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Heart Failure Site-Based Research in the United States: Results of the Heart Failure Society of America Research Network Survey

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Abstract

OBJECTIVES: This study aimed to determine clinician and scientist involvement in heart failure (HF) clinical research and to describe the challenges of conducting clinical trials in the United States (US).

BACKGROUND: Improvements in the current capability, potential, and deficiencies of the HF clinical research infrastructure in the US are needed to enhance efficiency and impact.

METHODS: The Heart Failure Society of America (HFSA) distributed an electronic survey regarding HF clinical trial activity purposed to understand the limitations to conduction of high-quality HF clinical research.

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RESULTS: Overall 1794 HFSA members were queried and 434 (24%) completed surveys, while 7589 total individuals with interest in HF were queried and 615 completed surveys. Of respondents, 410 (67%) were actively engaged in HF research and 120 (20%) were interested in research. Most respondents were physicians 270 (44%); 311 (76% of the total and 80% of physicians) practiced at academic institutions, 333 (81%) had served as principal investigators, and 73 (18%) as site coordinators. Respondents active in clinical research usually participated in 1–5 trials and enrolled 1–20 patients annually. Institutional review board (IRB) approval typically required 3 months and contract completion 3 to 6 months per site. The greatest barriers to research were insufficient site budgets, delay in contracting, inability to find participants meeting trial entry criteria, and unavailability of qualified study coordinators.

CONCLUSIONS: Many US clinical research sites are constrained by budgetary, staffing, and contractual issues. The HFSA Research Network seeks to unify interested sites and deconstruct barriers to permit high-value HF research.

Keywords

Heart Failure Clinical Research; Research Network; Site-Based Research; Clinical Trials

INTRODUCTION

Heart failure (HF) clinical research has become increasingly difficult to perform in the United States (US) (1). Nevertheless, randomized controlled clinical trials remain the gold standard to study therapeutic safety and efficacy. Slow enrollment and poor patient and clinician engagement are among the many reasons for high trial cost and diminishing evidence generation, but the breadth of detriments to feasibility of clinical research in the US remains incompletely characterized (2). Health system-based and regional research networks have demonstrated the capability to conduct more efficient clinical investigation and may provide a model to improve research on a broader scale (3–5). The Heart Failure Society of America (HFSA) is a member organization composed of physicians, surgeons, research scientists, nurses, advanced practice clinicians, pharmacologists, and other multidisciplinary professionals. Due to the diverse nature of HFSA membership, which has a primary focus on HF care, members were selected as an ideal group to survey. To determine and enhance the capability of the national HF clinical research infrastructure, the multidisciplinary HFSA Research Network Task Force designed and distributed an electronic survey to gain insights into the involvement of HFSA members and others in HF clinical research, and to describe the challenges of conducting clinical trials in the US.

METHODS

Survey Design and Population

This cross-sectional survey of clinicians and investigators active in the field of HF was designed to describe the current participation and barriers to performing clinical research in the US. The primary population included present or past members of the HFSA for whom contact information was available. The extended population included members of the American Heart Association (AHA), American College of Cardiology (ACC), and industry

partners who self-identified an interest in HF for whom contact information was available from their parent organizations. The eligible population consisted of physicians, researchers, nurses, nurse practitioners, pharmacists, pharmacologists, physician assistants, and research coordinators. Eligibility further required active or past participation in clinical HF research in the US as identified by the respondent. SurveyMonkey (San Mateo, California) was used for survey administration.

From May 2017 to December 2017, self-administered survey data were electronically collected from current or past HFSA members, or members of the American Heart Association (AHA), American College of Cardiology (ACC), and industry partners who self-identified an interest in HF. The survey was distributed to the HFSA mailing list and associated cardiovascular society mailing lists by electronic mail after a prenotification mailing was sent. Response was monitored closely, and to improve the reply rate reminders were distributed to the target population 5 times before study close. Additional promotion encouraging survey participation was posted on the HFSA website, the HFSA Twitter and Facebook accounts, and by flyers distributed at the HFSA 21st Annual Scientific Meeting in September 2017.

