

Identifying Barriers and Practical Solutions to Conducting Site-Based Research in North America

Exploring Acute Heart Failure Trials As a Case Study



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KEYWORDS

• Acute heart failure • Clinical trials • Site-based research

KEY POINTS

- There are more than 1 million hospitalizations for acute heart failure annually in the United States accounting for most of the \$40 billion spent directly on HF-related care.
- Although the treatment and prognosis of ambulatory HF patients has improved dramatically because of drug- and device-based therapies, there have been few advancements in the management of AHF and postdischarge readmissions and mortality remain unacceptably high.
- One of the emerging trends in global clinical trials has been the gradual shift of enrollment from predominantly North America and Western Europe to Eastern Europe, South America, and Asia-Pacific where the regulatory burden and cost of conducting research may be less prohibitive.
- The crisis in site-based research in North America is exacerbated by poor visibility of cardiovascular disease and clinical trials, an inability to identify highly performing centers in terms of volume and quality, time-consuming study protocols not reflective of the realities of patient care, inadequate infrastructure for recruitment and study conduct, underdeveloped relationships between the research team and emergency providers and hospital-based physicians, misaligned incentives between principle investigators and the parent clinical facilities, and limited training and support for study coordinators.

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INTRODUCTION

There are approximately 6 million patients with heart failure (HF) in the United States with the prevalence projected to exceed 8 million by the year 2030.^{1,2} In addition, there are more than 1 million hospital admissions annually in the United States accounting for most of the approximately \$40 billion in direct costs for HF-related care each year. Following an index hospitalization for HF, the risk of readmission and death, respectively, may be 30% and 15% within 60 to 90 days.³ Although the treatment of ambulatory HF has been revolutionized by drug- and device-based therapies over the past few decades, inpatient management has remained virtually unchanged over a similar time frame and nearly every clinical trial conducted to date has been neutral in terms of efficacy and/or safety.

The reasons for the lack of success with prior clinical trial programs is likely multifactorial and may be caused by issues related to the study drug and the target patient population (Fig. 1).⁴ However, more recently, problems with study execution and enrollment at the level of the trial site and geographic region have received increasing attention. One of the emerging trends in global clinical trials has been the gradual shift of enrollment from predominantly North America and Western Europe to Eastern Europe, South America, and Asia-Pacific where the regulatory burden and cost of conducting research may be less prohibitive (Table 1). However, major regional differences in patient characteristics, background therapy, and event rates (ie, rehospitalizations and mortality)

may limit the generalizability of research conducted exclusively outside of North America to the US patient population.⁵⁻⁷ This article uses acute HF (AHF) as a paradigm and identifies barriers and practical solutions to successfully conducting site-based research (SBR) in North America (Table 2).

BARRIER: POOR VISIBILITY OF CARDIOVASCULAR DISEASE AND CLINICAL TRIALS WITHIN THE INSTITUTION AND THE BROADER COMMUNITY

Cardiovascular disease (CVD) is the number one cause of morbidity and mortality worldwide killing more patients than all cancers combined.¹ In addition, in the developing world the burden of CVD continues to grow because of increased life expectancy as a result of improved sanitation, socioeconomic advancement, and the decline in deaths caused by communicable diseases. Similarly, because of aging of the population and the success of medical therapy, the number of patients worldwide with HF is growing at a truly exponential rate with estimates of the global prevalence approaching 40 million.⁸ However, compared with the pandemic proportions of HF-related morbidity and mortality, there is disproportionately low visibility among medical professionals and the general public. In contrast to many common cancers, there are few major not-for-profit organizations, outside of medical professional groups, or philanthropic fundraising efforts targeting CVD in general and HF in specific. Moreover, as compared with HF, patients

