ethnic minority groups, and rural residents disproportionately affected. For example, individuals living in rural settings have higher age-adjusted CVD death rates relative to urban counterparts.[4–9]

The pipeline of new cardiovascular drugs in the United States is relatively limited compared with many other specialties, partially due to the complexity and cost of evidence generation.[10] There has been substantial growth in the pipeline for cardiovascular medical devices, however, with products for minimally invasive surgery, heart health tracking, interventional products for restoring heart rhythm and reviewing blockages, and wearables.

Although drugs and medical devices are approved under different regulatory regimes and face different evidence generation challenges, both could benefit from increased patient participation in clinical trials and patient engagement in clinical trial design and end point selection, better leveraging real-world evidence, ensuring clinical trial evidence meets the needs of regulators and payers, and expanding the number of health care organizations involved in clinical trials.

Many of these issues are broad-based challenges for all stages of drug and device research, development, and trials—but cardiology may be poised to address them with population health impact. First, given that CVD is the leading cause of death and significantly affects quality of life for years before death, cardiology is an impactful testbed for population-level improvements in drug and device research, development, and clinical trials. Second, cardiology is well-suited to capitalize on data generation capabilities of current digital technology. Smartphones, for example, are widely (and relatively equitably) available.[11] Although they have limited ability to generate clinically meaningful data in most medical fields, they can capture data relevant to cardiology (eg, physical activity tracking, heart rate, rhythm monitoring).

This article describes the efforts and vision for improving the cardiovascular medical product pipeline of the Partnering with Regulators Learning Collaborative of The Value in Healthcare Initiative,[10] a collaboration of the American Heart Association (AHA) and the Robert J. Margolis, MD, Center for Health Policy at Duke University. The Learning Collaborative is comprised of diverse stakeholders: patients, clinicians (including cardiologists), health systems, clinical research organizations, academia, government, professional associations, payers, and industry.

The Collaborative developed short- and long-term recommendations (summarized in Tables 1 and 2) to expand cardiovascular drug and device innovation by improving the clinical research and clinical trial process. To do so, they reviewed peer-reviewed and gray literature, analyses of regulatory options, and insights from the expert multistakeholder Collaborative. The recommendations center on improving patient engagement and patient-centeredness of trials; expanding use of real-world evidence (RWE), ensuring trial evidence meets the needs of multiple stakeholders, including regulators and payers; and expanding the network of health care organizations participating in cardiovascular clinical research.

UNEVEN STATE OF CARDIOVASCULAR DRUG AND DEVICE INNOVATION AND EVIDENCE GENERATION

The stark contrast between therapeutic development for CVD and cancer, the leading and second leading causes of death nationally, exemplifies CVD's lagging pipeline. Fewer than 8% of ≈7300 drugs in development in the United States in 2017 addressed cardiovascular conditions.[10,12] From 1996 to 2015, only 40 cardiovascular-related substances entered the market compared with 110 new oncological substances. Overall development of oncology-focused drugs or biologic products was nearly 7× greater.[10,13,14]

Lagging drug innovation is partially due to challenges in evidence generation. One estimate put the cost of a single, pivotal cardiovascular clinical trial at $157 million—6× most other disease areas.[15] Moreover, there is a high chance the product will not make it to market; one study estimated only 1 in 4 cardiovascular drugs that make it to phase 1 trials are approved by the Food and Drug Administration (FDA).[16]

Cardiovascular evidence generation is more expensive than other specialties for several reasons. Their clinical trials require longer timeframes, more substantial data collection, and a larger number of participants relative to most other fields.[10,17,18] Many promising intermediary cardiovascular outcomes and biomarkers have failed to accurately predict clinical outcomes (even validated biomarkers for blood pressure and cholesterol are not good predictors of treatment side effects).[19] Additionally, because in many cases there are beneficial treatments already on the market, trials must demonstrate noninferiority or superiority to current standards of care (often requiring longer, multi-arm trials) in addition to standard requirements of safety and efficacy compared with no treatment to qualify for additional payment. Some evidence suggests that cardiovascular trials are beginning to leverage more pragmatic trial methods,[20] but high costs are still normal.

In contrast to the drug pipeline, investment in medical devices for cardiovascular use has grown substantially.

Table 1. Short-Term Actions to Improve the Research and Trial Process for Cardiovascular Drugs and Devices

