Opportunities and challenges in heart rhythm research: Rationale and development of an electrophysiology collaboratory

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Abstract

There are many challenges in the current landscape of electrophysiology (EP) clinical and translational research, including increasing costs and complexity, competing demands, regulatory requirements, and challenges with study implementation. This review seeks to broadly discuss the state of EP research, including challenges and opportunities. Included here are results from a Heart Rhythm Society (HRS) Research Committee member survey detailing HRS members' perspectives regarding both barriers to clinical and translational research and opportunities to address these challenges. We also provide stakeholder perspectives on barriers and opportunities for future EP research, including input from representatives of the U.S. Food and Drug Administration, industry, and research funding institutions that participated in a Research Collaboratory Summit convened by HRS. This review further summarizes the experiences of the heart failure and heart valve communities and how they have approached similar challenges in their own fields. We then explore potential solutions, including various models of research ecosystems designed to identify research challenges and to coordinate ways to address them in a collaborative fashion in order to optimize innovation, increase efficiency of evidence generation, and advance the development of new

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therapeutic products. The objectives of the proposed collaborative cardiac EP research community are to encourage and support scientific discourse, research efficiency, and evidence generation by exploring collaborative and equitable solutions in which stakeholders within the EP community can interact to address knowledge gaps, innovate, and advance new therapies.

KEYWORDS Electrophysiology; Research opportunities; Collaboratory; Collaborative community

ABBREVIATIONS **CDRH** = Center for Devices and Radiological Health; **CF** = cystic fibrosis; **CMS** = Centers for Medicare & Medicaid Services; **EP** = electrophysiology; **FDA** = U.S. Food and Drug Administration; **HFC** = Heart Failure Collaboratory; **HRS** = Heart Rhythm Society; **HVC** = Heart Valve Collaboratory; **IDE** = investigational device exemption; **NHI** = National Institutes of Health; **NHLBI** = National Heart, Lung, and Blood Institute; **PCORI** = Patient-Centered Outcomes Research Institute; **PCORnet** = National Patient-Centered Clinical Research Network; **PCT** = pragmatic clinical trial; **PI** = primary investigator; **QOL** = quality of life; **RCT** = randomized clinical trial

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1. Objectives and goals of this research white paper and the current electrophysiology research landscape

Heart rhythm disorders are a major cause of morbidity and mortality throughout the globe.[1] Despite major advances in diagnostics and therapeutics, the prevalence of atrial fibrillation continues to rise[2] and ventricular arrhythmias remain the major cause of sudden cardiac death, which accounts for an estimated 15% of all deaths.[3] Arrhythmias are now recognized as major corollaries of diverse cardiopulmonary, metabolic, and systemic disorders.[4] The diversity of arrhythmia phenotypes and mechanisms has led to vibrant research that has responded to the challenge with significant bench-to-bedside discoveries over the past few decades. Even with this progress, much work is still needed to achieve the vision of the Heart Rhythm Society (HRS): "[T]o end death and suffering due to heart rhythm disorders." Future research opportunities are promising, spanning artificial intelligence, digital health, device therapy advances, and ablation innovations.

There are a number of challenges in the current clinical and translational research landscape, including increasing costs and complexity, competing demands, regulatory requirements, and difficulties with study implementation. Acceleration of the pace of arrhythmia research will be important in translating discoveries into strategies that meaningfully improve patient outcomes. Ideally, research would be focused on important unmet needs in clinical arrhythmia medicine or scientific knowledge gaps, generating a framework to address "pieces of the puzzle."

This white paper seeks to broadly discuss the electrophysiology (EP) research landscape, including research opportunities and challenges, and how these challenges might be addressed. In this context, we consider the creation of a collaborative community, entitled the EP Collaboratory, representing a research ecosystem focused on important unmet research needs within the EP community.

This effort incorporates input from HRS members who participated in the *2020 HRS Member Survey on Barriers to Effective Research*, conducted by the HRS Research Committee, as well as perspectives of key stakeholders, including active basic, translational, and clinical researchers; the U.S. Food and Drug Administration (FDA); Centers for Medicare & Medicaid Services (CMS); industry; and funding institutions (National Heart, Lung, and Blood Institute [NHLBI] and Patient-Centered Outcomes Research Institute [PCORI]) that participated in an EP Collaboratory virtual summit convened by HRS in February 2021.

A central theme is smoothing "pain points" and addressing challenges in conducting research and participating in clinical trials. The proposed approach is collaborative and inclusive, involving clinical, translational, and basic science communities; industry; regulatory agencies; patient representatives; and ultimately funding agencies. We conclude with some recommendations on the formation of an EP Collaboratory and the role of a prominent professional society such as HRS in the Collaboratory.

2. Perspectives on challenges and opportunities for future EP research

In this section, we present perspectives on the current clinical research environment, the challenges that various stakeholders face and foresee in their areas of research, and how a multistakeholder collaborative community may help address those challenges.

2.1. HRS members' perspectives

2.1. a Results from the HRS Member Survey on Barriers to Clinical/Translational Research: Unmet needs

During the summer of 2020, the HRS Research Committee conducted an electronic survey to assess members' perceptions of barriers to successful heart rhythm research. Approximately 300 HRS members (5% of membership) completed the survey. There was international representation, with nearly 30% of respondents from outside the United States.

The order in which participants ranked the potential barriers to research, starting from the greatest barrier, was as follows: (1) funding; (2) protected time to manage research; (3) availability of research staff, such as clinical research coordinators; (4) need for access to clinical trial

databases and registries for secondary analysis; (5) limited support from home institution to perform research studies; (6) need for an industry partner to sponsor research; (7) need for assistance submitting an investigational new drug or investigational device exemption (IDE) application to the FDA; (8) need to identify collaborators at other institutions; (9) need for assistance identifying ideas for a research study; and (10) limited number of patients for enrollment. Of note, all barriers were considered significant by participants, with average rankings between 2 and 4 on a scale of 1–5.

Respondents of the survey were also asked how a collaborative community could be helpful in overcoming these barriers. The top 4 responses, as shown in Figure 1, were as follows: (1) identification of collaborators from other institutions; (2) identification of federal or private funding opportunities; (3) connections with industry partners who might sponsor a study; and (4) access to clinical trial and registry databases. At least 20% of respondents stated that an EP Collaboratory might also be able to assist in (1) submitting paperwork to the FDA; (2) creating a dialogue on research ideas, such as via the Research Connect HRS portal; (3) connecting basic science and clinical researchers; (4) working with other professional societies; (5) developing a protocol; (6) submitting institutional review board applications; and (7) recruiting research staff, such as coordinators, technicians, and postdoctoral fellows.

When asked about the most effective ways that a professional organization or a collaborative community could help them interact with other potential researchers, the following were identified as important by 50%–75% of respondents: (1) an HRS website such as Research Connect; (2) access to a member database to obtain contact information of potential collaborators; and (3) opportunities to facilitate research collaborations at national or regional scientific meetings.

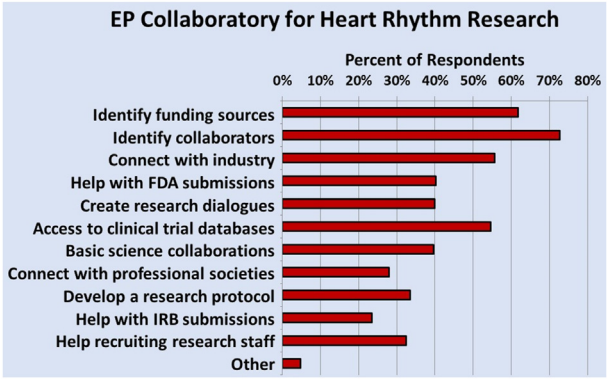

Figure 1 Key results from the 2020 Heart Rhythm Society Member Survey on Barriers to Effective Research. The percentage of respondents endorsing each of the barriers to effective research is shown graphically. EP = electrophysiology; FDA = U.S. Food and Drug Administration; IRB = institutional review board.

