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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.

Development and implementation of novel heart failure (HF) therapeutics is strained by deficiencies in the current clinical research infrastructure (1). Because this is a global challenge, international and regionally-specific remedies are needed. To cultivate potential solutions, stakeholders including patients, investigators, academic leaders, society representatives, industry

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ABBREVIATIONS AND ACRONYMS

CF = cystic fibrosis

CFF = Cystic Fibrosis Foundation

CRN = Clinical Research Network

EHR = electronic health record

FDA = U.S. Food and Drug Administration

HF = heart failure

IRB = institutional review board

TDN = Cystic Fibrosis Therapeutics Development Network

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).

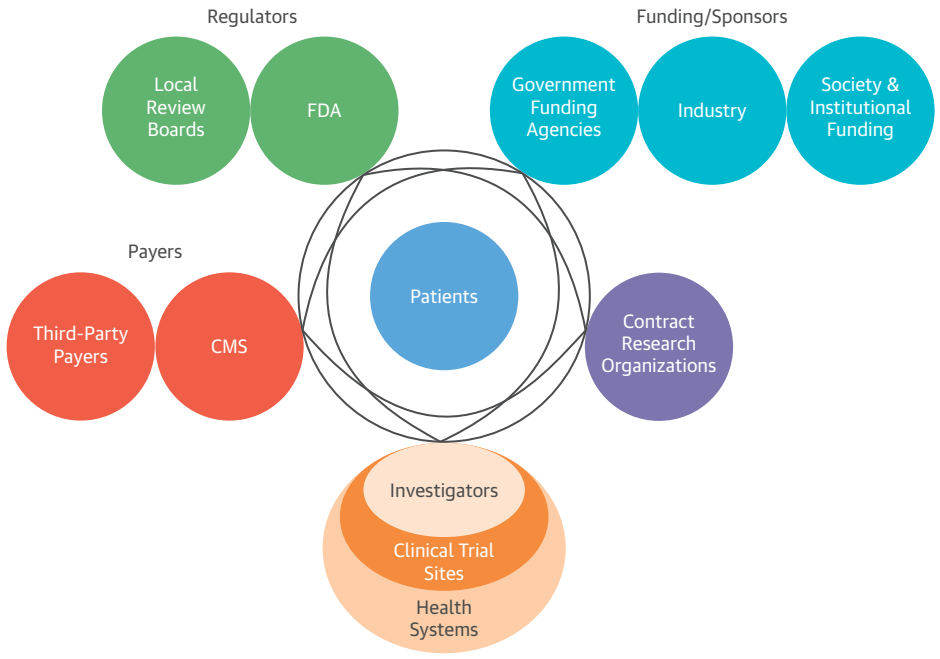
3. EVIDENCE GENERATION. HF clinical trials typically require large sample sizes and prolonged follow-up to demonstrate safety and efficacy; in contrast, a new therapeutic agent for orphan diseases or cancer subtypes, where no prior effective therapy may exist, may achieve a large and meaningful treatment 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

FIGURE 1 **Primary Stakeholders in the U.S. Heart Failure Clinical Trial Ecosystem**



Lines represent the interconnected interactions between major groups of clinical trial stakeholders, all revolving around patient care improvement. CMS = Centers for Medicare & Medicaid Services; FDA = U.S. Food and Drug Administration.