Establishing a more collaborative and inclusive research process
Conceptualizing and realizing opportunities for patient involvement. The FDA should recommend industry's pretrial Research and Development design include patients from a variety of backgrounds and perspectives.
Ensuring outcomes used in end points are meaningful to patients.
The FDA's PFDD should expand its reach to multiple cardiovascular conditions.
The AHA should build from PFDD infrastructure to create its own patient-centered cardiovascular therapy development forum.
Using new tools to enable convenient recruitment and participation. The AHA and FDA should focus their trial innovation convening efforts on how equitable use of technologies, including smartphones, wearables, and artificial intelligence, may streamline diverse participant recruitment and accessible "site-less" cardiovascular trials.
Expanding the research community network. The AHA should work to identify and actively connect community-based organizations, including patient advocacy groups, to the investigators, health systems, and hospitals participating in trials and expand their availability in underserved areas.
Developing a cardiovascular core outcome set. The AHA should work with FDA to build from the Clinical Outcome Assessment Compendium and develop a cardiovascular core outcome set.
Allowing patients to own, use, and share their trial data. The AHA and FDA should operationalize sharing trial data with patients, including bring your own device designs.
Leveraging real-world evidence and data to improve biomedical innovation
Using technology and real-world data to assess and improve currently licensed cardiovascular drugs and devices.
The AHA and FDA should focus their trial innovation convening efforts on how to use technology and patient data to streamline and enhance phase IV studies' patient-centricity.
The NHLBI should fund implementation science studies on cardiovascular therapy adherence, including strategies related to decision aids and communicating risks and benefits.
The FDA should provide guidance on equitable use of smart devices and other personal technologies in trials, which may include the direct provision of devices to patients.
Standardizing cardiovascular real-world data. The AHA and FDA should develop clear guidelines for obtaining and analyzing cardiovascular real-world data and transforming them into real-world evidence acceptable in cardiovascular clinical trials.
Ensuring clinical trials meet the evidence needs of regulators and payers
Including industry and researchers in trial design innovation.
The FDA/CDER should develop a forum similar to FDA/CDRH's Payor Communication Task Force where stakeholders can get feedback on a new drug submission.
The AHA should create a regular convening for industry, researchers, and other stakeholders to meet with the FDA and other regulators affecting research or implementation (eg, NIH, Centers for Medicare & Medicaid Services). This convening may focus on barriers to innovation and ideas for innovative design and may not be specific to a particular therapy application.
Creating cardiac research collaboratives of excellence
Better capturing trial successes by creating cardiac research collaboratives of excellence. The AHA should work with the NHLBI to create a program to recognize regional collaboratives of clinics, health systems, community-based organizations, and other relevant stakeholder groups with a demonstrated track record of successful cardiovascular trials.
Engaging a broader network of providers in research by creating a community cardiovascular research program. The AHA should create a research network to boost provider engagement in cardiovascular clinical trials, with a focus on community-based providers and underserved populations (similar to the National Cancer Institute's Community Oncology Research Program).

AHA indicates American Heart Association; CDRH, Center for Devices and Radiological Health; FDA, Food and Drug Administration; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; and PFDD, Patient-Focused Drug Development.

The global market for cardiovascular devices is expected to expand from $42.4 billion in 2017 to $59.1 billion in 2022,[21] and[22] potentially $121 billion by 2024, driven primarily by surgical, diagnostic, and monitoring devices.[23] Hundreds of premarket approvals[21] and 510(k) clearances were filed in 2019. Continued innovation in minimally invasive surgery,[24] advances in electronic and digitally enabled devices, and smart wearable devices and other technologies to measure cardiac function[25] all drive development.

Additionally, significant evidence generation over the past decade has fueled the robust medical device pipeline. Data on clinicaltrials.gov as of early 2020 show a steady increase in cardiovascular device trials: 147 in 2010, 233 in 2015, and 253 in 2019. In 2015 alone, 115 randomized control trials investigating effects of therapeutic cardiovascular medical devices were published in academic journals.[26] Additionally, strong patient registries, most often funded privately by academic institutions,[27] contribute to the depth of opportunity for research and investment.

INNOVATION CHALLENGES FOR CARDIOVASCULAR DRUGS

Patient participation in cardiovascular trials is low.[28] One study found trial participation by eligible acute myocardial infarction patients in a national registry declined from 5.2% in 2008 to 3.4% in 2011,[29] and another of

Table 2. Long-Term Strategies to Improve the Cardiovascular Drug and Device Pipeline

Establishing a more collaborative and inclusive research process
Conceptualizing and realizing opportunities for patient involvement. The NIH (particularly NHLBI) should have a diverse committee of patients advise their grant offerings for patient-centric research.
Ensuring outcomes used in end points are meaningful to patients.
The NIH (especially NHLBI) and other funders should support research to develop patient-centered cardiovascular outcomes for use in trials.
Existing cardiovascular registries (eg, for hypertension) should capture patient-centered and patient-generated health data.
Leveraging real-world evidence and data to improve biomedical innovation
Using technology and real-world data to assess and improve currently licensed cardiovascular drugs and devices.
The NHLBI should dedicate research funding to learn how to use smartphones, wearables, artificial intelligence, and other technologies to improve medication adherence and uptake of current cardiovascular drugs and devices, especially in underserved populations.
The FDA should place a higher weight on patient-centered end points and quality of life metrics in all clinical trial phases.
Standardizing cardiovascular real-world data. The NHLBI should dedicate research funding for implementation science studies to learn to scale interventions directly importing cardiovascular data from patients' third-party apps into electronic health records for clinicians and into trial portals as evidence.
Developing innovative, affordable, and equitably available personal technologies for cardiovascular trial use. The AHA and FDA should focus longer-term trial innovation efforts on working with industry and technology companies to encourage production of inexpensive wearables/smartphones capable of biometric data collection.
Creating cardiac research collaboratives of excellence
Expanding the research community network.
The FDA should consider stronger and broader recommendations that women and racial and ethnic minorities be equitably included in trials.
The AHA and FDA should focus longer-term trial innovation convening efforts on how to make recruitment, participation, and retention more equitable and culturally competent, including how to build better trust in the medical and research establishment, and how to better include underserved rural and urban community settings.

AHA indicates American Heart Association; FDA, Food and Drug Administration; NHLBI, National Heart, Lung, and Blood Institute; and NIH, National Institutes of Health.

the same population has even lower estimates, most recently 0.8% participation through 2014.[30] Enrollment is especially limited for high-risk groups such as elderly and rural patients[31,32] because these groups face multiple logistical barriers to participating in trials.