With respect to specific content areas for research, the following 4 areas were of roughly equal importance to respondents: digital health/monitoring, atrial fibrillation, cardiac implantable electronic devices, and ablation technologies.

In summary, HRS members highlighted several barriers to arrhythmia research and the majority thought that an EP Collaboratory might be able to address some of these barriers. Members were interested in a broad spectrum of EP research areas. These responses motivated subsequent discussions on an EP Collaboratory.

2.1. b *HRS members' perspective* from the research community at the EP Collaboratory summit

A panel of HRS member stakeholders that focus on clinical and translational EP research provided their perspectives on barriers to heart rhythm research. All panelists agreed that identifying funding sources, particularly for large clinical trials and observational studies, is a major challenge in the current climate. They also identified the relative lack of EP-focused research networks and registries in the United States as compared with those in Europe, such as the EURObservational Registry Programme. Another major challenge identified involved training and motivating the next generation of electrophysiologists to continue to participate in academic research, particularly in the current reimbursement environment with salaries based primarily on relative value units. An EP Collaboratory could serve to showcase the importance and impact of EP research through dissemination of results. The Collaboratory could also serve as a matchmaker for sponsors, investigators, mentees, and clinical electrophysiologists who wish to participate in research, providing the opportunity to share documents and case report forms and identify clinical trial sites. Finally, HRS and the Collaboratory could advocate for EP research with federal funding agencies, help set research priorities, and lend support to primary investigator (PI)–initiated studies. The focus could be on identifying unmet needs as well as defining and developing novel research ideas (eg, translational and basic science).

2.2. FDA perspective

In the United States, the FDA regulates drugs and devices used in the diagnosis and treatment of patients with heart rhythm disorders. The Center for Devices and Radiological Health (CDRH) regulates many of the tools that electrophysiologists use in the care of their patients, including mapping and ablation technology, implantable devices such as pacemakers and defibrillators, and a myriad of other devices. These include wearable monitors, applications of Software as a Medical Device,[5] and other applications in the realm of digital health. CDRH's current vision is that "patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world (p. 2)."[6] As such, the agency has a strong interest in accelerating the approval process, removing unnecessarily burdensome

requirements,[7] and encouraging innovative trial designs. For example, the agency encourages use of existing clinical data through Bayesian trial designs[8] or other statistical methods that allow the incorporation of existing external evidence to more efficiently develop inferences. Augmenting prospective clinical trials with existing external data often reduces the necessary numbers of subjects needed to achieve a desired statistical power in clinical trials. In addition, the agency is increasingly incorporating the analysis of relevant and reliable real-world evidence in the device approval process, such as using evidence from peer-reviewed publications describing clinical results outside the prospective clinical trials, and analyses of registry, health record, and claims data (https://www.fda.gov/media/146258/download). In the current era, real-world evidence from databases such as the Medicare claims database can be incorporated into postapproval studies. The Electrophysiology Predictable and Sustainable Implementation of National Registries paradigm is a good example of conducting postapproval studies of pacemaker and defibrillator leads, as it links data from the Medicare claims database to existing device registries and other sources to gather long-term performance data.[9]

One concern is the existence of distinct subpopulations within the larger group of patients with specific disease states for whom the results of large clinical trials may not be applicable. One important example is the development of devices and their labeling for children. Recognizing the need for developing pathways to device approval for children, the agency has developed a road map for leveraging relevant existing clinical data for use in device approval and clearances in children.[10] These existing data may be developed for adults from whom it may be reasonable to extrapolate to a pediatric population.

There is a common misperception that the FDA necessitates large randomized prospective clinical trials for approval of devices in all cases. As noted above, this is often not the case. The FDA provides mechanisms for investigators to engage with FDA staff in planning clinical studies that involve medical devices. The agency's presubmission process ("Q-Submission") allows investigators and device manufacturers to request answers to specific questions regarding device classification, regulatory requirements, plans for clinical studies, and the potential need for an IDE.[11] If a planned clinical trial involves a device that is a "significant risk" device and is not exempt, the agency works interactively with sponsors and investigators to expedite the approval of the IDE and maximize the likelihood that the study will subsequently support a successful marketing application. Investigators can gain expert and in-depth feedback from agency staff regarding their study design and plans for statistical analysis through the presubmission and IDE processes. The avenues for obtaining guidance from the FDA are perhaps underutilized by investigators in the heart rhythm space.

In summary, the FDA has a strong interest in working interactively with investigators and device manufacturers to facilitate the conduct of clinical research and eventual device clearance or approval.

2.3. Industry perspective

Industry plays an important role in EP clinical research as a critical funding source and driver of innovation, most notably considering increased costs of clinical trials and the importance of incorporating real-world data into the approval process. There was a general sentiment that the current evidence-generating system is too expensive, takes too long, does not enroll diverse populations, and does not answer priority patient questions. Then, after evidence is available, it is hard to translate results into practice. Industry partners outlined several actionable opportunities that an EP Collaboratory could address.

First, it is important to align research and innovation priorities of industry and other stakeholders. A Collaboratory could facilitate this process via discussions to identify questions that are clinically and scientifically important but are also feasible and fall within the strategic vision of industry partners. Discussions could focus on near-term and long-term goals, with an aim to increase the efficiency and reduce the duplication of effort.

Second, several inefficiencies were identified by industry in the current system of evidence generation. These inefficiencies include nonuniformity of definitions, clinical end points, data sources, and patient monitoring standards, which make it difficult to widely implement clinical studies and trials. An EP Collaboratory could encourage the establishment of universal definitions for clinically meaningful end points, standardized reporting, and patient monitoring. In addition, the current infrastructure for sharing data with industry collected at individual hospitals regarding the effectiveness of a particular product is suboptimal. A more efficient process could lead to more widespread use of real-world data for the purposes of improving products and securing FDA approval, which, in turn, could facilitate more widespread adoption of clinical trial designs based on registries to complement results from randomized clinical trials (RCTs). An EP Collaboratory would be the ideal entity to help improve these processes through interventions such as facilitating implementation of lean case report forms, helping to provide the system for sharing anonymized data from electronic health record systems, and others.

Industry identified the emphasis on traditional clinical trials as a limitation because they are increasingly costly and lengthy, may lack population diversity, and often leave important patient questions unanswered. Solutions that extend patient recruitment strategies beyond in-person encounters will be important. Potential solutions include utilizing virtual platforms for recruiting and engaging patients and broadening the diversity of recruited patients to include underrepresented minorities and thus widen the applicability of study results.

A final critical issue relates to difficulties in translating evidence into clinical practice. An EP Collaboratory could focus on testing and establishing methodologies that emphasize the integration of clinical trial results as well as real-world evidence and nontraditional evidence into clinical practice.

2.4. Research funding perspective

Funding organizations are critically important in shaping research priorities and directing resources to meet research challenges. An EP Collaboratory can seek to engage both traditional and nontraditional sources of funding. In fact, there are a number of important sources of funding for heart rhythm research, including the NHLBI, American Heart Association, PCORI, industry, and international collaborations such as the Global Cardiovascular Research Funders Forum. As it is beyond the scope of this work to provide perspectives for all potential funding sources, this section provides a representative perspective from the NHLBI as a major funding agency for heart rhythm research.