Survey Development

The HFSA Research Network Task Force designed the electronic survey to describe the involvement of HF-associated clinicians and investigators in clinical research and record the challenges impairing conduction of clinical trials in the US. Potential barriers to participation in clinical research and demographic variables that may modify those barriers were initially identified by review of the published literature. Key stakeholders from the HFSA community including clinicians and researchers, and with various training backgrounds including physicians, researchers, research coordinators, nurses, nurse practitioners, and pharmacists were included in the subsequent semi-structured focused discussions regarding item generation and reduction, including identifying potential barriers to research participation, as well as for pretesting. The survey was extensively pilot-tested within the HFSA Research Network Task Force, HFSA Research Committee, and HFSA Board of Directors to ensure appropriate content, and to improve readability and question clarity prior to full distribution; the survey was designed to require nominal responses (see Appendix for full content).

The resultant survey consisted of 42 individual response items. After determining eligibility, survey respondents were given questions to assess individual demographics, including whether they were HFSA members, their educational credentials, and practice settings. Subsequent items included type and number of trials conducted per year, annual total patient enrollment, staffing, regulatory and contracting issues, and use of electronic health records (EHR) for screening. When questions queried participation in heart failure clinical trials or academic productivity, the time-frame was restricted to the previous 3 years. All respondents were asked to rank the 8 consolidated potential barriers to high quality research on an 8-point scale, with 1 being the most important.

Statistical Analysis

Survey results were compiled and analyzed using descriptive statistics through the SurveyMonkey program and Stata 14 (StataCorp, College Station, Texas). Missing data was treated with pairwise deletion. Rankings were compared by the Kruskal-Wallis equality-of-populations rank test and by the Wilcoxon Rank-Sum; $p<0.05$ was considered statistically significant.

RESULTS

Characteristics of Survey Respondents

The survey was distributed to 1794 HFSA members and 7,589 total HFSA, AHA, and ACC members and colleagues (Figures 1 and 2). Overall, 23.6% of the survey mailings were opened by the recipient. Among the1794 HFSA members who received the distribution there were 434 (24%) completed surveys (Figure 1). In total, here were 615 (8%) surveys returned (Figure 2) and the survey typically required a mean of 6 minutes to complete. Respondents represented 45 US states and approximately 331 distinct private or academic institutions, and there were no more than 14 respondents from any single institution, with 41 institutions having ≥3 respondents. Of the total respondents, 410 (67%) were actively engaged in HF research, including 330 (76%) of the HFSA members, and another 120 (20%) of the total were not currently involved but interested in research opportunities. Physicians comprised the largest group of respondents followed by nurses or nurse practitioners (Table 1). The proportion of physician respondents was similar among the institutions with ≥3 survey respondents (64%) as those institutions with only 1–2 respondents (67%). More HFSA members were physicians (69%) than non-HFSA members (51%). Of those participating in research, most practiced at academic institutions (Table 1), though more HFSA members worked in an academic setting (80%) than non-HFSA members (54%). Of current researchers, 182 (44%) had published more than 5 manuscripts in the prior 3 years. There were 333 (81%) with experience as clinical trial site principal investigators, and 73 (18%) with experience as a study coordinator. The largest proportion of individual respondents with research experience 148 (36%) reported the employment of 2–3 HF research study coordinators as part of their research team.

Clinical Research Experience

A description of the types of trials in which respondents have participated in the 3 years prior to the survey is presented in Table 2. Respondents had most commonly participated in trials of pharmaceuticals for HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), or in registries or outcomes research for HF. Of those participating in clinical research, 230 (56%) reported participation in investigator-initiated clinical trials. Of those involved in clinical trials, most participated in 1–5 trials on average per year (238, 58%), enrolling most commonly 1–20 total patients per year (156 respondents, 38%). A sizeable group enrolled between 21–50 patients annually (95 respondents, 23%).