Low patient participation can also lead to unmet enrollment targets, which can contribute to the failure of a trial, either from a lack of participants or the inability to demonstrate efficacy due to a small sample size.[33] For example, in the AleCardio trial (a large, international, phase III cardiovascular clinical trial), only 18.2% of sites met enrollment targets, and 10% closed before the end of recruitment, mostly because they failed to enroll a single patient.[34] The trial was ultimately terminated when a futility analysis showed it was subsequently unlikely to prove clinical efficacy.[35]

One explanation for low rates of patient participation may be limited clinician engagement. Another is lack of hospital and health system participation in clinical trials (only about 5% of acute care hospitals consistently participate in clinical trials[36]), with many hospitals not properly trained in conducting clinical research.[30]

Low patient participation may also reflect limited patient engagement in development of the trials themselves. For example, patients and families are often not involved in developing the trial operational plan to help ensure trial procedures are convenient for patients. Patients are often interested in how therapies may affect quality of life,[37] but this information is often not represented in trial end points.

ESTABLISHING A MORE COLLABORATIVE AND INCLUSIVE RESEARCH PROCESS

The current biomedical research paradigm is based on the need to prompt and answer questions of scientists, payers, clinicians, and regulators, among others. Patients are often less involved but have important perspectives and experiences that must be leveraged in the development and design of clinical trials to improve patient participation in trials and the meaningfulness of trial results. Patient perspectives can be captured on multiple topics, including informed consent, study procedures, end points and outcomes, publication, approval, and evaluation (summarized in the Figure). By identifying opportunities to improve patient recruitment and continued participation, overall trial costs may decline, as patient recruitment is a major expense. Below, we discuss challenges, barriers, and potential solutions to move the research enterprise to a multistakeholder, patient-centric research process.

Better Inclusion of Diverse Patient Populations in Clinical Trials

Opportunities exist to increase diversity of clinical trials, whether by sex, racial and ethnic minorities, rural residents, or other dimensions.[9,39–44] Sex diversity is especially important given that biological sex influences

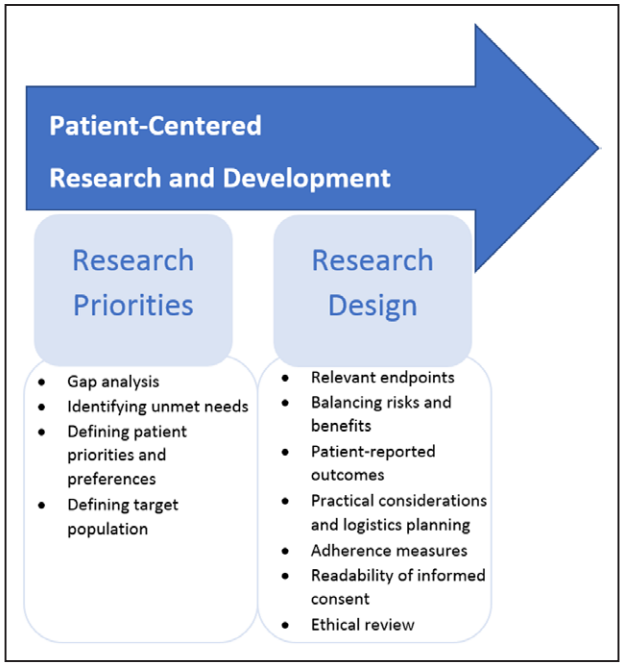

Figure. Areas for patient involvement in early-stage research of drugs and devices.
Guided by Geissler et al,[38] we highlight pretrial opportunities for patient involvement in the therapy research and development process. These opportunities were emphasized in Learning Collaborative discussions.

pharmacodynamics and pharmacokinetics, an emphasis reinforced by the National Institutes of Health (NIH) Revitalization Act of 1993.[45] Enrollment of women in cardiovascular trials has improved in recent years. For example, in 2018, 56% of the approved drug trial populations were women, although no cardiovascular indications were approved in this time period.[46] However, some research suggests clinical trial participation and analysis by sex could be improved. One study found that from 2011 to 2015 only one-third of cardiovascular trial participants were women,[47] and a review of clinical trials from 2005 to 2015 found women were significantly underrepresented in trials for heart failure, coronary artery disease, and acute coronary syndrome when compared with overall disease burden for women.[40] Of the 10 cardiovascular indications approved by FDA in 2015, 2 trials did not report efficacy statements on sex,[48] and 8 had study populations of <50% women.[49] Thirty percent of premarket approval supplement applications for high-risk medical devices do not report sex for all enrolled patients.[50] Of 11 cardiovascular devices approved by FDA's Center for Devices and Radiological Health (CDRH) in 2011, 10 had fewer than 50% female participation, with as little as 18% women in an endovascular occlusion device study.[51]

Several initiatives and groups, such as Research Goes Red, the FDA's Office on Women's Health, and the NIH's Office of Research on Women's Health, have greatly advanced women's representation in clinical cardiovascular research.[43] Research Goes Red empowers women to participate in clinical trial data collection by taking part in surveys, focus groups, and testing new tools and technologies.[52] Participants are also alerted when new studies open up meeting their preferences.[53]

Racial diversity in clinical trials has also significantly improved over time but racial and ethnic minorities are still underrepresented. In 2011, black patients, although 12% of the population, made up only 5% of participants[54–56] but has grown steadily to 7% in 2016 and 2017 to 11% in 2018.[46,49,57] Additionally, Hispanic representation over this time period increased from 4% in 2015 to a consistent 14% in 2017 and 2018.[46,49,57] Yet for some of these years, most or all of the studies for approved cardiovascular products still underrepresented black patients and did not report Hispanic representation.[49,51] There is still work to be done.

Cultural competency can greatly improve patients' trust in the medical establishment, interest in research participation, and retention in studies. For example, barbershop interventions have proven effective at increasing awareness and participation in members of black communities.[58] Studies in Hispanic communities have supported participation with Spanish-speaking investigators, advertising at churches, hair salons, and grocery stores, and speaking with families.[59] However, trust in the medical establishment and the research process, especially given the historical context of exploitative unethical studies, remains low.[60–62] Reconsiderations of patient motives and barriers to trial participation are needed, as well as a more robust suite of incentives to ethically encourage informed participation.