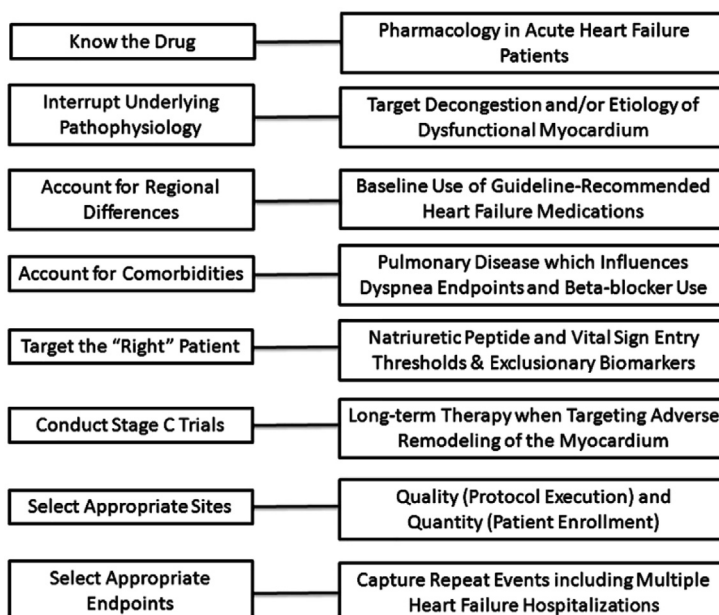


Fig. 1. Considerations for the successful design and conduct of acute heart failure trials. (Adapted from Mentz RJ. Learning from recent trials and shaping the future of acute heart failure trials. *Am Heart J* 2013;166(4):632; with permission.)

Table 1
North American enrollment in recent acute heart failure trials

Trial	Year Published	Patient Population	Total Enrollment	North American Enrollment	% Enrolled in North American Sites
EVEREST	2007	Hospitalized HFrEF	4133	1251	30
ASCEND-HF	2011	Hospitalized HFrEF and HFpEF	7007	3149	45
RELAX-AHF	2013	Hospitalized HFrEF and HFpEF	1161	114	10
ASTRONAUT	2013	Hospitalized HFrEF	1615	124	8
Total	—	—	13,916	4638	33

Abbreviations: ASCEND-HF, Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial; ASTRONAUT, The Aliskiren Trial on Acute Heart Failure Outcomes; EVEREST, Efficacy of Vasopressin Antagonism in Heart Failure: Outcomes Study with Tolvaptan; HFpEF, heart failure preserved ejection fraction; HFrEF, heart failure reduced ejection fraction; RELAX-AHF, A Study of Serelaxin Versus Placebo in Acute Heart Failure.

Adapted from Harinstein ME. Site selection for heart failure clinical trials in the USA. *Heart Fail Rev* 2015;20(4):377; with permission.

with cancer are generally more aware of their therapeutic options and prognosis, and oncologists reiterate that clinical trials may offer the one possible solution.⁹ Thus, a logical first step in improving AHF trial participation in North America may be increasing provider and public awareness of the scope of the problem and the attendant morbidity and mortality.

BARRIER: INABILITY OF STUDY SPONSORS TO IDENTIFY SITES CAPABLE OF ENROLLING HIGH VOLUME AND QUALITY PATIENTS

Perhaps the single greatest impediment to expanding clinical trial enrollment in the United States is identifying sites capable of recruiting high volumes of patients without sacrificing quality

in terms of violating inclusion/exclusion criteria, premature protocol termination, and lost to follow-up. For example, in the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) trial, there was a median per-site enrollment of six patients (range, 0–75) at 436 participating centers.¹⁰ Seventy-seven sites did not enroll a single patient and more than 60% of sites enrolled less than or equal to 10 patients. Furthermore, the highest proportion of sites failing to enroll any patients was in North America and although North American sites represented 48% of total sites, they only contributed to 30% of overall enrollment (Fig. 2). Finally, higher and lower enrolling sites differed significantly in terms of baseline characteristics, protocol completion, and outcomes.

Table 2
Barriers and practical solutions to conducting site-based research in North America

Barrier	Practical Solutions
Poor visibility of cardiovascular disease and clinical trials within the institution and the broader community	Improve awareness
Inability of study sponsors to identify sites capable of enrolling high volume and quality patients	Pretrial registry
Time-consuming study protocols that do not reflect the day-to-day realities of patient care	Pragmatic trials
Inadequate infrastructure for recruitment of participants and study conduct	Clinical trial networks
Underdeveloped relationships between cardiologists and other physicians caring for the cardiac patient	Multispecialty collaborations
Misalignment of incentives between principle investigators and parent clinical facility	The research RVU
Limited upfront training and ongoing support for study coordinators and other staff	Site-based support

Abbreviation: RVU, relative value unit.