Of the 410 participating in clinical research, 131 (32%) reported association with at least one organized research network: 69% with the National Institutes of Health, 30% with the Duke

Clinical Research Institute, 16% with the United States Department of Veterans Affairs, 6% with the Thrombolysis in Myocardial Infarction (TIMI) Study Group, and 5% with the Canadian Virtual Coordinating Centre for Global Collaborative Cardiovascular Research (VIGOUR) Group. Of the total respondents participating in clinical research, 213 (52%) had served in at least one local or national leadership role within a clinical trial, including 152 (37%) as national lead or co-principal investigator, 102 (25%) on a trial steering or executive committee, 92 (22%) on a data and safety monitoring board, 63 (15%) on a clinical events committee, 31 (8%) as a core lab director, and 13 as a national coordinator for a multi-center trial.

Institutional Review Board and Site Contracting

Only 183 (45%) respondents active in clinical research reported that it was possible to use a central institutional review board (IRB), while only 32 (8%) acknowledged current active use of a central IRB. Most reported it took less than 3 months to complete local IRB approval (209, 51%) but 122 (30%) replied that the wait was usually 3–6 months. Responses regarding central IRB approval were similar: 145 (35%) endorsed a wait of less than 3 months for central IRB approval, and 63 (15%) reported between 3 and 6 months. Contract completion most often took between 3 to 6 months to finalize (156 respondents, 38%) though 121 (30%) replied that it typically required less than 3 months. Of the respondents active in clinical research, 331 (81%) reported using the electronic health record (EHR) to screen for appropriate patients for clinical research, and the most common EHRs used in that group were Epic (Verona, WI) by 210 respondents (63%) and Cerner (North Kansas City, MO) by 77 respondents (23%).

Barriers to Site-Based Research

Respondents ranked the relative impact of 8 perceived barriers to high quality research (Figure 3). The most highly ranked impediment to clinical research was insufficient budget relative to study requirements; 27% of respondents believed this was the greatest barrier while 61% believed it was one of the top three. When any other topic was chosen as the most important barrier, budgeting was most likely to be chosen as the second most impactful issue. Budgetary issues were followed by delays due to legal review or contract completion (15% ranked 1st), lack of available patients meeting inclusion and exclusion criteria (16% ranked 1st), inability to hire and retain qualified study coordinators (10% ranked 1st), and delays due to IRB approval (6% ranked 1st).

Less influential but nonetheless identified by some were inadequate numbers of studies offered and difficulty with data collection, and least consequential was felt to be investigator experience and oversight. Additional barriers frequently identified by free text response included: lack of protected investigator time, specifically with regards to competing clinical productivity pressures, an absence of compensation or salary support for investigators' trial activities, high academic institutional overhead, poor access to research networks that facilitate research, burdensome trial documentation requirements, and lack of general institutional support or buy-in to the research endeavor.

When the respondent barriers were compared based on their employer (non-academic, academic, Veterans Affairs, or industry), there were only minor differences in the overall rankings between academic and non-academic responses (Table 3). Although more respondents from academic settings ranked insufficient budget as the top barrier (37% ranked 1st) compared to non-academics (15% ranked 1st), both groups gave the highest mean ranking to budgetary concerns. For respondents from both academic and non-academic settings, delayed contracting was the second highest ranked barrier. Individuals employed by the Department of Veterans Affairs also ranked delayed contracting and insufficient budget as the top two impediments to research, though IRB approval was the next most important issue. In contrast, the respondents from industry ranked the lack of eligible patients for enrollment as the greatest barrier to research followed by contracting and budgeting.