The AHA and the FDA should continue and expand their efforts to encourage equitable and culturally competent trial participation and recruitment opportunities. Engaging patients diverse in sex, race, and ethnic background in trial design may achieve the accessibility and cultural competency needed to draw a more diverse group of trial participants. The FDA should recommend industry's pretrial Research and Development designs to include patients from a variety of backgrounds and perspectives, especially those from underserved communities, as advisors at all points in the pretrial process.

Engaging Patients in Trial Design

Traditional approaches to clinical trial recruitment tend to be centered around convenience of the trial investigators and health institutions, not potential trial participants.[63] These approaches rely on identifying potential participants when those individuals come into contact with the health care environment (eg, during medical appointments) instead of reaching out directly to communities and neighborhoods of potential participants.

When patients and families are involved in developing a trial's operational plan, they can highlight potentially burdensome processes limiting enrollment, and

identify solutions ensuring people can take part in the trial's requirements. This is important as trial participation frequently requires individuals taking time away from their daily lives for various trial-related activities (eg, completing trial-related paperwork, gathering pertinent information on the potential therapy and trial, traveling to and from appointments for data collection). The frequent lack of support for transportation, appointment coordination, and child care limits who may participate and leads to smaller and less diverse study populations.

Although patient engagement can improve overall trial recruitment, it is especially important for improving diversity of recruited patients, which, in turn, generates evidence that can drive new treatments effective in underrepresented groups. For example, older adults' health status may make long trial-related activities uncomfortable and unfeasible. Many techniques for recruiting diverse study populations may also apply in reaching those willing to contribute to trial design. For example, engaging with patients at community centers like grocery stores and barbershops may reach patients from previously underrepresented groups that may contribute to defining study priorities and protocols.

Using New Tools to Enable Convenient Recruitment and Participation

Digital technologies can also enable less burdensome trial participation. For example, internet access enables flexibility for participants, which can reduce patient burden and inconvenience and increase trial retention. Recent technological advancements in the cardiology space, such as the ability to collect biometric data with smartphones, Amazon's Alexa having access to health information, targeted Facebook recruitment ads, and eCohort approaches offer unique routes for research recruitment and screening.[64–68] These improvements allow for site-less trial recruitment and participation that is convenient for patients and removes barriers to joining and completing a study. For geographies where internet access is limited or unavailable, trials should consider how to enhance access or develop alternative approaches to using these tools (eg, use smartphones for collecting and storing data, but data transfer to trial staff would occur at in-person appointments).

New technologies can also play a role in patient recruitment to trials. Artificial intelligence applied to clinical settings, especially in patient screening and participant enrollment, can help identify appropriate subjects and increase screening by almost 15% and enrollment by 11%.[69,70] Continuing to build these capabilities is important for identifying potential trial subjects and targeting direct outreach for recruitment. Of note, all strategies involving new technology and its data must be implemented alongside meaningful steps to address patient privacy and security of health information.

Beyond technology, patient recruitment can be improved by partnering with community-based organizations (including patient advocacy groups) to identify potential participants and by partnering with investigators to reach individuals who may not normally be accessed using traditional recruitment methods. Creative messaging approaches could inspire patients to be Clinical Trial Patient Heroes. The AHA may facilitate this work in conjunction with health systems, universities, and investigators conducting cardiovascular trials. This approach could help identify, leverage, and connect an existing base of activated and engaged patients to trials and provide supports that enable participation (eg, transportation, child care, peer network). Such supports would be particularly helpful in ensuring individuals from underrepresented, often high-risk, groups are able to participate.

Allowing Patients to Own, Use, and Share Trial Data

Participation in a clinical trial typically generates large amounts of patient data, yet sharing this data with patients is not standard practice. Communicating study results to participants alone is not sufficient, as valuable health information (such as lab or test results) are also generated through participation. Patients have expressed desire to record and save their data during and after a clinical trial.[71] Allowing for data-sharing back to patients may increase interest in trial participation and improve the patient experience.

Ensuring Trial End points Are Meaningful to Patients

Patient insights can improve products' value and usefulness to patients,[72] such as through outlining gaps in research, explaining perceptions of risks and benefits, and highlighting end points important to patients. Patients are uniquely qualified to describe their own experiences and can provide regulators and researchers with information that communicates the impact of conditions and treatment on their lives, goals, and priorities.[73] Patient-centered research also has practical value. If a drug or device does not address the problems most important to patients, they will be less likely to use it. For example, 92% of cardiovascular patients believe that medication adherence would improve if patients helped design clinical trials.[74]

Research has identified end points important to patients for cardiovascular conditions. For example, most cardiovascular patients prioritize heart attack as a more important end point than death by any cause

other than heart disease (a more common study end point) and perceive stroke as more detrimental than chest pain hospitalization or angioplasty (more common study end points).[74] Additional examples include prevention of a major stroke causing permanent disability was viewed as more important than prevention of death within 24 hours postintervention and redoing coronary artery bypass graft surgery was preferred over having recurrent angina.[75] Traditional end points (such as death and hospitalizations) are still important to both patients and clinicians, but additional end points can capture the range of outcomes meaningful to patients.

Patient-reported outcome measures may capture the most meaningful end points to patients. For example, to illustrate the meaningful effects of an intervention, heart failure trials could include the following patient-reported outcomes: physical interaction, social interaction, sexual activity, life dissatisfaction, somatic symptoms, self-efficacy, and psychological state.[76] Additional research should develop and validate more patient-reported outcome measures to be used in clinical trials.

