THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

Improving Heart Failure Therapeutics Development in the United States

The Heart Failure Collaboratory

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ABSTRACT

The current heart failure clinical trial environment is strained by increasing complexity and cost, regulatory requirements, competing demands on stakeholders, implementation challenges, and decreasing patient and investigator participation. To begin the process of developing potentially effective strategies and tactics, stakeholders including patients; investigators; academic leaders; pharmaceutical and device industry representatives; society representatives; third-party payers; and government representatives from the U.S. Food and Drug Administration, National Institutes of Health, and Centers for Medicare and Medicaid Services convened in March of 2017. This paper summarizes the discussions, outlines current challenges and actionable opportunities, and makes targeted recommendations to achieve the goals of improving efficiency in clinical trials and speeding the development of effective heart failure therapies, including the formation of an organized Heart Failure Collaboratory. (J Am Coll Cardiol 2018;71:443–53) © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation.
representatives, payers, regulators, and other representatives from government agencies convened in March of 2017 (Figure 1). This committed community of stakeholders has made major strides to improve patient care, but also recognizes multiple aspects of the clinical research system that need to be improved or reimagined.

**FACTORs ADVERSELY AFFECTING HF CLINICAL TRIALS**

Although randomized controlled trials are the gold standard for clinical evidence generation, they have become slow, cumbersome, and costly, and often have limited generalizability. There appears to be a myriad of causes.

1. **PATIENT ENGAGEMENT.** Poor patient enrollment leads to slow and costly clinical trials (2). A number of factors influence patients’ decisions to participate in clinical research, including trial complexity and burden, a favorable benefit to risk profile for the experimental treatment, and the potential to help others (3). However, patient input has rarely been utilized to improve these issues, and patients may struggle to find accessible information regarding clinical trials, support from members of the HF community with similar phenotypes, and time for discussion about clinical research during clinic visits.

2. **CULTURE OF PARTICIPATION.** Few clinicians participate as investigators in HF clinical trials, in part because of poor incentivization. In an online survey of 200 U.S. principal investigators, over one-half declared their intention to leave the investigator workforce (4). Commonly identified impediments and disincentives include lack of opportunity, burden from other obligations, required time and trial bureaucracy, difficulty navigating onerous eligibility criteria, lack of institutional support, country-specific legal requirements, and lack of financial or professional compensation. Clinical trial sites must support large direct and indirect costs associated with administering clinical trials, including adhering to regulatory requirements; mitigating potential risk; and constructing, training, and maintaining the site apparatus (5).

3. **EVIDENCE GENERATION.** HF clinical trials typically require large sample sizes and prolonged follow-up to demonstrate safety and efficacy; in contrast, a new therapeutic agent for orphan diseases or cancer subtypes, where no prior effective therapy may exist, may achieve a large and meaningful treatment effect (6,7). Incorporation of patient-reported outcomes (PROs) and other alternative endpoints has been slow. Inclusion and exclusion criteria intended to select a subpopulation most likely to respond to the intervention (predictive enrichment) and most likely to experience events of interest (prognostic enrichment) may delay enrollment and extend a trial (8). The brisk globalization of clinical trials leads to enrollment of fewer American patients and under-representation of American practice patterns, further impairing generalizability (9).

4. **DESIGN.** From 2000 to 2007, the number of eligibility criteria and procedures required for trial protocols across multiple therapeutic areas rose 50% while volunteer enrollment and retention fell 20% to 30% (10). Local institutional review boards (IRBs) request changes to protocols and consents over 90% of the time, often with multiple changes per study site (11). Broad data and adverse event reporting has been criticized as a critical element leading to overly complicated trials. Regulators, payers, and sponsors remain unaligned over which adverse events should be captured and reported, despite U.S. Food and Drug Administration (FDA) guidance suggesting that recording fewer events may be acceptable (12). Finally, complex protocols are difficult to incorporate into daily clinical practice, driving a wedge between health care delivery and medical research.

5. **COST.** Clinical trial costs, particularly for cardiovascular trials, have risen out of proportion to inflation. Total cost per enrolled patient has more than quadrupled between 1989 and 2011, compared with a doubling in expenditures for biomedical research and development (13). Clinical trials accounted for 70% of the $46 billion spent by members of the Pharmaceutical Research and Manufacturers of America on research and development in 2010, and industry sponsors fund a substantial proportion of randomized controlled trials published in highly-cited medical journals (14). The total cost to develop a novel therapeutic and bring it to market has doubled and is now estimated to exceed $2.5 billion (15). This growth is linked at least in part to expanding trial complexity associated with outsourcing of services to contract research organizations, with a doubling in person-effort required at each trial site to enroll one-half of the patients (1,16).