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

TABLE 1 Barriers to Heart Failure Clinical Trial Success and Potential Solutions

Barriers	Potential Solutions	Suitability for the Heart Failure Environment
Patient engagement		
Onerous informed consent	Streamline informed consent with improved communication	Widely applicable
Lack of information resources	Create a central clinical trial information clearinghouse and patient portal	Widely applicable
Travel costs and logistics	Limit study-specific visits with pragmatic methods	Widely applicable with some limitations
Culture of participation		
Incentives	Financial and academic rewards for investigator research, including by payers and health systems	Feasible for health systems, societies, and industry leadership to prioritize clinical trial activity
Complex contracting	Standardized contracting protocols and arrangements with clinical trial sites	Feasibility actively being investigated
Local regulatory (IRB) delays	Central IRBs for multisite trials	Feasibility actively being investigated
Evidence generation		
Modest treatment effects	Pragmatic methodology and novel data collection methods to achieve large sample sizes and follow-up	Widely applicable with some limitations
Generalizability	Identify methods to diversify enrollment during planning, including for populations likely to demonstrate heterogenous treatment effects; limit eligibility requirements (comorbidities); use diverse media outlets and online cohorts	Targeted enrollment is feasible in some cases, pragmatic methodology and electronic resources applicable with some limitations
Design		
Complexity and cost	Pragmatic and adaptive methodology, with novel data collection methods, as possible	Widely applicable with some limitations
Return on investment		
Regulatory and payer uncertainty	Coordinate stakeholders (including regulators and payers) throughout therapeutic development	Regulators are enthusiastic about early inclusion, the feasibility of including payers remains uncertain

IRB = institutional review board.

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

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

TABLE 2 International Heart Failure Trial Enrollment and Outcome Rates

Trial	Enrollment Period	Patients	Sites	Region	Crude Enrollment Rate* (Patients/Site/Month)	All-Cause Mortality (per 100 pt-yrs)	Cardiovascular Mortality (per 100 pt-yrs)
EVEREST (NCT00071331) (Online Ref. 1)	October 7, 2003 to February 3, 2006	4,133	436	Overall	0.33	25	NA
		1,251	220	North America	0.20	30.4	NA
		564	100	Western Europe	0.20	27.1	NA
		1,619	77	Eastern Europe	0.74	20.5	NA
		699	40	South America	0.62	27.2	NA
TOPCAT (NCT00094302) (Online Ref. 2)	August 10, 2006 to January 31, 2012	3,445	233	Overall	0.22	4.2–4.6	2.8–3.1
		1,767	188	North and South America	0.14	6.5–7.7	3.6–4.9
		1,676	45	Eastern Europe	0.56	2.0–2.3	1.6–2.0
ASTRONAUT (NCT00894387) (Online Ref. 3)	May 2009 to December 2011	1,639	316	Overall	0.16	18.0	16.3
		123	43	North America	0.09	7.3	6.5
		395	97	Western Europe	0.12	14.7	12.7
		495	70	Eastern Europe	0.22	16.8	15.4
		163	33	Latin America	0.15	15.3	13.5
		495	70	Asia/Pacific	0.29	26.7	24.8
PARADIGM-HF (NCT01035255) (Online Ref. 4)	December 8, 2009 to November 23, 2012	8,399	1,043	Overall	0.22	NA	NA
		602	183	North America	0.09	NA	NA
		7,797	960	Worldwide	0.22	NA	NA

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.

ASTRONAUT = Aliskiren Trial on Acute Heart Failure Outcomes; EVEREST = Efficacy of Vasopressin Antagonism in hEart failuRE: Outcome Study With Tolvaptan; NA = not available; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist.

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.

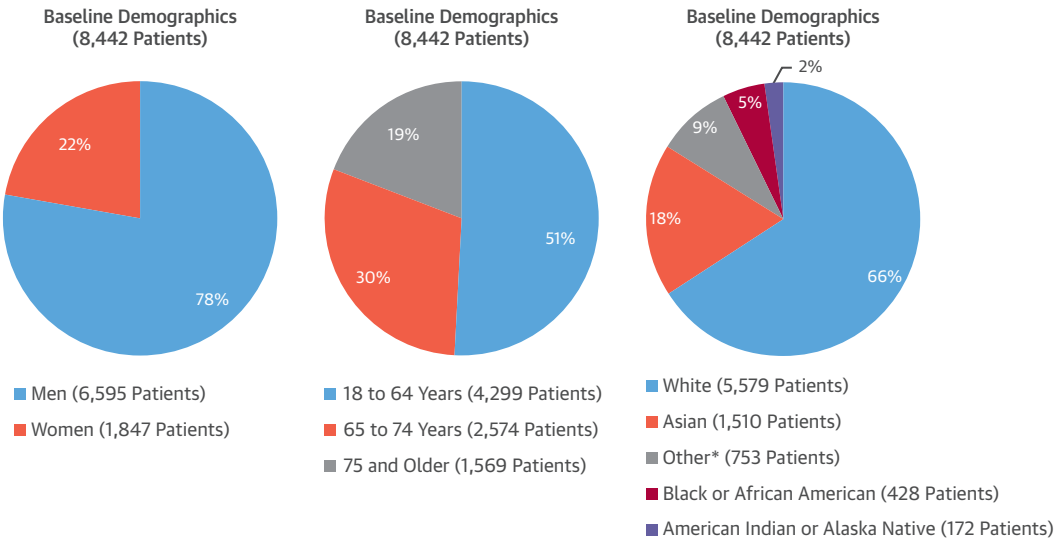
TABLE 3 Example Pragmatic Trials and Demonstration Projects