A relevant example of how to systematically identify key end points important to patients comes FDA efforts related to patients with heart failure with preserved ejection fraction. Heart failure with preserved ejection fraction causes significant functional capacity impairment and quality of life impact far beyond the risk of traditional clinical end points of death and hospitalization. The FDA convened patients to develop patient-focused alternative end points for heart failure with preserved ejection fraction studies and identified more meaningful outcomes to include in trials, such as the 6-minute walk test.[77]

Patient convenings, organized by the FDA, AHA, or other key organizations, can identify patient-centered end points that may shape development of cardiovascular studies and products. Such convenings have been expanded as part of the FDA's Patient-Focused Drug Development effort, which seeks to provide a "systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation."[78] Meetings convened under this initiative have focused on the impact of patients' conditions on their daily life, their most significant symptoms, and their current approaches to treatment.[73] To enhance the patient perspective, the AHA and other stakeholders may advocate for more cardiovascular conditions to be included in this formal infrastructure (thus far, pulmonary arterial hypertension has benefited from this type of structured inclusion in drug and device research and development).[73] Alternatively, the AHA may convene forums exclusively focused on patient-centered cardiovascular therapy development.

The routine and feasible collection of new patient-report end points in clinical trials is also critical. Ensuring consistent collection of these data may be achieved through multiple approaches. For example, FDA publishes a COA (Clinical Outcome Assessment) Compendium as a resource for identifying patient-focused outcomes for clinical trial design, which currently contains more than a dozen cardiovascular-related clinical outcomes.[79] Similarly, the COMET (Core Outcome Measures in Effectiveness Trials) Initiative is a collaborative effort to compile core outcome sets that could provide a backbone to cardiovascular trial design.[80]

In the short term, we recommend building on the Compendium and COMET Initiative to identify a core set of cardiovascular outcomes (including patient-reported outcomes, clinician-reported outcomes, observer-reported outcomes, and performance outcomes) meaningful to multiple stakeholders, especially patients. The FDA recently convened a public meeting in partnership with the American Society of Clinical Oncology for cancer clinical trials that built off of prior workshops to discuss core outcome sets[81]; the AHA could work with the FDA to develop a similar workshop focused on CVD. Such a core outcome set may standardize patient-centered cardiovascular information collected in clinical trials, and facilitate clear comparisons across therapies. Furthermore, if important patient-centered concepts are included in core outcome sets, it would make their collection more routine in clinical practice.

LEVERAGING RWE AND DATA TO IMPROVE BIOMEDICAL INNOVATION

The traditional clinical research paradigm has advanced our understanding of cardiovascular conditions and effectiveness of various interventions. However, it is also time-consuming, expensive, and limited in ability to describe effects in real-world settings. RWE and real-world data (RWD) can help overcome these challenges, and using personal devices to do so is an exciting opportunity in the cardiovascular trial space.

There are practical issues in using RWE and RWD for regulatory decisions. Most wearable devices are designed for consumer use, not clinical trial data collection, raising questions about trial appropriateness, data validity, and data security.[82] One short-term opportunity to overcome these challenges is for AHA and FDA to convene stakeholders, especially clinical researchers, on how to use technology and patient-generated health data to simplify and improve existing postmarket surveillance requirements (stage IV clinical trials). In the longer term, the National Heart, Lung, and Blood Institute could dedicate funding for studies on how RWD and RWE may improve medication adherence and uptake of current cardiovascular drugs and devices. These studies should examine how enhanced adherence and uptake methods may need to be tailored to

be effective in high-risk groups or settings with limited resources (eg, rural health clinics or hospitals).

Potential Impact of RWE and Data

Understanding the real-world experience of patients using a drug or device, which may differ from the clinical trial context, is challenging. Patients often struggle to correctly use drugs currently on the market due to issues with adherence, costs, or side effects. For example, 40% to 50% of patients with a chronic condition are nonadherent to medications and cite costs and perceived usefulness of the drugs as barriers.[83,84] Real-world data and evidence may provide a better understanding of the less-than-ideal real-world use of products already on the market while monitoring safety and adverse effects of recently approved medical products.[85–87]

Smartphones, wearables, and other personal technologies may collect data in a convenient and potentially cost-effective way that can be translated into evidence used to improve patient-centeredness of current drugs and devices. As defined by FDA, RWD encompasses "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources," and RWE includes "*clinical* evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD."[88]

Although there are different sources of RWD, there is particular interest in patient-generated health data. Technological advances, particularly in wearables and other personal technologies, offer new mechanisms to facilitate novel data collection and improve patient participation in pretrial Research and Development and clinical trials. Most importantly, these technologies offer unique abilities to improve cardiovascular drugs and devices relative to other medical fields. RWD, such as activity tracking and heart rate and rhythm monitoring, can be relatively easily captured on smartphones. There are opportunities for expanding existing registries by incorporating patient-generated health data. Moreover, new technology could be used to improve data quality in clinical trials, by making data collection more complete or filling in missing data.