There was little difference seen between rankings made by principal investigators and study coordinators, with mildly higher importance placed by coordinators on investigator experience (Table 4). There were also only minor differences in rankings made by HFSA members compared to non-members (Supplemental Table 1). Clinical physicians and nurses or nurse practitioners participating in research responded with similar ranking schemes, while pharmacists ranked availability of study coordinators and difficulty with data entry higher, and full-time researchers ranked patient eligibility difficulties as the most important concern (Supplemental Table 2).

DISCUSSION

Using a broadly distributed survey we have demonstrated substantial but incompletely realized clinical trial potential within the HF community. We identified many experienced and published clinical researchers, as well as some with less prior participation, all with interest and enthusiasm to participate in future HF clinical research, and we elucidated their most common and impactful barriers to successful involvement. Of the total respondents, 92% desired to be or currently were involved with HF clinical trials, and many of these have a resume of success performing HF research. These diverse current and would-be investigators may be molded into a unified HF research network to generate future evidence in a more efficient manner. This is the intention of the HFSA Research Network: in ongoing work it seeks to establish an integrated and high-quality HF network of investigators committed to conducting high-value clinical research.

To improve HF clinical trial productivity and efficiency, the identified barriers to clinical trial participation and site-based research will require amelioration. The three principal limitations to clinical trial participation were insufficient budget to support the trial activities, difficulty with legal and prolonged contracting, and trouble enrolling patients within the confines of trial inclusion and exclusion criteria. Although none of the described obstacles to site-based clinical research will come as a surprise to experienced investigators in the field, this study highlights the need to assuage and overcome these impediments to improve clinical trial efficiency and performance in the US (1,6). These obstacles permeate all types of research enterprises and infrastructure, as even academic programs, with

additional resources including fellows and protected research time, struggle to overcome them (Table 3).

Respondents identified budgetary concerns as the most prominent and influential roadblock impeding clinical trial participation (Figure 3). Part of this stems from the complicated and costly needs of research sites to hire and maintain coordinators, associates, and other necessary infrastructure, as well as to perform burdensome high-frequency study follow-up visits with substantial data entry. However, much of this budgetary concern appears due to the competing demands of clinical practice and productivity such that research activity is financially under-supported or even discouraged for fellows, faculty, and staff. Thus, these budgetary concerns appear intricately intertwined with the systemic issue of a weakened research culture that has been previously described (7). One potential solution is to design and implement novel clinical trial methods including streamlined and pragmatic trial protocols with decreased workload and cost, such as the ToRsemide compArisoN With furoSemide FORManagement of Heart Failure (TRANSFORM-HF; NCT03296813) clinical trial (1,8,9). The creation and increased utilization of standardized case report forms and automated EHR data extraction to reduce manual data entry burden should also aid this process. Finally, reorganized incentive structures can better promote research alongside clinical performance and re-instill a research culture (7). These solutions are complementary.

The second most commonly identified deterrent to clinical research participation was difficulty with contracting. Contracting is not typically engaged in directly by the local site investigators, coordinators, or staff, but rather is performed by attorneys from the potential research site and those from the trial sponsor, typically industry or government, or the involved clinical research organization (CRO). Contracts typically seek to insure appropriately complete data collection, non-disclosure agreements to protect the sponsor's proprietary information, legal language to comply with local, national, and international rules and regulations, compensation frameworks, publication rights, and indemnification or protection for the research site in case of hazard from the trial (10). This process should be simplified and expedited by utilization of central contracting such as an Accelerated Clinical Trial Agreement (ACTA) as a standard template by investigation sites and sponsors (11,12). Unfortunately, institutional uptake of these type of contracting solutions has been slow and remains incomplete.

Inability to find eligible patients for trial enrollment was the third most commonly identified hindrance to clinical trial participation. Although patients with HF are ubiquitous within the US medical system, increasingly complex inclusion and exclusion criteria limit enrollment potential for trial sites (13,14). Again, novel trial designs including the use of more pragmatic and less exclusive criteria for patient selection have the potential to mitigate this barrier while improving the generalizability of trial results (8). More importantly, less restrictive criteria for patient enrollment should appreciably diminish the extensive paid coordinator time needed for patient identification, thereby streamlining coordinator workload and reducing the cost for sites to perform. EHRs also should be used to facilitate patient identification and make clinical trial enrollment more efficient.