The NHLBI has played an important role in supporting clinical research ranging from basic experimental studies in humans to early-phase trials to phase 3 trials, observational studies, pragmatic trials, and implementation trials. Objective 6 of the NHLBI Strategic Vision specifically focuses on the optimization of clinical and implementation research to improve health and reduce disease through new methodologies, technologies, and research frameworks. The NHLBI considers multiple criteria relevant to scientific merit, program balance, and strategic priorities in decision making. Of note, clinical and public health relevance may be considered in developing proposals such as studies that have the potential for filling a knowledge gap, influencing a change in current guidelines and supporting practice change, or advancing science.

In supporting trial research, the NHLBI looks for evidence of feasibility and, in general, encourages investigators to conduct trials that are as pragmatic and streamlined as possible. It is preferred that clinical trial investigators have a demonstrable ability to recruit trial participants and that investigators consider including potential risks and mitigation plans. The NHLBI also encourages diversity in the investigator team. Another aspect is diversity in trial participants, with the expectation that the trial's population will reflect the U.S. census, unless the disease under study has a different distribution. The NHLBI implements a milestone-based, staged-award approach for early-phase, phase 2, and beyond single- and multisite clinical trials in an effort to enhance performance.[12] The NHLBI encourages investigators to pay particular attention to the budget and to adapt to streamlined approaches for conducting a clinical trial in order to decrease the cost. The NHLBI emphasizes investigator-initiated studies in response to appropriate National Institutes of Health (NIH) parent funding opportunity announcements or NHLBI clinical trial funding opportunity announcements (https://www.nhlbi.nih.gov/grants-and-training/funding-opportunities-and-contacts/clinical-trials-optimization). For investigator-initiated studies, the NHLBI encourages collaboration with industry, registries, and other resources when possible. A recent article by the NHLBI team outlines contemporary funding options as well as select important NHLBI policies and priorities for investigators interested in clinical trial research.[12]

An EP Collaboratory could facilitate productive interactions among funding organizations, individual investigators, industry, FDA, and patient groups to help align key research priorities for the field among these groups. While funding organizations by necessity will continue to remain independent and set their own research priorities, these interactions have the potential to provide important feedback to funding organizations about the research interests of key stakeholders. In this way, independent investigators stand to benefit from involvement in these conversations.

3. Future opportunities for growth in EP research

EP is one of the most rapidly growing fields in cardiology. This growth can be supported and catalyzed by opportunities for advancing EP research. These opportunities include implementing innovative research designs, incorporating digital health technology and social media, maximizing diversity and representation of research participants and those who conduct research, leveraging international collaborative initiatives, expanding the use of implementation science, and innovating in translational research. Opportunities that are likely to be achieved through an EP Collaboratory are discussed below.

3.1. Pragmatic trial designs and evidence generation

Pragmatic clinical trials (PCTs) measure the benefits and risks of a treatment or intervention in routine clinical practice, while traditional explanatory randomized trials measure efficacy under ideal conditions.[13] Table 1 presents a comparison of the characteristics of PCTs and those of explanatory trials. Large-scale PCTs are usually embedded within routine clinical care and often involve cluster randomization of hospitals, clinics, primary care providers, etc.[14] Interventions can be implemented by health system personnel through usual communication channels and quality improvement infrastructure, and data are collected as part of routine clinical care. For trials assessing implementation of a policy and/or intervention, stepped-wedge cluster RCTs (Figure 2), in which all sites transition from the control to the active intervention but with randomized assignments with respect to the timing of transition, have significant advantages.[15]

The PRagmatic Explanatory Continuum Indicator Summary 2 tool remains the standard for assessing pragmatism in a trial. This tool encompasses 9 domains that include eligibility, recruitment, setting, organization, flexibility of delivery, flexibility of adherence, follow-up, primary outcome, and primary analysis.[16]

While there has yet to be an extensive uptake of PCTs in EP, implementation of this research design is a significant unfulfilled opportunity. Given the expense and time commitment needed to conduct arrhythmia-based clinical trials, pragmatic designs could yield timely results, use fewer resources, and inform current gaps in clinical practice. Benefits include generating real-world evidence that is more generalizable and inclusive of historically underrepresented patient groups, including racial and ethnic minorities, individuals over the age of 70 years, women, and other systemically disadvantaged populations. Ideally, PCTs in EP measure outcomes important to patients most consistent with their values and preferences, consistently incorporate social determinants of health, and improve patient recruitment, engagement, and retention. Such trials are likely to bring value to all stakeholders, including patients, clinicians, community leaders, the health care system, and funding and regulatory agencies, and will increase the delivery of high-quality care.

Examples of research questions that could be addressed using PCTs include optimal management of asymptomatic atrial fibrillation in younger individuals, management and outcomes of asymptomatic device-detected atrial fibrillation, assessment of the benefits and risks of conduction system pacing, and strategies to approach ablation techniques in persistent atrial fibrillation and ventricular arrhythmias. Incorporating large data sets and site-based infrastructures inclusive of electronic health records provides the opportunity for innovative arrhythmia research that elevates the impact of emerging digital technologies. In conducting such PCTs, it will be critical to leverage best practices and lessons learned from entities such as the NIH Collaboratory and the National Patient-Centered Clinical Research Network (PCORnet), both founded to accelerate pragmatic clinical research.[17]

An EP Collaboratory can be structured to provide the necessary framework to cultivate PCTs to test important arrhythmia-based research questions that incorporate routine medical care, promote data collection from electronic health records and claims, incorporate large sample sizes, and unite constituents, including health care delivery organizations, providers, researchers, and representatives from industry and other government and regulatory agencies.

Table 1 Pragmatic and explanatory clinical trials

Pragmatic	Explanatory
Representative participants	Highly selected participants
Considers social determinants of health/environment	Focuses on biology
Recruits in usual care, many centers	Recruits using nonusual care screening or recruitment strategies, fewer centers
Incorporates settings where results apply	Limits applicability to many settings
Interventions "slotted" into usual care	Interventions may need additional resources
Flexibility in delivery and adherence	Standardized delivery and highly controlled adherence
Follow-up parallels usual care	More intensive follow-up
Often multiple primary outcomes that are patient centered	Primary outcome may not be relevant to participants
Primary analysis is intention-to-treat	Primary analysis is per protocol

3.2. Digital health, technology, and social media

The tremendous growth in the digital health sector over the last decade is well documented, with more than 1200 companies focused on digital health offering a wide array of services, including prevention, detection, and management of disease. Among digital health and commercial technology companies working in the cardiovascular space, many focus on the use of wearables and biosensors for heart monitoring or detection.[18] Broadened adoption by older adults of smartphones and low-cost commercial wearables capable of accurate heart rate and rhythm assessment represents an

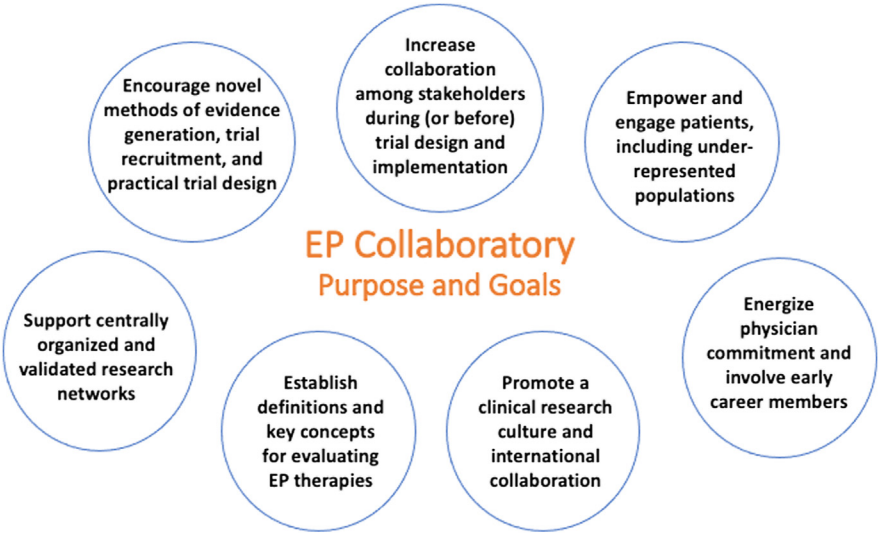

Figure 2 Potential goals in establishing an EP Collaboratory. The graphic summarizes the proposed interventions associated with an EP Collaboratory. EP = electrophysiology.