Trial	Name	Pragmatic Attributes and Successes
ADAPTABLE (NCT02697916) (Online Ref. 5)	Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-Term Effectiveness	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
TASTE (NCT01093404) (Online Ref. 6)	Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia	Swedish national registry design Achieved 61% enrollment of screened candidates
DCP (NCT02185417) (Online Ref. 7)	Diuretic Comparison Project	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
CleanUP IPF (NCT02759120) (Online Ref. 8)	CleanUP IPF for the Pulmonary Trials Cooperative	Unblinded Includes baseline genotyping for participants
WOSCOPS (Online Ref. 9)	West of Scotland Coronary Prevention Study Group	Outcomes and adverse events derived from participant records linked to national datasets of routinely collected health information

References in this table can be found in the Online Appendix.

EHR = electronic health record.

FIGURE 2 **Clinical Trial Snapshot Example: Sacubitril-Valsartan**



Were there any differences in side effects among sex, race and age?

Subgroup analyses were conducted for sex, race, and age.

Sex: The risk of side effects appeared to be similar in men and women.

Race: There was an increased risk of an allergic reaction called angioedema in black patients.

Age: The risk of low blood pressure was higher in patients 65 years and older.

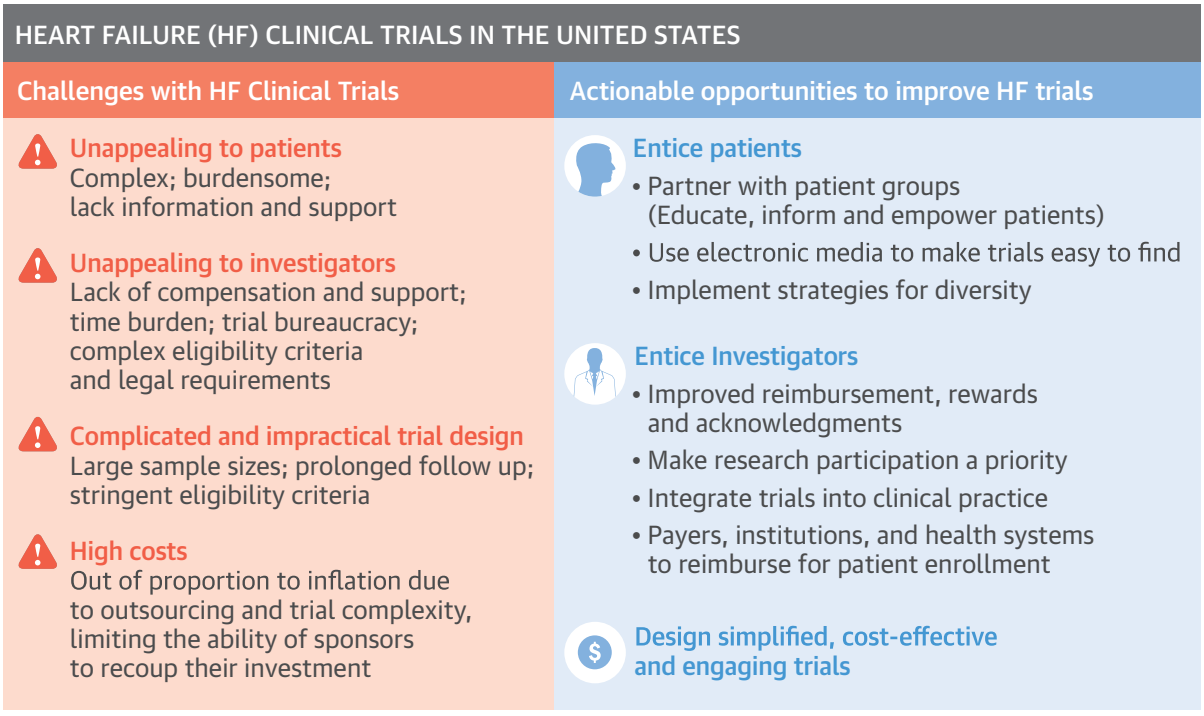
Example of the Drug Trial Snapshots published by the U.S. Food and Drug Administration to communicate trial population representativeness to consumers and clinical care providers. *Other: all other races combined. Data from the U.S. Food and Drug Administration (62).