Commercial activity trackers (such as FitBit, Apple Watch, etc) are becoming increasingly popular. The consumer-directed wearable technology market presents an opportunity for the use of technology in cardiovascular trials.[89] Cardiovascular care has some history of using wearable technologies in diagnosis and management of disease, although use of consumer-directed wearables in clinical trials is a relatively newer concept. However, innovation in this space is not entirely untested; for example, a recent systematic review identified 127 clinical trials across specialties and research areas that used consumer physical activity trackers.[90] Beyond generating data for trials, wearables-generated data may also be able to inform patients or caregivers of clinical status, adherence to medication, or effects of certain patient actions on health outcomes.[89]

Standardizing Cardiovascular RWD

To make meaningful use of patient-reported data collected by personal technologies, collection and analysis processes must be reliable. There is currently a lack of well-validated, standardized ways to collect and incorporate patient-generated data into drug and device outcomes assessments. The FDA could ameliorate this process by recommending research and development of clear guidelines for obtaining and analyzing cardiovascular data from nontraditional sources in clinical trials. Given the size of the technology market, it will be difficult for the entire technology industry to meet new standards (even minimal ones). Therefore, the FDA and the AHA should work with industry to ensure standards are implementable and identify practical strategies for overcoming limited standardization. Implementation science can be used in conjunction with this research to generate and employ a toolkit of best practices.

Streamlining the development and review process necessitates platforms that enable patients and their data to be brought together efficiently. Despite challenges, there are tools that use standard data formats (eg, Fast Healthcare Interoperability Resources) to directly import data from third-party apps (ie, on smartphones) into electronic medical records for clinicians to see.[91]

Data Quality, Completeness, and Comparability

Increasing usage of bring-your-own-device trial designs could allow for easier evidence generation by leveraging the increasingly prevalent ownership of smart devices. In these trials, patients use their phone, tablet, or other devices to enter data and retain access to their data after trial conclusion. Patients often prefer these methods, which may result in more complete data and lower costs.[92–94] However, data quality and comparability of technical data are challenges requiring additional research. Moreover, this trial design can limit the eligible patient population as patients are required to have a device meeting certain technical requirements.[95] Further guidelines are needed to ensure bring-your-own-device trials are conducted in ways that address data quality, comparability, and equity challenges.

Data completeness is another challenge when solely using smartphones to conduct clinical trials. For example, patients enrolled in the MyHeart Counts Cardiovascular Heart Study used a smartphone-based application to record physical activity, answer health question-

naires, and complete a 6-minute walk test.[96] Of those who consented, 18.3% uploaded no data, and 9.3% completed all 7 days of data collection. In total, only 2.7% completed enough data collection and health questionnaires to compute a 10-year risk score.[96]

Technology and Health Equity

Despite the widespread use of smartphones and other personal technologies, there remains concern that use of these technologies in clinical trials can worsen health inequalities.[97] Variations in access to the internet, smartphones, and other smart devices remain prevalent between age and income groups.[98,99] The use of technology in clinical trials may also provide fewer benefits for certain groups, which could in turn lead to health disparities. For example, underserved populations are more likely to experience challenges in accessing online resources and understanding health information.[100]

If smartphones or other smart device ownership are required for trials, there could be issues in equity as those who are unable to purchase such a device would effectively be barred from trial participation. Smartphones and wearables tend to be expensive; the average US cost of a new smartphone was $363 in 2018. Furthermore, differential ownership and understanding of smart devices by age is a concern.[99,101] Some surveys indicate that only half of those aged ≥65 years own a smartphone, which is particularly important considering the burden of CVD in this age group. Although the prevalence of smart device ownership in all age groups has steadily increased over time, trial designs that utilize these devices will need to ensure equitable representation across age groups. Still, the majority of Americans (81%) own a smartphone, with little difference in ownership between sex and racial groups.[11] Although almost all smartphones allow for patients to input data into apps, only more advanced smartphones include step counters or heart rate and rhythm monitors and can cost around $1000.[102] In addition, new technologies other than smartphones may be needed to maximize potential of using personal devices in cardiovascular clinical trials. The direct provision of devices to trial participants may be necessary in some cases to ensure equitable participation of underserved populations.

ENSURING CLINICAL TRIALS MEET THE EVIDENCE NEEDS OF REGULATORS AND PAYERS

This section focuses on distinct opportunities for how regulators and payers must work together to meet each others' evidence needs and move trial innovation conversations and process upstream.

Partnering With Regulators on New Trial Designs and Protocols

As the cost of trials pushes industry to revolutionize trial design and innovate on study protocols, regulators can partner with professional societies like the AHA to foster innovation in trial design. Regulators' flexibility, commitment to innovation, and willingness to support and accept novel trial designs will determine the extent to which industry can innovate on existing trial protocols.

The FDA encourages industry to interact with FDA early in the process (especially related to patient experience data collection[103]). Furthermore, both the FDA's Center for Drug Evaluation and Research and CDRH have recently released draft guidance or recommendations on how to interact with FDA about complex, innovative trial design, and early feedback on new drug or device submissions.[104,105] For device approvals, CDRH aims to engage device developers, especially small businesses or start-ups, and provide early regulatory assistance through informational meetings and The Q-Submission Program,[105,106] a presubmission program that allows developers to receive formal feedback on specific questions related to product development and the application process.[105] CDRH has also partnered with the National Heart, Lung, and Blood Institute to provide grants to device developers to receive additional regulatory support in the early stages of device development. Additional support can also be found in the FDA Innovation Challenge, which supports development of devices addressing urgent public health issues (eg, opioid use disorder).[107] It is unclear what cardiovascular focused device developers have leveraged these programs, but they represent promising pathways for encouraging greater innovation in device trials. These documents and efforts are helpful in laying out the ways for industry to approach the FDA about appropriate end points and new trial designs, and the guidance should be expanded.

These avenues are limited to new or potentially new applications, however, and industry and researchers are interested in broader, earlier, and more consistent feedback. Additionally, we understand that it will take more than guidance, recommendation, and a new forum to change current practice and encourage new interactions between FDA, payers, and industry. We recommend a systematic, standardized approach to facilitate clear communication between the regulatory and industry arms of cardiovascular Research and Development and trial innovation, independent of an individual case application. One approach could be a regular (1–2× a year) convening for industry, researchers, payers, and other stakeholders in the therapy pipeline ecosystem to meet with FDA and other regulators affecting cardiovascular research or implementation (eg, NIH, Centers for Medicare & Medicaid Services) about bar-

riers to innovation and ideas they are considering for innovative design. To avoid federal advisory committee limitations, the AHA could convene the meetings.