Limitations to this survey include a modest response rate at 24% of the HFSA members and 8% of the total survey distribution despite multiple efforts to engage and increase returns. This is in part due to the low proportion of survey mailings that were opened by recipients, in spite of repeated attempts and alternative promotions, and may also reflect duplicate mailings to recipients included in each of the HFSA, ACC, and AHA member databases. In this regard, the data collected may not be generally representative to all clinical trial site-based research or HF clinicians in the US. Response to the survey may correlate with interest in HF clinical research and the results may thus overestimate site enthusiasm for research due to response bias. Additionally, no demographic information is available for non-respondents, which prevents comparison with the respondent population. As with all surveys, a potential source of error includes the inadvertent exclusion of potential survey respondents who did not receive the original distribution. Further potential sources of error include that the data is self-described and cannot be verified, unrecognized systematic biases and variations may be present in the survey questionnaire.

In summary, this survey-based assessment of the current HF research infrastructure in the US identified opportunities for enhancement and barriers to investigator and institutional participation. It is our hope that the results of this survey can be used to springboard HF research in the US into the future by rectifying major current barriers to research participation, and potentially with the creation of a unified and broad HF research network coordinated by the HFSA. Many of the developments required to solve the most commonly identified impediments to research participation are in early stages of implementation; however, the research community will need to further utilize these solutions to improve the current research culture. The HFSA Research Network seeks to achieve these goals by promoting research awareness among clinicians and patients to increase participation, standardizing site training, education, and maintenance to improve quality and performance, creating and promoting a patient-centered HF clinical trial digital warehouse to facilitate patient understanding and interest, and centralizing IRB evaluation, contracting, and budgeting to smooth site initiation. The research community identified and activated with this survey will form the nidus for unification, collaboration, and growth of the network to facilitate high-value HF research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HFSA	Heart Failure Society of America
IRB	Institutional Review Board
US	United States

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CLINICAL PERSPECTIVES:

Current barriers to enhanced HF clinical research in the US include insufficient budgets, slow contracting, and difficult inclusion criteria. Modifying these barriers will be necessary to generate needed evidence and improve patient care.

TRANSLATIONAL OUTLOOK:

The HFSA Research Network seeks to alleviate these barriers and unify trial sites but ongoing work will be needed to identify new solutions and local and national research champions.