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.

CENTRAL ILLUSTRATION **Heart Failure Collaboratory Working Groups and Anticipated Achievements**



O'Connor, C.M. et al. J Am Coll Cardiol. 2018;71(4):443–53.

Difficulties conducting HF clinical trials brought together a multidisciplinary stakeholder group focused on improving the design, performance, and utility of future HF research. HF = heart failure.

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 distrust 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 PatientsLikeMe (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 reinvigorating 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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REFERENCES

1. Fordyce CB, Roe MT, Ahmad T, et al. Cardiovascular drug development: is it dead or just hibernating? J Am Coll Cardiol 2015;65:1567–82.

2. Butler J, Tahhan AS, Georgiopoulou VV, et al. Trends in characteristics of cardiovascular clinical trials 2001–2012. Am Heart J 2015;170:263–72.

3. The Center for Information and Study on Clinical Research Participation. 2015 Perceptions & Insights Study. Available at: https://www.ciscrp.org/our-programs/research-services/perceptions-insights-studies/. Accessed April 21, 2017.

4. Corneli A, Pierre C, Hinkley T, et al. One and done: reasons principal investigators conduct only one FDA-regulated drug trial. Contemp Clin Trials Commun 2017;6:31–8.

5. Fost N, Levine RJ. The dysregulation of human subjects research. JAMA 2007;298:2196–8.

6. Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005–2012. JAMA 2014;311:368–77.

7. Cowie MR, Filippatos GS, Alonso Garcia MLA, et al. New medicinal products for chronic heart failure: advances in clinical trial design and efficacy assessment. Eur J Heart Fail 2017;19:718–27.

8. Masoudi FA, Havranek EP, Wolfe P, et al. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. Am Heart J 2003;146:250–7.

9. Kim ES, Carrigan TP, Menon V. International participation in cardiovascular randomized controlled trials sponsored by the National Heart, Lung, and Blood Institute. J Am Coll Cardiol 2011;58:671–6.

10. Tufts Center for the Study of Drug Development. Outlook 2011. Available at: http://csdd.tufts.edu/files/uploads/outlook-2011.pdf. Accessed April 21, 2017.

11. Stair TO, Reed CR, Radeos MS, Koski G, Camargo CA, for the MARC Investigators. Variation in institutional review board responses to a standard protocol for a multicenter clinical trial. Acad Emerg Med 2001;8:636–41.

12. Department of Health and Human Services, Food and Drug Administration. Determining the extent of safety data collection needed in late-stage premarket and postapproval clinical investigations—guidance for industry. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291158.pdf. Accessed April 21, 2017.

13. Berndt ER, Cockburn IM. Price indexes for clinical trial research: a feasibility study. Monthly Labor Review 2014. Washington, DC: U.S. Bureau of Labor Statistics, 2014.

14. Lundh A, Krogsboll LT, Gotzsche PC. Sponsors' participation in conduct and reporting of industry trials: a descriptive study. Trials 2012;13:146.

15. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. J Health Econ 2016;47:20–33.