opportunity to leverage these tools in EP clinical trials for longitudinal assessment of patient-reported exposures and biosensor outcomes.[19,20] Several large cohort studies, including the Framingham Heart Study, the All of Us Research Program, the RURAL (Risk Underlying Rural Areas Longitudinal) Heart and Lung Study, and the Health eHeart Study, are using digital technologies to expand understanding of triggers of arrhythmias and relations between activity, sleep quality, and heart rhythm abnormalities.[20]

Heart rhythm specialists are increasingly utilizing digital health technologies in their clinical practice.[21] Significant opportunities exist to better understand how digital health metrics relate to clinical outcomes and how these tools can be better integrated into contemporary systems of care and clinical workflows.[22] Future opportunities (Table 2) also exist for developing new capabilities, including heart rhythm disease prediction, disease or drug monitoring, and large-scale population management, using software powered by artificial intelligence and machine-learning approaches.[23] Finally, within the social media space, significant opportunity exists to create new public health, personal health, and study awareness with patient advocacy groups (eg, StopAfib.org) and influencers.[24] In addition, the social media platform, along with other digital platforms, represents an emerging research environment within which researchers can develop tools to recruit, e-consent, engage, and follow research participants; curate better experiences; convey more accurate content; and promote more informed conversations between clinicians and patients with heart rhythm disorders.[25] An EP Collaboratory could connect various stakeholders so that they can access and develop these promising digital health initiatives.

3.3. Maximizing diversity and representative populations

Clinical research provides the critical evidence base for evaluating the efficacy, effectiveness, and safety of therapies. Since treatment response may differ among population subgroups, it is imperative that the approach to data generation is fully representative. Increasing diversity improves health care quality.[26] Barriers to diversity in clinical trials are well recognized,[27] and the potential solutions for overcoming them remain a challenge. Several actionable opportunities exist that may help to narrow the diversity gap in EP research (Table 2).

- *Collaborative community infrastructure.* The organization of a Collaboratory will include diversity champions to ensure diversity and representation of the enrolled populations. In addition, the inclusion of a diverse stakeholder group may further cultivate potential solutions.

Table 2 Opportunities and challenges in heart rhythm research

Research area	Opportunities	Challenges	Solutions
Digital health, technology, and social media	Longitudinal patient assessment. Digital health metrics and clinical outcomes. Heart rhythm disease prediction. Large-scale population management.	Regulatory and reimbursement barriers. Reliability of data. Health privacy and ownership of health data. Institutional inertia to digital adoption.	Incorporate digital data and tools into clinical trials. Create public health and study awareness with patient advocacy groups. Develop digital tools to engage research participants.
Diversity and representative populations	Increasing diversity improves health care quality. Learning from prior studies with diverse enrollment.	Lack of diversity and representation in clinical trials.	Diversity working group and diversity champions. Diverse stakeholders. Diverse research and clinical trial leadership.
International collaboration	Diverse populations. Results generalizability. Broad result dissemination. Large sample size.	Communication complexities. Complex, diverse regulatory processes.	Repositories of regulatory documents. International study leads, clinical research organizations, translation services.
Implementation science	Provider education and training. Representative clinical trial populations. Patient-reported outcomes/ quality of life measures.	Lack of clinical trial data adoption. Results generalizability. Applied results to clinical practice. Coverage for new therapies.	Upstream pragmatic clinical trial designs. Robust registries. Incorporate patient input. Engage regulators, payers. Research finding and trial result dissemination.
Translational research	Develop new treatments. Transform discoveries to clinical practice. Determine treatment dosing. Provide foundation for regulatory approval and clinical trials.	Difficult replication of the clinical state. Costly animal models and translational facilities. Decline in physician-scientists and protected research time.	Standardized protocols. Establish core resources and core expertise. Identify unmet needs/knowledge gaps. Translational research curriculum/ mentorship.

- *Diversity working group.* The goal of a dedicated diversity working group would be to work in collaboration with various stakeholders (eg, funding agencies and industry) to identify key priority areas and deliverables, specifically defining diversity benchmarks, best practices, and mechanisms for accountability. For example, this group could establish enrollment targets for sex, racial, or ethnic groups based on specific disease prevalence as well as diversity targets for leadership positions in trials and measures of accountability.
- *Lessons learned from the past.* There are several notable examples of cardiovascular clinical trials that have exclusively focused on enrolling underrepresented populations.[28–30] Establishing a mechanism to learn from prior studies that were successful at enrolling diverse patients will be important. The follow-through would be to have a platform where successful strategies could be summarized and shared. This may help inform the design of future studies that could formally test those strategies.
- *Protocol to practice.* A strong research system would ideally be examined to determine ways for improving the representation of diverse populations. Examples include (1) review of eligibility criteria that would promote diverse enrollment, (2) use of technologies such as electronic health records for screening, (3) identification of sites with diverse populations, (4) providing local investigators with a tool kit to help maximize diversity, and (5) ensuring educational material is tailored to diverse populations.
- *Building capacity.* Prior studies have shown that diverse research leadership results in more diverse patient enrollment. This begins by developing initiatives that increase diversity at all levels of the medical workforce.[31] Identifying and training diverse research team members (local PI, national PI, steering committee, and executive committee), particularly in leadership positions, may maximize the recruitment of representative populations.

3.4. International collaborative research

International collaborative research offers unique opportunities and challenges (Table 2).[32,33] International involvement increases the likelihood of enrolling diverse patient populations and of generalizability of study results. Consequently, the results are more likely to be incorporated in local and regional practice guidelines, resulting in better dissemination of study treatments.

International participation is also key when a large sample size is needed, as it allows an adequate number of centers to complete the study successfully. Creation of a database of international centers that have performed well and that is accessible to investigators would be of immense value. Basic information on past performance (eg, time to obtain regulatory approvals, percentage of enrollment targets, and quality of data collection) would be of most importance in aiding the selection of sites when launching a new study. The optimal database would be maintained and be modular based on the type of intervention tested and the specialty of the center (eg, pharmacologic, device, and ablation). Similarly, it is important that novel techniques evaluated by studies are equally possible in a variety of centers outside the just large specialized programs limited to one geographic location.

In leveraging international collaborative research, several potential challenges are to be considered. First, fundamental to the successful deployment and execution of an international study is communication between the study leadership/management team and international sites. The communication methods are now rapid and diverse, but challenges remain with regard to language barriers and time differences. Due to time zone differences, something as simple as randomization could pose a challenge if it is to occur shortly before a procedure. Carefully choosing the timing of randomization during study design will allow sufficient flexibility when involving international sites.

Second, a fundamental component of starting a study is the regulatory process. Securing ethics approval can be lengthy because of a lack of knowledge of approval processes, study documents, and legislation among participating sites in different countries. Overcoming these hurdles involves strong local or country project leaders that are familiar with the procedures and documents at each institution/country. Other potential solutions are listed in Table 2.

Third, selection of international partners could have either positive or negative impacts on study budgets. Generally, costs to conduct studies outside the United States are much more competitive and are designed to encourage international collaboration. Of course, foreign exchange rates are a consideration when building the budget, particularly for lengthy studies, as there could be important rate fluctuations with the resulting budget impact.