6. **RETURN ON INVESTMENT.** Development of a clinically effective and commercially viable product is fraught with regulatory and payer uncertainty. Following phase 1 trials, only 29% of drugs for the treatment of rare diseases and 10% of drugs for cardiovascular disease eventually achieve regulatory
approval (17). Even following phase 3 pivotal trials, only 46% become internationally approved, whereas 36% are approved by the FDA (18). Recently, rare successes in new molecular entity development have been greeted by slow physician uptake and prescribing, limiting the ability of sponsors to recoup their financial investment (19). Payers tend to prioritize health gains per expenditure and limit their financial hazard to the most cost-effective agents, which may not favor novel therapies (20). Payers have also become more restrictive in coverage determinations, requiring increasing evidence prior to approval. To boost their chances, sponsors may seek to collect proactively what might otherwise be considered extraneous data, further ballooning trial cost and complexity.

LESSONS LEARNED FROM COLLEAGUES

ONCOLOGY. Although the oncology clinical trial environment has faced similar difficulties, it is flourishing, in part because of systemic reforms drafted by the oncology community in 2010 and the collaborative work of the National Comprehensive Cancer Network (21). A central accessible trial registry was created to improve clinical research awareness. Patient advocate involvement was encouraged to design engaging trials, assist in patient recruitment, and make research participation a principal component of clinical practice. Improved reimbursement rates and suitable rewards for academic investigators were recommended, such that clinicians could be paid for their research contributions akin to their clinical work. A monthly confidential global regulators’ meeting was established to improve global interactions with regulatory bodies. Alternative clinical trial designs were prioritized, including master protocols for each tumor type, molecular target protocols, and use of central IRBs. A “breakthrough” designation for novel agents with the highest potential for clinical success was created, exemplified by the adaptive phase 2 and 3 trials of pembrolizumab for solid tumors; the trials enrolled 1,253 patients from 101 sites over 3 years as part of numerous variably timed expansion cohorts, culminating with rapid FDA approval (22). Due in part to these changes and differences in trial design, the oncology pipeline currently boasts the largest number of preclinical therapeutics in development of any field (17).

Some trends in oncology trials are, however, less applicable to the HF ecosystem (Table 1). Use of surrogate endpoints and biomarkers has allowed earlier
approval and subpopulation targeting of novel therapies in oncology settings where no effective treatments exist. Nonetheless, large effect size estimates from unvalidated surrogates may disproportionately increase uptake and reasonable payer compensation compared with more modest and clinically relevant results from trials with robust mortality endpoints (23). In 150 cardiovascular trials with positive surrogate endpoints, only 15% had a subsequent published outcomes trial that validated the earlier results, and some large, appropriately powered outcomes trials of HF and cancer therapeutics have demonstrated harm following promising surrogate endpoint studies (23–26).

**Cystic Fibrosis.** The cystic fibrosis (CF) clinical trial ecosystem was principally constructed by a patient advocacy foundation. Despite a worldwide CF population of only 70,000, CF has had 7 new therapies approved in the last 25 years since the Cystic Fibrosis Foundation (CFF) launched the CF Therapeutics Development Network (TDN) (27). The CFF developed this strategically aligned research network by coordinating pharmaceutical companies and investigators; the CFF oversees the pharmaceutical evaluation platform. It successfully established uniform research endpoints, defined standard clinical care, developed appropriate clinical research site assessment strategies, and provided centralized study appraisal and review. Pharmaceutical rights from 2 novel medications approved in 2011 and 2015 have fed over $3 billion in revenue to the CFF, which it reinvested into core research team funding (28). The CFF also oversees accreditation of over 120 U.S. CF clinical care centers that form a large longitudinal patient registry used for phase 4, post-marketing, and epidemiological data collection. This system continues to bear fruit, with diverse novel agents populating various stages of development in 55 ongoing clinical trials at 89 TDN centers.