16. Kaitin KI. Deconstructing the drug development process: the new face of innovation. Clin Pharmacol Ther 2010;87:356–61.

17. Smietana K, Siatkowski M, Moller M. Trends in clinical success rates. Nat Rev Drug Discov 2016;15:379–80.

18. Hwang TJ, Carpenter D, Lauffenburger JC, et al. Failure of investigational drugs in late-stage clinical development and publication of trial results. JAMA Intern Med 2016;176:1826–33.

19. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.

20. Chambers JD, Chenoweth M, Cangelosi MJ, Pyo J, Cohen JT, Neumann PJ. Medicare is scrutinizing evidence more tightly for national coverage determinations. Health Aff (Millwood) 2015;34:253–60.

21. Institute of Medicine (US) Committee on Cancer Clinical Trials and the NCI Cooperative Group Program. A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program. Washington, DC: National Academies Press, 2010.

22. Prowell TM, Theoret MR, Pazdur R. Seamless oncology-drug development. N Engl J Med 2016;374:2001–3.

23. Bikdeli B, Punnanithinont N, Akram Y, et al. Two decades of cardiovascular trials with primary surrogate endpoints: 1990–2011. J Am Heart Assoc 2017;6:e005285.

24. Pfeffer MA, Skali H. PRAISE (Prospective Randomized Amlodipine Survival Evaluation) and criticism. J Am Coll Cardiol HF 2013;1:315–7.

25. Cohn JN, Goldstein SO, Greenberg BH, et al., for the Vesnarinone Trial Investigators. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. N Engl J Med 1998;339:1810–6.

26. Kim C, Prasad V. Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival: an analysis of 5 years of US Food and Drug Administration Approvals. JAMA Intern Med 2015;175:1992–4.

27. Rowe SM, Borowitz DS, Burns JL, et al. Progress in cystic fibrosis and the CF Therapeutics Development Network. Thorax 2012;67:882–90.

28. Ramsey BW, Nepom GT, Lonial S. Academic, foundation, and industry collaboration in finding new therapies. N Engl J Med 2017;376:1762–9.

29. Cystic Fibrosis Foundation. Clinical trial finder. Available at: https://www.cff.org/Trials/Finder. Accessed December 5, 2017.

30. Majumdar SR, Roe MT, Peterson ED, Chen AY, Gibler WB, Armstrong PW. Better outcomes for patients treated at hospitals that participate in clinical trials. Arch Intern Med 2008;168:657–62.

31. Lewis SJ, Mehta LS, Douglas PS, et al. Changes in the professional lives of cardiologists over 2 decades. J Am Coll Cardiol 2017;69:452–62.

32. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797–805.

33. O'Connor CM, Meese R, Carney R, et al. A randomized trial of intravenous heparin in conjunction with anistreplase (anisoylated plasminogen streptokinase activator complex) in acute myocardial infarction: the Duke University Clinical Cardiology Study (DUCCS) 1. J Am Coll Cardiol 1994;23:11–8.

34. Centers for Medicare & Medicaid Services. MEDCAC Meeting 3/22/2017—health outcomes in heart failure treatment technology studies. Available at: https://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=73. Accessed April 9, 2017.

35. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Available at: https://www.fda.gov/downloads/Drugs/.../Guidances/ucm071627.pdf. Accessed April 21, 2017.

36. Ford I, Norrie J. Pragmatic trials. N Engl J Med 2016;375:454–63.

37. Maddox TM, Albert NM, Borden WB, et al. The learning healthcare system and cardiovascular care: a scientific statement from the American Heart Association. Circulation 2017;135:e826–57.

38. Familial Hypercholesterolemia Foundation. Find FH. Available at: https://thefhfoundation.org/find-fh. Accessed December 5, 2017.

39. Stanford Medicine. MyHeart Counts. Available at: https://med.stanford.edu/myheartcounts.html. Accessed December 5, 2017.

40. National Institutes of Health. Eureka Mobile Research. Available at: http://info.eurekaplatform.org/. Accessed December 5, 2017.