Fourth, social, cultural, and sometimes political differences can impact recruitment at international sites. Recruitment could be influenced by differences in local practice due to health care system restraints. For example, expensive device therapy may not be as accessible in countries where patients need to pay for health care themselves. In such countries, a study may need to pay all costs for a given procedure (eg, hospitalization and operating room time) rather than limiting the cost to the study device or intervention. Credibility of the study may be questioned depending on the funding source (outside government, industry, etc). Finally, equipoise of a study question may vary across different countries that may follow different clinical practice guidelines.

Fifth, data quality can vary significantly among various international centers. Designing simple, efficient electronic case report forms is key to the success of any study. An efficient electronic case report form will minimize extraneous data collection, streamline the process for local study coordinators, and minimize the costs associated with translation. Study monitoring for data quality can be performed remotely.

Finally, the funding source has to be considered carefully. Certain funding agencies or corporate divisions may limit the choice of sites outside their jurisdiction. An EP Collaboratory could establish an infrastructure for international

collaborative research that leverages its unique opportunities while addressing the aforementioned challenges.

3.5 Implementation science

Implementation science brings the latest therapies and technologies to routine clinical care. Specific challenges (Table 2) in implementation of scientific results include clinicians' education and engagement, compilation and synthesis of relevant results in a way that can be applied to clinical practice, generalizability of results to various patient populations or a variety of practice settings, and coverage and reimbursement for novel therapies. Clinicians' education, training, and engagement, especially with an ongoing development of new procedures, are key aspects of implementation science and improving awareness of studies' findings.[34] This is not limited to the electrophysiologist; it is equally important for non-EP cardiologists and primary care providers who refer patients to electrophysiologists. In this regard, guidelines can play an important role in disseminating the results of clinical studies, but, at times, even guidelines may not be easily adopted into clinical practice. In 2018, the NHLBI assembled an implementation science work group to evaluate clinical practice guideline implementation strategies and found that educational outreach visits and audits and feedback were generally effective in improving implementation, with reminders and provider incentives showing mixed effectiveness.[35]

Generalizability of results is another key factor as, often, clinical trial patients may not be reflective of the general population. Several studies have suggested that guidelines/clinical trial results may be applicable to less than a third of the target population,[36,37] which is especially true of the very elderly population, women, and racial and ethnic minorities who are not well represented in many trials.[38,39] It is therefore appropriate to consider generalizability in the design of clinical trials so that a population that is more representative of clinical practice is targeted. This may be particularly important for ablation procedures, in which registries have either confirmed the results of RCTs or suggested more modest benefit than that observed in RCTs.[40,41] Finally, focusing on patient-reported outcomes such as quality of life (QOL) and symptoms could lead to greater adoption of therapies and more engagement of patients. Patient-reported outcomes are underreported and underused, limiting a thorough evaluation of therapies, particularly ablation.[42] Greater use of QOL measures is paramount in giving patients a voice in studies and generating more meaningful comparisons of treatment strategies.[42] This can also help address another challenge to implementation of therapies, reimbursement, and coverage, which are often focused on hard outcomes of rehospitalization and mortality rather than QOL.

An EP Collaboratory may play an important role in addressing these challenges. It could assist in upstream alignment of clinical trial design, so the results are more applicable to clinical practice and could assure that patients have a voice. It may help design robust registries and serve as a forum for visualization of the "bigger picture," informing CMS and other agencies on coverage and reimbursement and potentially including or engaging these regulatory agencies early in the design of trials. The EP Collaboratory could be instrumental in disseminating research findings and improving implementation of science in clinical practice.

3.6. Translational research

Translational, or bench-to-bedside, research plays an essential role in developing new and effective treatments for arrhythmias and transforming molecular and cellular discoveries into clinical practice. Translational research is also key for determining treatment dosing, obtaining regulatory approval for therapies, and providing a foundation for subsequent clinical trials. Despite these benefits, less than a third of translational research findings are reproduced in clinical trials,[43,44] suggesting that significant challenges remain.

Most translational research relies on models that, ideally, mimic human clinical conditions. However, results from varied species (murine, canine, and porcine) are often difficult to extrapolate to a diverse human population.[45] Moreover, the complexity and diversity of a clinical condition, as with atrial fibrillation (eg, familial, paroxysmal, persistent, and in the presence of various comorbidities), can be difficult to replicate in an animal model.[46] It is also difficult to create a translational model that can reveal fundamental mechanisms (eg, mouse genetic models) and at the same time translate well to complex human disease (eg, large animal models). For large animal disease models in particular, a dedicated fully outfitted operating room/laboratory with fluoroscopy, modern 3-dimensional mapping and recording systems, and the technical support to keep such a laboratory running are costly and often beyond the scope of most funding mechanisms. Additionally, adhering to and reporting study design elements such as randomization, blinding, and sex as a biological variable will benefit from improvement.[47] As with animal models, computational modeling can play an essential role in translational research by personalizing treatments; yet, significant limitations currently exist that are related to the incorporation of patient-specific features.[48] Finally, collaboration between physician-scientists and basic scientists is a vital component of translational research. Notably, the number of physician-scientists has steadily declined,[49] and securing protected time for research has become more difficult. Unless these trends are reversed and some of the challenges overcome, the future of translational research is at risk.

An EP Collaboratory could overcome many challenges of translational research (Table 2). For example, working groups that include all stakeholders (academia, industry, NIH, and FDA) can identify important gaps in knowledge and unmet needs. The translational research community itself can ensure rigorous study design methods and identify standardized animal, cellular, or computational models that are best suited to either address specific clinical questions or mimic more complex disease. An EP Collaboratory could recommend establishing core resources and cultivate

collaborations among groups that have exceptional expertise in specific aspects of translational research such as clinical EP, computational modeling, benchtop research, cell models, or large or small animal models. Finally, an EP Collaboratory could encourage trainees and established investigators to stay on the scientific path by identifying and/or collaborating with funding sources for both early- and mid-career physician-scientists, establishing a "translational research curriculum,"[49] and providing early career mentorship for the next generation of translational research scientists.

4. Potential blueprints for addressing the challenges to growth in EP research

Potential mechanisms to approach the challenges and opportunities that have been identified can be drawn from a variety of other fields in which the clinical research environment has faced similar experiences. These include models such as a patient-centered foundation's clinical trial ecosystem akin to that of the Cystic Fibrosis (CF) Foundation or federal funding initiatives from the NIH or PCORI. Collaborative groups have been initiated in the heart failure and heart valve communities to take on research challenges in their respective fields, and they may serve as blueprints for how an EP Collaboratory might help to advance EP research and provide an outline for the structure and design of an EP Collaboratory.

4.1. Patient-centered foundation's clinical trial ecosystem

Patient-centered foundations that focus on specific disease states have several strengths, including (1) engaging with the community affected by the specific disease state, (2) developing innovative funding paradigms, (3) assisting with recruitment for clinical studies, (4) identifying meaningful patient-reported outcomes, and (5) disseminating results to patients and relevant practitioners. The CF Foundation has successfully achieved these goals and provides an aspirational example from outside the realm of cardiovascular disease for a research ecosystem promoted by a patient-centered organization. The CF Foundation's innovative business model venture philanthropy provides funds for CF-specific drug development programs, encouraging pharmaceutical companies to invest in rare disease research. In 2020, the foundation itself provided $258 million in funding for CF research and care.[50] The CF Foundation patient registry contains more than 31,000 patients with CF.[51,52] Patients with CF can search for actively enrolling clinical trials, with filters for specific mutation type, and therapeutic approach (anti-inflammatory, anti-infective, nutritional, observational, etc) using an intuitive interactive website that provides study sites with contact information for investigators. A similar framework can be initiated by the EP Collaboratory where patients can access a website with ongoing studies in EP. The CF Foundation has its own Therapeutics Lab, a custom-built facility, mostly dedicated to identifying promising drugs for rare and nonsense mutations of the CF gene. An EP Collaboratory can similarly leverage these strengths by engaging patient-centered foundations affected by arrhythmias including the SADS (Sudden Arrhythmia Death Syndromes) Foundation, the Hypertrophic Cardiomyopathy Association, and the Atrial Fibrillation Association.