The crown jewel of the CF model is patient empowerment. This was achieved by partnering with advocates and care groups to educate and inform patients of their crucial role in promoting and improving their health through clinical research. The TDN steering committee ensures that preclinical and clinical research decisions focus on safely improving patient lives, which encourages patients to seek out clinical trials as part of an embedded research culture (28). The user-friendly CF clinical trial finder (29) facilitates patient engagement; patients may browse available trials and patient-accessible inclusion and exclusion criteria, and can use direct links to contact

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Barriers to Heart Failure Clinical Trial Success and Potential Solutions</th>
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<tbody>
<tr>
<td><strong>Barriers</strong></td>
<td><strong>Potential Solutions</strong></td>
</tr>
<tr>
<td>Patient engagement</td>
<td>Onerous informed consent</td>
</tr>
<tr>
<td></td>
<td>Lack of information resources</td>
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<td></td>
<td>Travel costs and logistics</td>
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<tr>
<td>Culture of participation</td>
<td>Incentives</td>
</tr>
<tr>
<td></td>
<td>Complex contracting</td>
</tr>
<tr>
<td></td>
<td>Local regulatory (IRB) delays</td>
</tr>
<tr>
<td>Evidence generation</td>
<td>Modest treatment effects</td>
</tr>
<tr>
<td></td>
<td>Generalizability</td>
</tr>
<tr>
<td>Design</td>
<td>Complexity and cost</td>
</tr>
<tr>
<td>Return on investment</td>
<td>Regulatory and payer uncertainty</td>
</tr>
</tbody>
</table>

IRB = institutional review board.
local study coordinators. In the first month of the site’s existence, there were over 25,000 page views and 300 direct links between patients and research coordinators. This site also provides participants with their clinical trial results, reinforcing how they have improved future patient care. Actively monitored peer-to-peer forums are provided by the CFF to further distribute comprehensive and accurate information and build clinical research enthusiasm.

**SUITABILITY OF THE CF FRAMEWORK FOR THE HF ENVIRONMENT**

Although the CF model cannot be replicated for HF en bloc, successful features may be transportable (Table 1). A patient-accessible clearinghouse could explain trial rationale, purported mechanisms of action, and anticipated side effects; be used as a portal to connect patients and enrolling clinical trials’ coordinators; and serve as a gateway to improved informed consent. A culture of research must be established, as fostering patient engagement alone will not reform the HF ecosystem. HF research and clinical practice will need to be integrated into a single comprehensive system where participation of physicians and patients will be the norm. The beneficial effects of clinical trial participation on adherence to guideline-directed therapy and education could, and should, be touted (30). Investigators should be nurtured, acknowledged, and rewarded for their participation and successful target achievement with meaningful financial and academic compensation. The CFF mandates that senior principal investigators mentor a junior investigator in every clinical trial, indoctrinating and developing them in a self-perpetuating reinvestment cycle. Payers, institutions, and health systems can reimburse for patient enrollment and the production of high-quality data, and recertification could be supported by investigator activity. As most cardiologists have shifted their practice over the last 2 decades to direct employment or close alignment with large health systems, management within these systems has the opportunity to employ creative payment structures that encourage research participation, such as quality incentives linked to bonuses (31). Leadership on the behalf of payers, industry, and societies will be vital.

Replicating a disease-specific clinical research network (CRN) like the CF TDN would be welcomed by HF trial stakeholders. The current National Institutes of Health (NIH)-supported Heart Failure Network focuses on smaller studies at a limited number of centers compared with organizations in other therapeutic domains (32,33). A broad-reaching CRN of vetted HF clinical trial sites overseen by a centralized patient-centered organization could nurture young investigators, train and monitor sites and coordinators, establish centralized IRBs, facilitate contracting, partially mitigate risk, attract industry partners to expand the drug development pipeline, and establish a vast HF registry. Such a CRN could align hundreds of centers to produce coordinated and compatible data with consistent adverse event reporting and standardized trial endpoints, definitions, and standard practices. A CRN could also coordinate stakeholders throughout the therapeutic development process to ensure agreement on necessary trial attributes and comparator interventions for regulatory approval and payer coverage. This is particularly crucial with potential alternative and adaptive trial designs that may use novel endpoints such as PROs, highlighted by a recent Medicare Evidence Development & Coverage Advisory Committee meeting (34).

**LESSONS LEARNED FROM GLOBAL EFFORTS**

International trial communities have proposed integration of trials into clinical practice and medical training, improved analytics, utilization of alternative endpoints that include PROs and worsening HF, and identification of reassuring safety margins for mortality and morbidity (7). Employment of a cardiovascular risk assessment model similar to the 2008 FDA guidance for diabetes therapies, in which the upper bound of the 95% confidence interval can be used to determine the need for a large safety trial, may promote novel development plans and the use of patient-centered endpoints (35). Despite these efforts, enrollment rates worldwide remain unacceptable, and deficiencies in the United States compared with international enrollment suggest that some solutions should be specific to the region (Table 2).