41. McConnell MV, Shcherbina A, Pavlovic A, et al. Feasibility of obtaining measures of lifestyle from a smartphone app: The MyHeart Counts Cardiovascular Health Study. JAMA Cardiol 2017;2:67–76.

42. Guo X, Vittinghoff E, Olgin JE, Marcus GM, Pletcher MJ. Volunteer participation in the Health eHeart Study: a comparison with the US population. Sci Rep 2017;7:1956.

43. McAlindon T, Formica M, Kabbara K, LaValley M, Lehmer M. Conducting clinical trials over the internet: feasibility study. BMJ 2003;327:484–7.

44. Redfield MM, Velazquez EJ, Braunwald E. Nitrates in heart failure with preserved ejection fraction. N Engl J Med 2016;374:1589.

45. Exner DV, Dries DL, Domanski MJ, Cohn JN. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. N Engl J Med 2001;344:1351–7.

46. Ramamoorthy A, Pacanowski MA, Bull J, Zhang L. Racial/ethnic differences in drug disposition and response: review of recently approved drugs. Clin Pharmacol Ther 2015;97:263–73.

47. United States Census Bureau. Population. Available at: https://www.census.gov/topics/population.html. Accessed April 21, 2017.

48. Sardar MR, Badri M, Prince CT, Seltzer J, Kowey PR. Underrepresentation of women, elderly

patients, and racial minorities in the randomized trials used for cardiovascular guidelines. JAMA Intern Med 2014;174:1868–70.

49. United States Food and Drug Administration. Drug trials snapshot: Entresto. Available at: https://www.fda.gov/Drugs/InformationOnDrugs/ucm457521.htm. Accessed April 21, 2017.

50. National Institutes of Health. NIH policy and guidelines on the inclusion of women and minorities as subjects in clinical research—amended, October, 2001. Available at: https://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. Accessed April 21, 2017.

51. Department of Health and Human Services, Food and Drug Administration. Collection of race and ethnicity data in clinical trials—guidance for industry and Food and Drug Administration Staff. Available at: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf. Accessed April 21, 2017.

52. Lindenfeld J, Fiske KS, Stevens BR, Debuhr J, Havranek EP, Abrams FR. Age, but not sex, influences the measurement of ejection fraction in elderly patients hospitalized for heart failure. J Card Fail 2003;9:100–6.

53. Masoudi FA, Havranek EP, Smith G, et al. Gender, age, and heart failure with preserved left ventricular systolic function. J Am Coll Cardiol 2003;41:217–23.

54. Wendler D, Kington R, Madans J, et al. Are racial and ethnic minorities less willing to participate in health research? PLoS Med 2006;3:e19.

55. Corbie-Smith G, Thomas SB, St George DM. Distrust, race, and research. Arch Intern Med 2002;162:2458–63.

56. Sherber NS, Powe NR, Braunstein JB. Personal physicians as study investigators: impact on patients' willingness to participate in clinical trials. Contemp Clin Trials 2009;30:227–32.

57. PatientsLikeMe. Available at: http://www.patientslikeme.com. Accessed December 5, 2017.

58. Pew Research Center. Social media update 2016. Available at: http://www.pewinternet.org/2016/11/11/social-media-update-2016/. Accesssed April 21, 2017.

59. Vivo RP, Krim SR, Liang L, et al. Short- and long-term rehospitalization and mortality for heart failure in 4 racial/ethnic populations. J Am Heart Assoc 2014;3:e001134.

60. Kao DP, Lewsey JD, Anand IS, et al. Characterization of subgroups of heart failure patients with preserved ejection fraction with possible implications for prognosis and treatment response. Eur J Heart Fail 2015;17:925–35.

61. Kao DP, Wagner BD, Robertson AD, Bristow MR, Lowes BD. A personalized BEST: characterization of latent clinical classes of nonischemic heart failure that predict outcomes and response to bucindolol. PLoS One 2012;7:e48184.

62. U.S. Food and Drug Administration. Drug trials snapshots. Available at: https://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm. Accessed December 5, 2017.

KEY WORDS cardiovascular, clinical trial, enrollment, Food and Drug Administration, heart failure, recruitment

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