4.2. Federal funding initiatives

The NHLBI of the NIH predominantly supports hypothesis-driven research, with the majority of the budget funding investigator-initiated applications. Federal funding for a collaborative community could be targeted toward specific projects and thus dovetail with the established mechanisms of NIH support.

The NIH has recently implemented reforms to improve stewardship over clinical trials and rectify high rates of trial completion failure and slow publication rates.[53] These initiatives at the NHLBI include a series of funding announcements to support applications for clinical trials at all phases.[54] There are funding mechanisms to support pilot studies, mechanistic and early-phase clinical trials, and single-center and multicenter phase 2 and beyond clinical trials. This HRS writing group believes it is essential to have EP representation on these and all other NIH study sections that evaluate basic, translational, population-based, and clinical trials in EP. At present, many study sections do not have members with arrhythmia expertise, which places EP investigator-initiated proposals at a relative disadvantage. An EP Collaboratory can help to identify gaps and lack of representation, prompt discussions on inclusivity, and encourage arrhythmia experts to participate on relevant study sections.

The NHLBI also has a history of partnering with industry to support clinical trials. Various models of collaboration exist, from industry providing devices or drugs to specific site support to extensive support for trial operations. The Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation trial[55] is an example of collaborative funding between NHLBI and industry.

Another framework for addressing EP research challenges is the clinical study network. The NHLBI funds several such networks, including the Pediatric Heart Network and Cardiothoracic Surgical Trials Network. Networks enable efficiencies through common infrastructure and a standardized approach to recruiting, monitoring, and clinical follow-up. Networks also allow a flexible management of trials so that failing studies can be efficiently terminated and replaced by other studies. An EP Collaboratory could facilitate and coalesce an "Arrhythmia" Network.

Another approach could emulate the PCORI-funded PCORnet.[56] PCORnet uses real-world data from electronic health records and insurance claims to answer pragmatic research questions. PCORnet uses a robust governance and oversight process along with standardized data models to knit together multiple health systems, providing a massive source of patient information. This research infrastructure represents the diversity of the U.S. population and is able to support numerous projects at the same time. An important

feature of both PCORnet and the clinical study networks is that they rely on substantial ongoing financial investment.

PCORI is an independent nonprofit organization authorized by the U.S. Congress to fund comparative clinical effectiveness research focused on outcomes important to patients, caregivers, and the broader health care community. A centerpiece of PCORI's approach is the engagement of patients and other stakeholders in its work as a funder of research and in the projects and studies it awards. This includes involvement across all aspects of the research process (from identification of research priorities to review of proposals for funding to sharing and uptake of findings). PCORI's mission is to help people make informed health care decisions and improve health care delivery and outcomes by producing and promoting high-integrity, evidence-based information that comes from research guided by patients, caregivers, and the broader health care community. As of December 2021, PCORI has committed $3.4 billion to fund more than 1900 research, dissemination and implementation, infrastructure, and engagement projects.

4.3. Role of the FDA

Participation and commitment of multiple stakeholders is important for scientific advances in heart rhythm care. Too often, however, the scientific community is split into silos, with inadequate communication and collaboration. There are multiple lost opportunities for cross-fertilization and the sharing of ideas and solutions. Indeed, FDA is principally involved in the segment of this field that involves bringing new medical products to market and monitoring their postapproval performance. In contrast, funding agencies tend to be more focused on basic science and clinical research not typically directly involved with device evaluation. Recognizing these challenges in all areas of device development, CDRH, in their strategic priorities for 2018–2020, identified the participation in "Collaborative Communities" as a priority.[57] As defined by CDRH, a Collaborative Community is a continuing forum that includes multiple stakeholders, who work together to achieve common objectives and outcomes. Membership can come from both the public and private sectors, including FDA staff, and patient and caregiver participation is encouraged. In addition to the advantage of cross-fertilization and avoidance of duplication of efforts, they provide the opportunity to make clinical trials more efficient by identifying best practices for clinical research in the field, standardization of clinical end points, and the development of reusable clinical research infrastructure such as case report forms. Perhaps most importantly, Collaborative Communities can develop consensus around the most important clinical questions in the field. It is important to note that while the FDA seeks to inspire the development of Collaborative Communities, these communities are not established or led by the FDA. FDA staff members can participate as members and may participate in the work of the community. The ability to lend a regulatory perspective to discussions is expected to be particularly important.

4.4. Collaboratory experience in the cardiac space: Genesis, design, and activities of the Heart Valve and Heart Failure Collaboratories

Similar challenges to the current research infrastructure exist across the cardiovascular specialties. The Heart Valve Collaboratory (HVC) and the Heart Failure Collaboratory (HFC) provide two examples of how to successfully establish a Collaboratory to improve their respective research environments.

The HVC is a physician-initiated, patient-centric consortium of multidisciplinary stakeholders (clinicians, patients, industry, regulatory agencies, and government) established in 2020 to identify and address knowledge gaps and foster initiatives in the diagnosis, prevention, and treatment of valvular heart disease. The structure comprises working groups focused on knowledge and evidence gaps, clinical trial design, regulatory opportunities, implementation science, digital health, and underserved populations. To date, HVC has collaborated with 15 partner organizations, hosted two webinars with more than 100 faculty participants, implemented at least a dozen projects,[58] and identified early- and mid-career faculty for project participation.

The HFC is also a multidisciplinary Collaboratory that evolved from an FDA think tank meeting in 2017. The HFC also consists of working groups including digital health, regulatory policy and implementation science, drugs, devices, and representative populations. Each working group comprises health care professionals, government and patient care partners, and industry. The HFC has been highly productive, including hosting annual meetings, creating lean case report forms,[59] providing statistical concept workshops, establishing standardized definitions,[60,61] and utilizing novel technology, ie, social media, for clinical trial intervention and integrating lean case report forms into electronic health records.

Both Collaboratories operate chiefly with in-kind contributions of time rather than utilizing large central budgets. In addition to clinician members, both the HVC and the HFC have included payers and representatives from industry. This inclusiveness has occurred by operating outside the bounds of the traditional professional societies. The HFC and HVC leadership have emphasized that their independence allows for a nimbler organization that is less hindered by bureaucratic limitations. Each highlighted the importance of identifying deliverables that could serve as early wins to help build momentum and keep stakeholders invested.

4.5. An EP Collaboratory

Based on the challenges and opportunities in the EP research landscape, there is ample justification for the formation of a collaborative community such as an EP Collaboratory. An EP Collaboratory can serve to encourage scientific discourse, efficiency of research, and evidence generation by creating a

collaborative environment for stakeholders within the EP community to interact, address knowledge gaps, and advance new therapies for patient care. Potential goals (Figure 2) for an EP Collaboratory include (1) facilitating novel methods of evidence generation, trial recruitment, and practical trial design; (2) increasing collaboration among stakeholders during (or preferably before) trial design and implementation; (3) empowering and engaging patients, including underrepresented populations; (4) supporting centrally organized and validated research networks; (5) promoting a research culture and international collaboration; (6) energizing medical provider commitment and involving early-career members and allied professionals; and (7) identifying key areas and priorities for arrhythmia research and establishing definitions or central concepts for evaluating EP therapies.