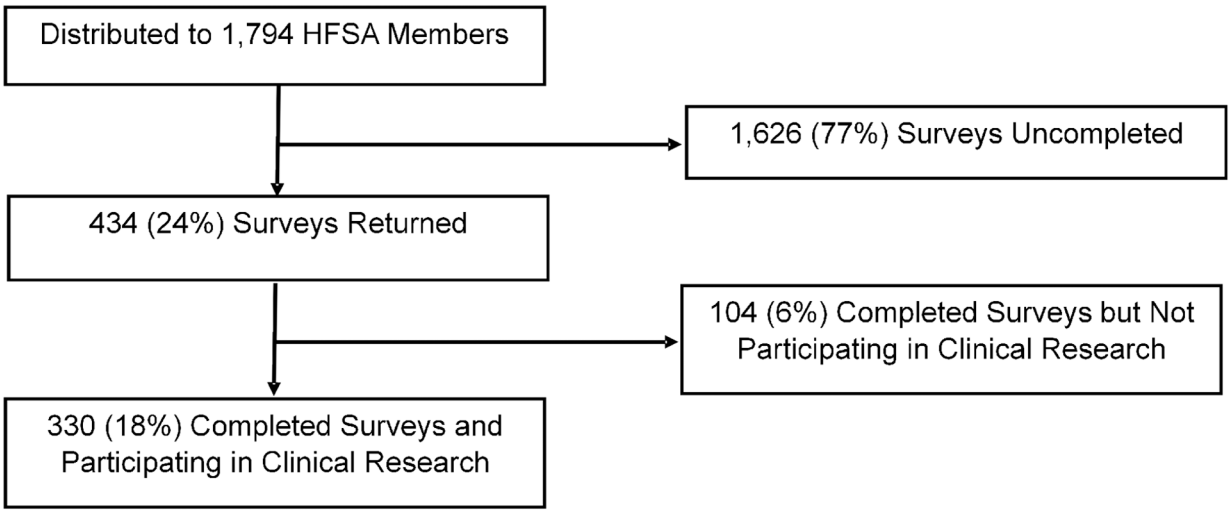

Figure 1.
Consort Diagram of Partial and Complete Survey Respondents Among Members of the Heart Failure Society of America

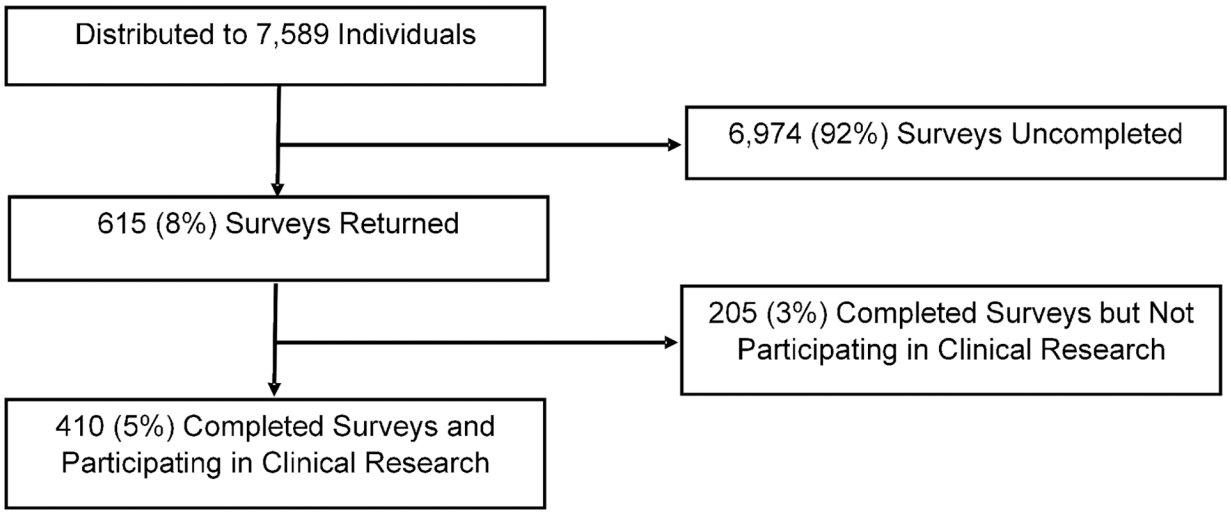

Figure 2.
Consort Diagram of Partial and Complete Survey Respondents in the Extended Cohort