**NEW METHODOLOGIES**

Multiple organizations are working with regulators to establish methods to perform and interpret clinical trials at lower cost and with greater efficiency, often by using data from extant registries or administrative databases. Such designs have been termed “pragmatic” because of their scaled-down infrastructure with decreased site monitoring and safety reporting; intention to test real-world effectiveness of interventions in usual care settings with minimal
trial-specific visits, procedures, or exclusion criteria; and focused outcome collection that avoids costly and time-consuming extraneous information. The NIH has partnered with the FDA and the National Patient-Centered Clinical Research Network to establish multiple demonstration projects that seek to prove the effectiveness and efficiency of pragmatic methodology (Table 3).

Nevertheless, current iterations of pragmatic trials have limitations (Table 1). Because pragmatic trials accept the heterogeneity of standard clinical care, they must be large enough to appropriately overcome this variability (36). Although blinding of treatment allocation and outcome assessment is not typical of real-world care, important safety events other than major outcomes may be altered by unmasked bias.

### TABLE 2

<table>
<thead>
<tr>
<th>Trial</th>
<th>Enrollment Period</th>
<th>Patients</th>
<th>Sites</th>
<th>Region</th>
<th>Crude Enrollment Rate*(Patients/Site/Month)</th>
<th>All-Cause Mortality (per 100 pt-ys)</th>
<th>Cardiovascular Mortality (per 100 pt-ys)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVEREST (NCT00071331) (Online Ref. 1)</td>
<td>October 7, 2003 to February 3, 2006</td>
<td>4,133</td>
<td>436</td>
<td>Overall</td>
<td>0.33</td>
<td>25</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,251</td>
<td>220</td>
<td>North America</td>
<td>0.20</td>
<td>30.4</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>564</td>
<td>100</td>
<td>Western Europe</td>
<td>0.20</td>
<td>27.1</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,619</td>
<td>77</td>
<td>Eastern Europe</td>
<td>0.74</td>
<td>20.5</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>699</td>
<td>40</td>
<td>South America</td>
<td>0.62</td>
<td>27.2</td>
<td>NA</td>
</tr>
<tr>
<td>TOPCAT (NCT00094302) (Online Ref. 2)</td>
<td>August 10, 2006 to January 31, 2012</td>
<td>3,445</td>
<td>233</td>
<td>Overall</td>
<td>0.22</td>
<td>4.2-4.6</td>
<td>2.8-3.1</td>
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<tr>
<td></td>
<td></td>
<td>1,767</td>
<td>188</td>
<td>North and South America</td>
<td>0.14</td>
<td>6.5-7.7</td>
<td>3.6-4.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,676</td>
<td>45</td>
<td>Eastern Europe</td>
<td>0.36</td>
<td>2.0-2.3</td>
<td>1.6-2.0</td>
</tr>
<tr>
<td>ASTRONAUT (NCT00894387) (Online Ref. 3)</td>
<td>May 2009 to December 2011</td>
<td>1,639</td>
<td>316</td>
<td>Overall</td>
<td>0.16</td>
<td>18.0</td>
<td>16.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>123</td>
<td>43</td>
<td>North America</td>
<td>0.09</td>
<td>7.3</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>395</td>
<td>97</td>
<td>Western Europe</td>
<td>0.12</td>
<td>14.7</td>
<td>12.7</td>
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<tr>
<td></td>
<td></td>
<td>495</td>
<td>70</td>
<td>Eastern Europe</td>
<td>0.22</td>
<td>16.8</td>
<td>15.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>163</td>
<td>33</td>
<td>Latin America</td>
<td>0.15</td>
<td>15.3</td>
<td>13.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>495</td>
<td>70</td>
<td>Asia/Pacific</td>
<td>0.29</td>
<td>26.7</td>
<td>24.8</td>
</tr>
<tr>
<td>PARADIGM-HF (NCT01035255) (Online Ref. 4)</td>
<td>December 8, 2009 to November 23, 2012</td>
<td>8,399</td>
<td>1,043</td>
<td>Overall</td>
<td>0.22</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>602</td>
<td>183</td>
<td>North America</td>
<td>0.09</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7,797</td>
<td>960</td>
<td>Worldwide</td>
<td>0.22</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

References in this table can be found in the Online Appendix. *Crude enrollment rates calculated by dividing the published number of enrolled patients by the enrollment period and number of enrollment sites for the overall trials and specific geographic regions. All-cause and cardiovascular mortality reported from published trial results.