In practical terms, an EP Collaboratory can help accomplish these goals by providing opportunities for a larger number of young investigators through a mentorship and networking program. A Collaboratory structure could also facilitate involving more investigators in ongoing projects very early in their training. Diversity of clinical trials can be enhanced through the inclusion of more diverse principal investigators, broader site selection, and use of digital media. In addition, a Collaboratory can facilitate novel clinical trial designs that are more likely to include diverse patients typically underrepresented in traditional clinical trials, even though they might stand to benefit the most from the intervention being evaluated.

An EP Collaboratory could also promote the collection of real-world data from electronic health records, consumer technology, and other digital data to create evidence specific to key clinical end points. It could endorse policies and practices that enhance patient value through inclusion of patient-reported outcomes and engagement of patient preferences. A Collaboratory can also be advantageous with respect to facilitating international collaboration and research through sharing common regulatory steps, maintaining research repositories, and generally bringing together intercontinental research partners.

The development of study methodologies, guidelines, and minimum requirements is another advantage of creating a Collaboratory, which could improve proposals in terms of trial design, incorporation of real-world evidence, and promote the use of appropriate end points. In addition, a Collaboratory may provide infrastructure to increase efficiency by making trials simpler, more standardized, and more streamlined. Such interventions would be expected, in turn, to decrease costs and make patient-centric outcomes easier. Another desired result would be realignment of expectations for success in a trial through consideration of what patients prefer with respect to technology and their preferences for risk tolerance. There is also the opportunity to diversify patient involvement from an equity and inclusion footprint as well, with studies that are representative and that address social disparities, as well as the prospect for more involvement of other disciplines and to reach deeper into collaborations and partnerships with other professional and patient organizations.

By creating a safe place where stakeholders can efficiently interact with each other and a forum for brainstorming regarding clinical studies likely to result in "early wins" for patients, an EP Collaboratory could catalyze interactions among diverse stakeholders. There is also the potential for efficiency, with all groups being able to have upfront conversations. Industry, for example, could benefit from feedback on how to improve implementation of trials, take advantage of real-world evidence, standardize electronic health records and other databases, and garner input regarding the opinions of the FDA, EP providers, and patients. A Collaboratory could also provide a resource to rapidly identify interested clinical trial sites. Funding organizations can have more confidence that a trial endorsed by the EP Collaboratory will impact clinical practice. As a real-world example of the Collaboratory cross talk, last year the HVC provided rapid feedback on some CMS-proposed rules and coverage decisions based on a consensus among stakeholders. They have also helped the agency implement coverage more efficiently with evidence development.

In developing an EP Collaboratory, the structure may rely on working groups, project-based groups, or a mix of both. The advantage of a working group is that it could develop a knowledge base and level of expertise, whereas a project-centered approach may be more focused and have clearer end points and specific timetables. Standing working groups would provide a means of identifying needs and gaps, and then prioritize them. While groups may evolve, a working group has defined tasks, clear goals, and deliverables related to the overall goal of the Collaboratory. Working groups benefit from appropriate representation and may have project-based subgroups that stem from it.

Working groups are centered on general approaches to solving big problems as opposed to specific disease states. Potential working groups include those focusing on standardization or harmonization of definitions and processes for clinical studies; reviewing clinical guidelines and identification of knowledge gaps; integration with electronic health records; digital health; resource development and tools for researchers/study implementation; communication, dissemination, and mentorship; and diversity and patient representation. While clinical trials provide the basis for evidence-based care, there has been slow uptake of clinical evidence and guidelines into real-world clinical practice. An EP Collaboratory may also be helpful in development of an implementation framework to promote translation of research findings to clinical practice and more rapid dissemination of evidence-based heart rhythm therapies through broad stakeholder collaboration and investment.

5. Governance and structure of an EP Collaboratory: Role of HRS

To ensure the most meaningful benefits, an EP Collaboratory will involve a wide range of participants with equal footing to ensure true collaboration. The HFC and HVC have operated outside the traditional professional societies. This "Switzerland approach"—of an independent, neutral third party that facilitates collaboration among entities—has been credited with allowing the Collaboratories to be nimble, not encumbered with bureaucracy, and thus more successful. However, one size does not fit all, and this model may not be as applicable to the EP space, where HRS has been a major driver and convener of collaboration, research, and best practices for clinical care.

While the leadership of a collaborative community is usually shared among all members and is not commonly hierarchical, the community may have a facilitator to convene and coordinate effective collaboration. As it is a collaboration among multiple stakeholders, it is preferable to design the EP Collaboratory to avoid dependence personally or geographically on any one person, location, or entity. Establishing trust is a core tenet of many collaborations. Without steadfast and enduring efforts to build trust, well-intentioned collaborations may not be successful. This might include expressing perceptions of bias, designating expectations and responsibilities, and narrowing the perceived gaps between members' viewpoints. Trust can only exist in the setting of mutual respect, well-defined roles, shared visions, and transparency.

While the structure and governance of an EP Collaboratory could evolve over time, an institutional-based structure is most likely to stand the test of time. A Collaboratory is one of equals, potentially with voting and engagement across participants. If an EP Collaboratory is organized outside HRS, HRS has been instrumental and could continue to provide a way to convene a large but cohesive community of organizations. It will be important that resources, including funding and staffing, to create the Collaboratory infrastructure will come from diverse sources. HRS, with more than 40 years representing the heart rhythm professional community and long-standing collaborative relationships with industry partners, FDA, partner societies, and other stakeholders, is ideally positioned to provide the necessary leadership. These accomplishments can serve as building blocks for HRS to facilitate a successful EP Collaboratory that enables common research efforts with the shared aim of ending death and suffering due to heart rhythm disorders.

Appendix 1

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2022.08.004.

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Table A1 Author disclosure table

Name	Employment	Honoraria/speaking/consulting	Speakers' bureau	Research*	Fellowship support*	Ownership/partnership/principal/majority stockholder	Stock or stock options	Intellectual property/royalties	Other
Duy T. Nguyen, MA, MD, FHRS	Stanford University, Stanford, California	None	None	None	None	None	None	None	None
Kenneth C. Bilchick, MD, MS, FHRS	University of Virginia Health System, Charlottesville, Virginia	None	None	3: Siemens; 4: University of Virginia; 5: AHA; 5: NIH/NHLBI	None	None	None	None	None
Sanjiv M. Narayan, MD, PhD, FHRS	Stanford University, Stanford, California	1: TDK Inc; 1: *UpToDate*; 2: LifeSignals; 3: Abbott	None	5: NIH	None	None	None	2: University of California Regents	None
Mina K. Chung, MD, FHRS	Cleveland Clinic, Department of Cardiovascular Medicine, Heart, Vascular & Thoracic Institute, and Department of Cardiovascular and Metabolic Sciences, Lerner Research Institute, Cleveland, Ohio	1: Columbia University School of Medicine; 1: Kansas City Heart Rhythm Society; 1: Geisinger Health Systems; 1: Arrhythmia Education, Inc; 1: Cleveland Clinic; 1: France ANR; 2: ABIM	None	5: NIH; 5: AHA	None	None	None	1: Elsevier; 1: *UpToDate*	3: AHA
Kevin Thomas, MD, FHRS	Duke University Medical Center, Durham, North Carolina	1: Biosense Webster, Inc; 1: Janssen Pharmaceuticals	None	2: NIH/NHLBI	None	None	None	None	None
Kenneth R. Laurita, PhD	Case Western Reserve University, Cleveland, Ohio	None	None	0: NIH	None	None	None	None	None
Marmar Vaseghi, MD, MS, PhD, FHRS	University of California, Los Angeles Cardiac Arrhythmia Center, Los Angeles, California	1: Biosense Webster, Inc; 1: Medtronic, Inc	None	None	None	None	0: NeuCures	None	None
Roopinder Sandhu, MD, MPH, FHRS	Cedars-Sinai Medical Center, Los Angeles, California	None	None	3: BMS-Pfizer Alliance; 5: Servier	None	None	None	None	None
Mihail G. Chelu, MD, PhD, FHRS	Baylor College of Medicine, Houston, Texas	1: Medtronic; 1: Impulse Dynamics USA	None	0: Abbott; 0: Impulse Dynamics USA	None	None	None	None	1: Biosense Webster, Inc