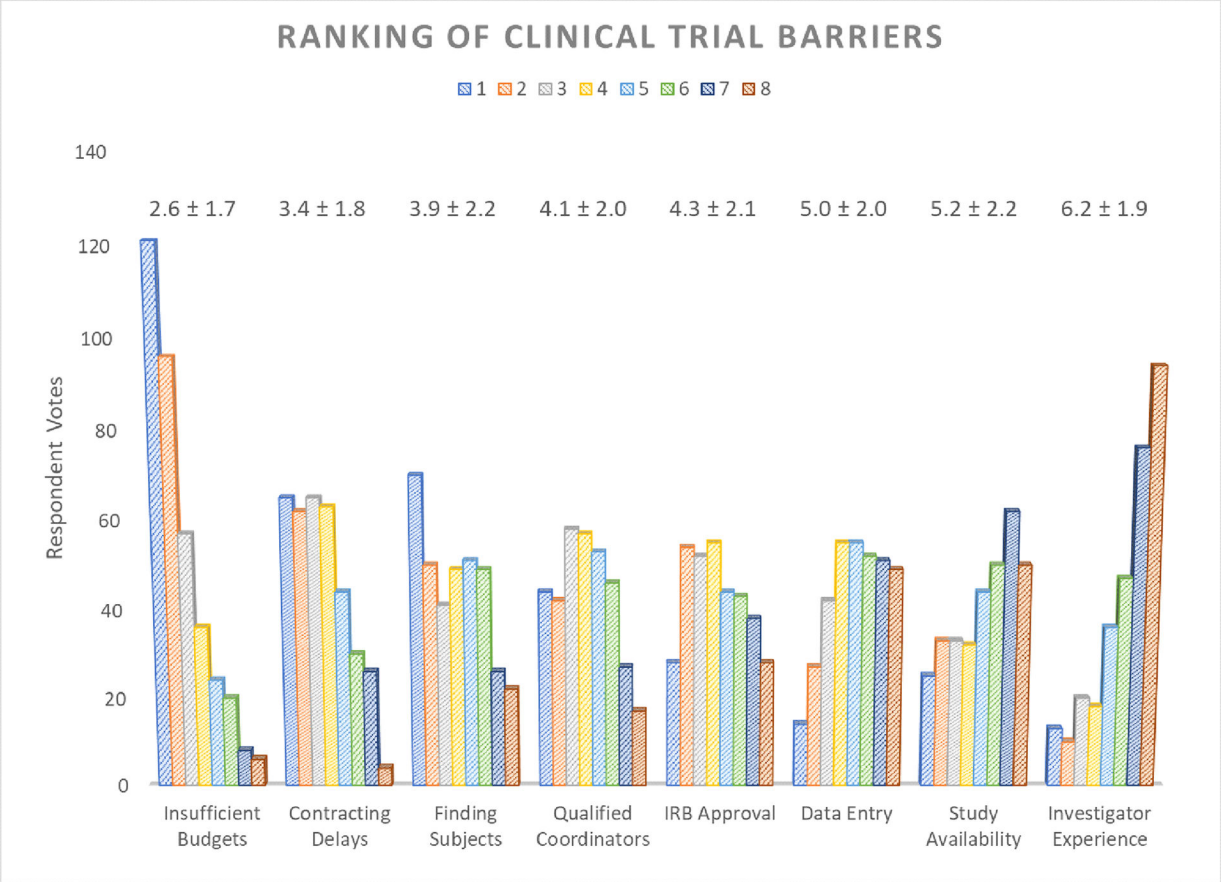

Figure 3 (Central Illustration).

Respondent Votes by Barrier to Clinical Trial Participation Compiled ranking responses for the biggest barriers to conducting high quality heart failure research, 1 being the most important and 8 the least important. Mean Ranking ± Standard Deviation displayed above for each barrier. IRB = institutional review board.

Table 1.

Characteristics of Survey Respondents

Characteristic	Number of Respondents (%)
Employer	
Non-Academic or Private Practice	59 (14%)
Academic	306 (75%)
Veterans Affairs Medical Center	17 (4%)
Industry	22 (5%)
Government	1 (<1%)
Other or Declined Response	5 (1%)
Credentials	
Physician	269 (66%)
Nurse or Nurse Practitioner	83 (20%)
Pharmacist	20 (5%)
Research Only	10 (2%)
Other or Declined Response	28 (7%)

Total Respondents n=410. Totals may exceed 100% due to rounding.

Table 2.