### TABLE 3

<table>
<thead>
<tr>
<th>Trial</th>
<th>Name</th>
<th>Pragmatic Attributes and Successes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAPTABLE (NCT02697916) (Online Ref. 5)</td>
<td>Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-Term Effectiveness</td>
<td>Randomized registry design Recruitment based on patient risk phenotype derived from administrative claims codes and clinical documentation Patient advocates to ensure patient-centeredness Consent, randomization, and trial assessments via an electronic portal</td>
</tr>
<tr>
<td>TASTE (NCT01093404) (Online Ref. 6)</td>
<td>Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia</td>
<td>Swedish national registry design Achieved 61% enrollment of screened candidates</td>
</tr>
<tr>
<td>DCP (NCT02185417) (Online Ref. 7)</td>
<td>Diuretic Comparison Project</td>
<td>Veterans Affairs EHR-embedded Patients identified via EHR enrolled in ‘opt-out design’: enrolled by primary care physicians unless they actively decline Informed consent by central telephone bank Outcomes and adherence data collected from EHR, Medicare, and national databases</td>
</tr>
<tr>
<td>CleanUP IPF (NCT02759120) (Online Ref. 8)</td>
<td>CleanUP IPF for the Pulmonary Trials Cooperative</td>
<td>Unblinded Includes baseline genotyping for participants</td>
</tr>
<tr>
<td>WOSCOPS (Online Ref. 9)</td>
<td>West of Scotland Coronary Prevention Study Group</td>
<td>Outcomes and adverse events derived from participant records linked to national datasets of routinely collected health information</td>
</tr>
</tbody>
</table>

References in this table can be found in the Online Appendix. EHR = electronic health record.
Pragmatic trials may have difficulty collecting PRO questionnaires, and have had trouble balancing efficiency, rigor, and variable practice patterns that may reduce the ability to detect differential effects of interventions (36). New analytic methods need to be adopted to interpret data from these novel schemes, in part because incomplete ascertainment and trial drop out may play a larger role, and it may take time before the research community achieves consensus over how to interpret the results.

A broader goal potentiated by the proliferation of electronic health records (EHRs) is creation of a “learning healthcare system” in which medical practice continuously generates clinical research data that itself continuously informs clinical care (37). Unfortunately, even though 95% of hospitals and 62% of cardiology practices employ an EHR, this concept has not yet proven functional or reliable, limited by incomplete and incorrectly entered information, erratic and potentially biased coding by providers and assistants, difficulty following patients if they transition to a separate medical system or payer plan, and the inherent ambiguity of analog text in clinical notes (37). Although clinical decision support tools and predictive analytics display potential, as well as using the EHR and machine learning to identify subjects for trial enrollment, such as with the Flag, Identify, Network, Deliver Familial Hypercholesterolemia program (38), they will require further development, input of high-quality data, and likely changes in ingrained clinical documentation behaviors.

Novel electronic trial organization and data collection technologies may separately improve the efficiency of the clinical trial apparatus in an interconnected electronic society with almost ubiquitous personal smartphone use (Table 1). The MyHeart Counts platform (39) and Eureka (40), an NIH-funded internet-based clinical trial system, are 2 burgeoning research portals that allow scalable clinical trial enrollment and data collection at reduced cost. MyHeart Counts functions through an application from the Apple ResearchKit (41). Participant activity data suggested its potential to assist in rapid trial enrollment, but also demonstrated limitations.
Almost 50,000 registrants consented to participate over 8 months, with 81% uploading at least some data; however, only 3% submitted complete data. The Eureka platform, powered by Amazon Web Services, has a currently accessible cohort of over 100,000 subjects, including more than 50% women, and its proportionally few minorities can be enriched in subgroups created for trial purposes (42). Utilization of similar systems has been associated with 50% financial savings over conventional strategies (43).

Novel electronically captured HF clinical trial endpoints may characterize disease impact and drug or device treatment effect better than traditional endpoints, although validation is needed (44).

**GENERALIZABILITY AND REPRESENTATIVE POPULATIONS**

Discordant HF therapeutic responses between demographic subgroups are common, including with newly approved pharmaceuticals (45). A review of all new molecular entities approved by the FDA from 2008 to 2013 demonstrated that 21% displayed racial or ethnic differences in pharmacokinetics, safety, or efficacy (46). Nonetheless, HF clinical trials have persistently enrolled a large number of younger white males, creating a misalignment with the racial, ethnic, sex, age, and socioeconomic diversity present in the United States (47,48). Because of these issues, the FDA created freely available drug trial snapshots to highlight the enrollment diversity and generalizability of clinical trials (Figure 2) (49).