Partnering With Payers to Ensure Appropriate Evidence Is Collected

Traditionally, clinical trials are designed, and their end points selected, to provide detailed information related to safety and efficacy of a product for regulatory decisions and market entry. However, the ultimate use of a medical product will depend on whether it is covered by various public and private payers, and clinical trials often are not designed to provide evidence for coverage decisions. CDRH established a Payor Communication Task Force to help those interested in a new medical device submission get feedback on trial design.[108] This could be a useful vehicle on the drug side, and Center for Drug Evaluation and Research should investigate creating a similar structure.

EXPANDING THE RESEARCH COMMUNITY

This section focuses on creative opportunities for institutionalizing recognition for excellence in cardiac research and patient recruitment and retention.

Creating Cardiac Research Collaboratives of Excellence to Highlight Top Tier Investigators and Research Sites

To help identify and capitalize on best practices around recruitment and participation of diverse groups of trial participants, a designation program recognizing partnerships with a demonstrated track record of successful cardiovascular trials with a special title (eg, Cardiovascular Research Collaboratives of Excellence) would be a significant step. There are relevant examples to build from to accomplish this. First, the Heart Failure Society of America developed a collaborative research network to direct patients and providers to high-value clinical research opportunities.[109,110] In addition to their focus on patient education and engagement, the Heart Failure Society of America research network compiles a list of trials that are particularly patient-centered.[109,110] Second, the field of oncology's National Cancer Institute–Designated Cancer Centers offer a model of NIH engagement for recognizing clinical trial success in a specialty field.[111] The AHA could benefit from the structures, lessons learned, and successes from these initiatives. The AHA, potentially in collaboration with National Heart, Lung, and Blood Institute, could expand upon the National Cancer Institute professional distinction program and Heart Failure Society of America's compilation of high-value research opportunities to identify and highlight key investigators and sites in Cardiovascular Collaborative for Research Excellence (CVCREs) that are performing excellent cardiovascular clinical research.

Through such a designation program, information on best practices would be collected and spread to other facilities with the goal of expanding the network of facilities and institutions that are able to successfully recruit and retain trial participants from underrepresented groups. The CVCREs would send AHA data on recruitment and retention strategies and outcomes. In return, health systems and hospitals recognized in this program would gain access to a learning network of other successful regional collaboratives to disseminate and learn from successes, including knowledge of what strategies were successful.

Establish a Community Cardiovascular Research Program to Reach a Broader Network of Researchers and Patients

Though designating CVCREs may stimulate research and disseminate best practices across the research community, they may be concentrated within academic health centers and systems, missing patients who do not receive care at such centers and possibly exacerbating underrepresentation of minority groups. In light of this, we recommend AHA establish a Community Cardiovascular Research Program, modeled after the National Cancer Institute's Community Oncology Research Program, which brings clinical trials and research to patients in their communities.[112] The Community Cardiovascular Research Program network should include a diverse selection of community sites and research bases; the National Cancer Institute's Community Oncology Research Program network, for example, is comprised of 7 research bases and 46 community sites, 14 of which are designated as minority or underserved sites.[112]

Although provider-based research networks are believed to increase diversity and clinical trial participation by making clinical trials available in the community, provider incentives to participation are also critical.[113,114] Providers who have participated in the National Cancer Institute's Community Oncology Research Program have cited altruistic feelings of obligation to patients and desire to enhance accessibility of clinical research, a desire to enhance their reputation, and a need to better integrate and coordinate the complex oncology care of patients.[113] The Community Cardiovascular Research Program may learn from the National Cancer Institute's Community Oncology Research Program's experiences and work with provider groups in rural, urban, and suburban communities to encourage equitable and diverse provider and patient participation in research.

ENVISIONING A FUTURE CARDIOVASCULAR RESEARCH EXPERIENCE

Although many clinical trials are not yet incorporating strategies needed to improve the research and trial process, there are examples of progress. The ADAPTABLE [115] (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness) and PREVENTABLE[116] (Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in Older Adults) clinical trials are taking a pragmatic approach to patient-centered research. Both trials aim to enroll a large and diverse patient population and conduct the trial in the patient's usual care setting. In the ADAPTABLE trial, patients were involved in study design from the outset, collaborating with researchers to create the study protocol, consent form, and other materials. Notably, the PREVENTABLE trial is the first clinical trial evaluating statins with a noncardiovascular primary outcome. The study is instead focusing on the ability of statins to prevent dementia or physical disability, which are particularly patient-centered outcomes. Although it is too early to evaluate results of these trials (both are still ongoing), they represent a promising step forward in making cardiovascular clinical trials more patient-centered.

One focus of this work was an intentional exercise to envision an ideal hypothetical, future cardiovascular research experience from multiple perspectives (patient, clinician, industry, regulators). Based on the above recommendations, we sought to capture that potential future vision in narrative form in the text below. Tables 1 and 2 then summarize this paper's recommendations in the short and long term that could encourage better progress toward the vision.

Narrative Vision of a Future Cardiovascular Research Experience

Patient Brenda is involved with and supported by a local network of women with CVD and hears of an upcoming trial with open enrollment. She is eager to learn more and easily accesses information about the trial on a centralized, reputable website. She is immediately put in touch with a contact person who can better describe the trial and its purpose. She speaks with her cardiologist and the trial's clinical investigators to get a better sense of risks and benefits to herself and her loved ones and possible outcomes of participating in the trial. After completing a simple video-enabled consent process that includes a diverse group of participants, reflecting her own experiences as well as different perspectives, she enrolls in the trial.