Clinical Trial Participation by Respondents

Type of Trial	Number of Respondents (%)
Pharmaceutical Trials in HFrEF	272 (66%)
Outcomes Trials or Registries in HF	194 (47%)
Pharmaceutical Trials in HFpEF	193 (47%)
Inpatient Trials in ADHF	153 (37%)
National Institutes of Health Sponsored Trials in HF	138 (34%)
Mechanical Circulatory Support Device Trials	133 (32%)
HF Disease Management Trials	116 (28%)
Trials of Diagnostics in HF	104 (25%)
Trials Focusing on HF Comorbidities	102 (25%)
Implantable Device Trials Including ICD/CRT in HF	83 (20%)
Other Descriptive Studies	76 (19%)
Heart Transplant Trials or Registries	71 (17%)
Stem Cell or Gene Therapy Trials in HF	58 (14%)
Other Comparative Effectiveness of Outcomes Research	44 (11%)
Other Trials	36 (9%)

Total respondents participating in clinical research, n=410. ADHF = acute decompensated heart failure; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; % = Percent of respondents that reported participation in a heart failure clinical trial in the proceeding 3 years.

Table 3.

Mean Rankings of Barriers to High Quality Research by Respondent Employer

Barrier to High Quality Research	Non-Academic	Academic	Veterans Affairs	Industry
	Mean Rank ± SD			
Insufficient Budget for Study Requirements	3.0 ± 1.6	2.5 ± 1.7	2.9 ± 1.9	3.5 ± 2.5
Slow Contract Completion or Legal Approval	3.4 ± 2.0	3.4 ± 1.8	2.7 ± 1.6	3.3 ± 1.3
Lack of Eligible Patients (Not Meeting Inclusion & Exclusion Criteria)	3.7 ± 2.3	4.0 ± 2.2	5.4 ± 2.6	1.9 ± 1.0
Availability of Qualified Study Coordinators or Coordinator Turnover	4.2 ± 1.9	4.0 ± 2.0	3.9 ± 2.1	4.0 ± 1.8
Slow Institutional Review Board (IRB) Approval	3.9 ± 2.0	4.4 ±2.1	3.3 ± 1.6	4.9 ±2.0
Difficulty with Data Entry or Case Report Form Completion	5.5 ± 2.1	4.9 ±2.0	4.8 ± 1.5	5.8 ± 1.9
Lack of Available Studies Offered to Site	4.8 ± 2.2	5.2 ± 2.1	4.8 ± 2.0	6.2 ± 1.9
Insufficient Investigator Oversight or Experience	6.4 ± 1.8	6.2 ± 1.9	6.8 ± 1.0	4.2 ± 2.8

Summary data on barriers ranked from 1–8 by respondents, with 1 designated the most important. SD = standard deviation. *p*-valve by Kruskal-Wallis equality-of-populations rank test.

Table 4.

Mean Rankings of Barriers to High Quality Research by Principal Investigators and Study Coordinators

Barrier to High Quality Research	Principal Investigator Mean Rank ± SD	Study Coordinator Mean Rank ± SD
Insufficient Budget for Study Requirements	2.6 ± 1.7	2.7 ± 1.8
Slow Contract Completion or Legal Approval	3.2 ± 1.8	3.3 ± 1.7
Lack of Eligible Patients (Not Meeting Inclusion & Exclusion Criteria)	3.6 ± 2.1	4.0 ± 2.2
Availability of Qualified Study Coordinators or Coordinator Turnover	4.2 ± 2.0	4.3 ± 2.1
Slow Institutional Review Board (IRB) Approval	4.2 ± 2.0	4.5 ± 2.1
Difficulty with Data Entry or Case Report Form Completion	5.1 ± 1.9	5.1 ± 2.0
Lack of Available Studies Offered to Site	5.4 ±2.1	4.8 ±2.3
Insufficient Investigator Oversight or Experience	6.5 ± 1.7	5.9 ±2.2

Summary data on barriers ranked from 1–8 by respondents, with 1 designated the most important. SD = standard deviation. *p*-valve by Wilcoxon Rank-Sum.