(*Continued*)

Table A1 (*Continued*)

Name	Employment	Honoraria/speaking/consulting	Speakers' bureau	Research*	Fellowship support*	Ownership/partnership/principal/majority stockholder	Stock or stock options	Intellectual property/royalties	Other
Duy T. Nguyen, MA, MD, FHRS	Stanford University, Stanford, California	None	None	None	None	None	None	None	None
Prince J. Kannankeril, MD, MSci, FHRS, CEPS-P	Vanderbilt University Medical Center, Nashville, Tennessee	None	None	5: NIH	None	None	None	None	0: PACES
Douglas L. Packer, MD, FHRS	Mayo Clinic-St. Mary's Hospital, Rochester, Minnesota	0: Johnson & Johnson; 0: Atrifix, Inc; 0: Medlumics; 0: Centrix; 0: NeuCures; 0: Xenter, Inc; 0: Biosense Webster, Inc; 0: CardioFocus, Inc; 0: St. Jude Medical; 0: Sig.num Pre-emptive Healthcare, Inc; 0: Thermedical; 0: Spectrum Dynamics; 0: Medtronic; 0: Abbott; 1: Mediasphere Medical	None	0: Abbott; 0: Siemens; 0: Robertson Foundation; 0: Medtronic; 1: University of Utah; 2: Boston Scientific; 3: Biosense Webster, Inc; 3: Mayo Clinic Heart Rhythm Development; 4: Thermedical; 4: Goldsmith Foundation; 5: NIH; 5: St. Jude Medical	None	None	None	0: AHA; 4: Wiley-Blackwell; 4: St. Jude Medical	1: Abbott; 1: Medtronic; 1: Thermedical; 1: Cordis–Johnson & Johnson
David D. McManus, MD, MSci, FHRS	University of Massachusetts Medical School, Worcester, Massachusetts	0: Mobile Sense; 1: Samsung; 1: Rose Consulting; 1: FLEXcon; 1: Philips; 1: Avania; 2: Fitbit; 2: BMS; 2: Pfizer, Inc; 3: Heart Rhythm Society	None	0: Samsung; 0: Apple Inc; 0: Care Evolution; 0: Fitbit; 4: Otsuka Pharmaceuticals; 4: Sanofi; 4: FLEXcon; 5: Biotronik; 5: Pfizer, Inc; 5: BMS; 5: Boehringer Ingelheim; 5: Philips	None	None	None	None	2: Boston Biomedical Associates

Atul Verma, MD, FRCPC, FHRS	Southlake Regional Health Center, Newmarket, Ontario, Canada	1: Kardium; 1: Galaxy Medical, Inc; 1: Bayer HealthCare Pharmaceuticals; 1: Thermedical; 2: Biosense Webster, Inc; 2: Medtronic	None	2: Adagio Medical	None	None	None	None	None
Matthew Singleton, MD, MHS, MSci	WellSpan Health, York, Pennsylvania	1: Biosense Webster, Inc	None	None	None	None	None	None	None
Khaldoun Tarakji, MD, MPH, FHRS	Cleveland Clinic, Cleveland, Ohio	1: Medtronic; 1: Janssen Pharmaceuticals; 2: AliveCor	None	None	None	None	None	None	None
Sana M. Al-Khatib, MD, MHS, FHRS, CCDS	Duke University Medical Center, Durham, North Carolina	None	None	1: Medtronic; 1: Abbott; 1: Boston Scientific	None	None	None	None	3: AHA
Jonathan R. Kaltman, MD	Children's National Hospital, Washington, District of Columbia	None	None	None	None	None	None	None	None
Ravi C. Balijepalli, PhD	NHLBI, NIH, Bethesda, Maryland	None	None	None	None	None	None	None	None
George F. Van Hare, MD, FHRS, CEPS-P	Office of Cardiovascular Devices, Center for Devices and Radiological Health, U.S. Food and Drug Administration, Silver Spring, Maryland	None	None	None	None	None	None	None	0: International Board of Heart Rhythm Examiners
Jodie L. Hurwitz, MD, FHRS	North Texas Heart Center, Dallas, Texas	None	None	None	None	None	None	None	None
Andrea M. Russo, MD, FHRS	Cooper University Hospital, Camden, New Jersey	1: Biosense Webster, Inc; 1: PaceMate; 1: Biotronik; 1: BMS-Pfizer Alliance	None	1: MediLynx; 1: Kestra, Inc; 2: Boston Scientific	None	None	None	1: Up to Date	1: Medtronic; 1: ABIM; 1: Boston Scientific
Fred M. Kusumoto, MD, FHRS	Mayo Clinic Jacksonville, EP and Pacing Services, Jacksonville, Florida	None	None	None	None	None	None	None	None

(*Continued*)

Table A1 (*Continued*)

Name	Employment	Honoraria/speaking/ consulting	Speakers' bureau	Research*	Fellowship support*	Ownership/ partnership/ principal/ majority stockholder	Stock or stock options	Intellectual property/ royalties	Other
Duy T. Nguyen, MA, MD, FHRS	Stanford University, Stanford, California	None	None	None	None	None	None	None	None
Christine M. Albert, MD, MPH, FHRS	Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California	None	None	5: Abbott; 5: Roche Diagnostics; 5: St. Jude Medical; 5: NIH	None	None	None	None	None

Number value: **0** = $0; **1** = ≤$10,000; **2** = >$10,000–≤$25,000; **3** = >$25,000–≤$50,000; **4** = >$50,000–≤$100,000; **5** = >$100,000.

ABIM = American Board of Internal Medicine; AHA = American Heart Association; ANR = National Research Agency; BMS = Bristol Myers Squibb; NHLBI = National Heart, Lung, and Blood Institute; NIH = National Institutes of Health; PACES = Pediatric and Congenital Electrophysiology Society.

*Research and fellowship support is classed as programmatic support. Sources of programmatic support are disclosed but are not regarded as a relevant relationship with industry for writing group members or reviewers.

Table A2 Reviewer disclosure table

Name	Employment	Honoraria/speaking/consulting	Speakers' bureau	Research*	Fellowship support*	Ownership/partnership/principal/majority stockholder	Stock or stock options	Intellectual property/royalties	Other
Kristen B. Campbell, PharmD	Duke University Hospital, Durham, North Carolina	None	None	None	None	None	None	None	None
Nassir F. Marrouche, MD, FHRS	Tulane University School of Medicine, New Orleans, Louisiana	0: Sanofi; 1: Biotronik; 1: Biosense Webster, Inc; 1: Bristol Myers Squibb; 1: AtriCure, Inc	None	0: Abbott; 0: Boston Scientific; 1: Janssen Pharmaceuticals	None	0: Cardiac Design	None	None	None
Daniel P. Morin, MD, MPH, FHRS	Ochsner Clinic, New Orleans, Louisiana	1: Abbott	1: Boston Scientific; 2: Zoll Medical Corporation	None	None	None	None	None	None
Jayasree Pillarisetti, MD, FHRS	UT Health San Antonio, San Antonio, Texas	None	None	None	None	None	None	None	None

Number value: **0** = $0; **1** = ≤$10,000; **2** = >$10,000–≤$25,000; **3** = >$25,000–≤$50,000; **4** = >$50,000–≤$100,000; **5** = >$100,000.

*Research and fellowship support is classed as programmatic support. Sources of programmatic support are disclosed but are not regarded as a relevant relationship with industry for writing group members or reviewers.