Throughout the duration of the trial, she has a point of contact where she can ask questions and voice any concerns. Participation is convenient; data collection occurs mostly on her smartphone via a secure trial application, so she is able to participate from virtually anywhere and only very infrequently needs to schedule physical appointments, arrange transportation, take time off of work, or arrange childcare. Brenda receives frequent updates on emerging trial results as well as individualized reports of her data. Many of the trial's end points are of interest to Brenda, reflecting her quality of life with end points like 6-minute walking distance. She feels understood and validated when uploading data specifically related to those preferred end points and quality of life outcomes. Her social support is enhanced by the trial participant community, where she can message and share experiences with other trial participants beyond her typical support network.

Upon conclusion of the trial, Brenda is debriefed in an understandable way on the use of her data and the next steps of the research project beyond her participation, including on the therapy's progress in the evaluation process. If approved for marketing by the regulatory authority, she may receive expedited access to the treatment that her data helped advance, if clinically appropriate. Given her convenient and empowering experience with this clinical trial, she volunteers to be on a mailing list through which she can be notified of future research.

Brenda's home base for her participation in the trial is her local community health clinic, which belongs to a regional collaborative of clinics, hospital systems, and community-based organizations, including faith-based organizations and local senior or community centers. This collaborative is committed to working together to facilitate and support patient recruitment and participation in cardiovascular clinical trials. The collaborative recently received a renewal of its status as an AHA–National Heart, Lung, and Blood Institute–recognized CVCRE. This designation signals to the health care system, patient, and clinical trial communities that a regional group of stakeholders and organizations are committed to working together to actively engage in activities to achieve high quality and clinically impactful cardiovascular trials, and ensure their patients have rapid access to cutting edge diagnostics and therapeutics.

The CVCRE is required to share data with AHA on their recruitment efforts and effectiveness, including data on the number of potential patients within the collaborative, patient recruitment and retention rates, time to start up recruitment, and Institutional Review Board decision times. In return, the CVCRE participates in the CVCRE Learning Group where the CVCRE has access to other CVCREs' data and experiences. Through this, the CVCRE learns about new, innovative recruitment and retention strategies that worked in other regional collaboratives, such as communication tools that effectively communicate trial benefits and risks to potential participants, video-enabled consent pro-

cesses, web-based patient portals that provide patients with personalized trial-related information, and transportation services that can help trial participants travel to trial sites. The CVCRE has leveraged these resources to improve their trial participation numbers and lower their costs to conduct cardiovascular trials.

The cardiovascular drug and the FDA-approved trial to evaluate it was developed by Pharmaceutical Development Company (PDC). Two recent developments on the regulatory and industry side led PDC to invest in research resulting in this trial. First, since the FDA's Center for Drug Evaluation and Research released guidance indicating a range of new, innovative, and efficient trial design flexibility in the hypothetical future year of 20XX, PDC corporate leaders changed their minds about investing in Research and Development for this new cardiovascular drug. Previously, they were concerned that traditional trial designs would be so long, complicated, inefficient, and inconvenient for patients that developing this particular drug would take a decade, be very expensive, and would have a higher probability of failure; thus, they deemed it to be too risky. However, one of the trial designs mentioned in the 20XX guidance made sense for evaluating this drug and PDC greenlit the project. They worked with payers to help ensure that the outcomes of the trial, beyond being patient-centered, demonstrated care improvements that increased the payers' likelihood of rapidly adopting the new therapy. Second, the AHA, collaborating with FDA, began convening regular cardiovascular trial effectiveness, efficiency, and innovation forums twice a year. These meetings are attended by the eco-system of stakeholders—not just industry, but health systems, researchers, government (beyond FDA, also including relevant NIH, Centers for Disease Control and Prevention, and CMS representatives), patients, and others. At these meetings, PDC was able to discuss in general terms the new method they were considering and received feedback from other researchers and regulators at the meeting that allowed them to tweak their design. This increased their confidence in submitting an application to FDA, which they did.

After the application was accepted, they worked with Brenda's local CVCRE to conduct the trial, a process that resulted in an effectively and efficiently run trial. They were eventually able to get the new drug to market at a cheaper price than previous comparable cardiovascular therapies they had developed, and because the payers had been involved in the process, approval for the new therapy was more likely and more timely—ultimately benefiting Brenda.

CONCLUSIONS AND NEXT STEPS

CVD continues to be the leading cause of death and disability and remains highly costly, complicated, and burdensome. Despite this, drug innovation is lagging and US enrollment in drug and device trials is limited. New strategies are needed to streamline and reduce the costs of clinical trials, all the while placing greater emphasis on the patient voice and experience. New technologies offer a promising path forward and can help improve upon current patient participation, generate high-quality evidence in real-world settings, and ensure evidence meets the needs of all stakeholders. Industry and regulators must also commit to partnering in upstream discussions of trial innovation. We offer short- and long-terms recommendations related to all of these areas. Adopting these recommendations would help achieve the hypothetical narrative vision, potentially lowering the costs for evidence generation of new cardiovascular therapies downstream, especially when paired with continued policy research on better ways to pay for and equitably develop drugs and devices. Ultimately, these strategies could improve the cardiovascular pipeline while making cardiovascular therapies more effective, meaningful, and equitable to patients.

ARTICLE INFORMATION

*A list of all American Heart Association Partnering with Regulators Learning Collaborative is given in the Data Supplement.

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