Unfortunately, imbalances in clinical trial enrollment have been stubbornly resistant to recent interventions. A statutory mandate to include women and minority groups in federally sponsored trials exists, and published FDA guidance requests reporting of age, race, ethnicity, and sex data, as well as the expectation that trial subjects will be demographically similar to their intended target populations (50,51). Some apparent enrollment disparities may be due to underlying...
pathophysiological differences between demographic groups. For instance, HF with reduced ejection fraction tends to be more associated with male sex and HF with preserved ejection fraction with female sex (52,53). Nevertheless, the pivotal outcomes trial of sacubitril-valsartan, the most recent drug approved for HF with reduced ejection fraction, included only 22% women. Only 5% black or African-American subjects out of 8,442 total patients were enrolled, despite an extensive and continuous planned recruitment effort that did sign up 428 African-American patients constituting 26% of the U.S. enrollment (Figure 2) (19).

Novel remedies are needed to improve enrollment diversity (Table 1). Investigators and sponsors are now required to detail recruitment strategies for diverse populations in regulatory planning documents. Improved patient engagement and education may increase diversity, as educated participants acknowledge the benefits and value of clinical trial participation (3,54). Minority groups may mistrust research because of historical medical exploitation; thus, a diverse research team may help broaden enrollment (55,56). Connections with community leaders and institutions; extending outreach to include clinics in underserved communities, churches, and other cultural centers; and ongoing collaboration with local and national advocacy groups may improve diversity. An established HF CRN could assist in this regard, and prudent use of electronic media or online patient portals such as PatientLikeMe (57), which boasts 66% female registrants, may be able to access more diverse user communities (58).

Nonetheless, equal enrollment by sex, race, and ethnicity does not ensure generalizability. Demographic attributes, underlying social and economic factors, and cultural belief systems can meaningfully affect baseline risk, comorbidities, health outcomes, and responses to therapeutics (59). Comorbidities have been routinely excluded from HF clinical trials, despite evidence that they substantially affect the likelihood of adverse outcomes and are clinically meaningful to patients and providers (60).

Analytical schemes to describe and simplify these complex interactions in HF patients have been initiated (61). Multidomain phenotyping of patients has repeatedly identified combinations of factors that predict adverse outcomes in learning and validation cohorts (60). Unfortunately, the complexity of these interactions currently makes their routine clinical assessment unwieldy, although their use for therapeutic targeting and population comparisons may represent the future for determining personalized risk and benefit. In the meantime, the FDA and expert trialists agree that banking of genetic samples for later analyses and association studies is crucial if unforeseen heterogeneity arises following clinical trial conclusion, as genomic data may help to tease out the bases for described differences (51).

CONCLUSIONS

The current state of HF clinical research is in critical need of attention, with specific barriers for research in the United States to overcome. The clinical research infrastructures for other disease states suggest some feasible ways in which the HF ecosystem can be reformed. Patient engagement, rejuvenated physician commitment, promotion of a clinical research culture, collaboration among the stakeholders during trial conceptualization and performance, centrally organized and vetted research networks, novel methods of evidence generation and trial recruitment, and a focus on implementation of new therapies may help reverse the deleterious trend threatening cardiovascular therapeutic innovation. Establishment of a functional, multifaceted HF clinical trial apparatus will require more than a simple recapitulation of the successes realized by others, and novel methodologies will be needed in addition to active teamwork among community. To achieve success, the ideas expressed here are being used as a launch pad for ongoing endeavors through a multistakeholder effort entitled the “Heart Failure Collaboratory” (Central Illustration). This new effort has established 5 working groups to tackle individual issues with short- and long-term goals for improving the current environment by producing, distributing, and enacting guidance and recommendations: 1) Electronic or Digital Health; 2) Regulatory Policy and Implementation Science in Drug Development; 3) Regulatory Policy and Implementation Science in Device Development; 4) Research Networks and the Role of Societies; and 5) Representative Populations. These endeavors will be crucial to rejuvenating the HF evidence development apparatus, and can provide a framework for other disease states to nurture their own evidence-generation programs.

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APPENDIX For details regarding the Heart Failure Collaboratory and supplemental references, please see the online version of this article.