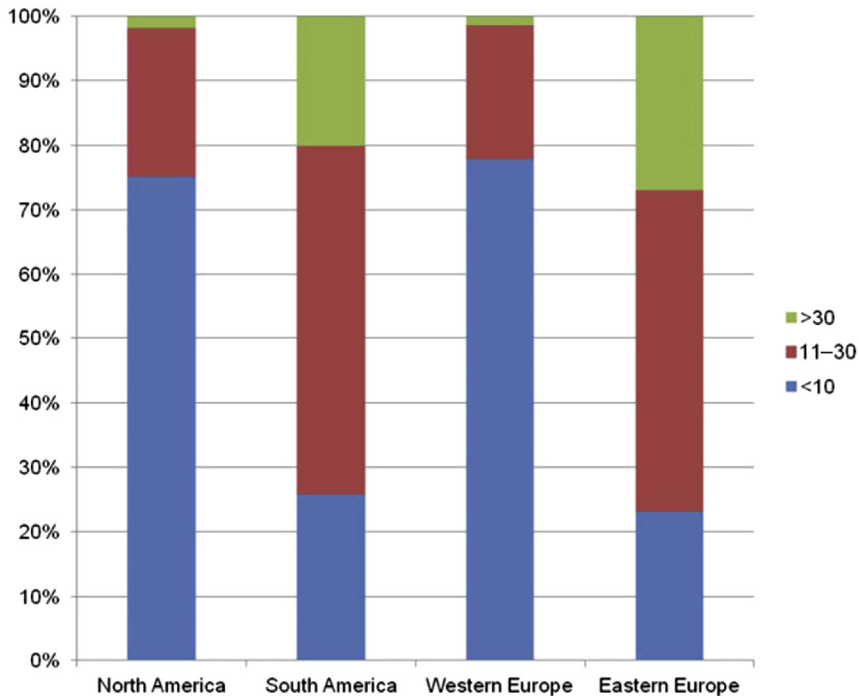


Fig. 2. Regional variation in site enrollment volume in the EVEREST trial. (From Butler J. Relationship between clinical trial site enrollment with participant characteristics, protocol completion, and outcomes: insights from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) trial. *J Am Coll Cardiol* 2013;61(5):573.)

Although SBR is currently in a state of crisis in the United States, it is important to keep in mind that in the EVEREST trial, there were centers with relatively higher enrollment scattered throughout the world. Identifying these high-enrolling sites, while maintaining sufficient quality control, remains the goal of future drug development programs. It has been proposed that a pretrial registry may serve as a screening tool for subsequent trial participation (Boxes 1 and 2).¹¹⁻¹³ Incorporating a pretrial registry would allow investigators the opportunity to preview patient characteristics, evaluate protocol adherence, and estimate study enrollment. This up-front investment may facilitate study execution and be modest in comparison with the costs of maintaining poorly performing sites and conducting unsuccessful clinical trials. A global registry is currently underway that may integrate the pretrial paradigm on a global scale and inform future clinical development programs.¹⁴

BARRIER: TIME-CONSUMING STUDY PROTOCOLS THAT DO NOT REFLECT THE DAY-TO-DAY REALITIES OF PATIENT CARE

One of the major concerns raised by site-based researchers is that patient recruitments in AHF trials often disrupt the usual flow of patient care.

First, AHF trials have a high ratio of screened to enrolled patients because signs and symptoms of HF are neither sensitive nor specific and it is often too difficult to distinguish true “AHF” from “undifferentiated dyspnea” in the urgent or emergent setting.¹⁵ In contrast, other CVD states, such as acute coronary syndrome (ACS), have a common pathophysiologic substrate (ie, plaque rupture and thrombosis) and clear presentation (ie, crushing substernal chest pain, electrocardiogram changes, and biomarker release) facilitating diagnosis and enrollment at the point-of-care. As a result, ACS trials have been able to rapidly and efficiently recruit thousands to tens of thousands of patients over a relatively shorter timeframe.

Second, AHF trials often use restrictive inclusion/exclusion criteria to enrich the study population for a homogenous group of patients more likely to respond favorably to study drug administration.¹⁶ For example, one recent study applied the entry criteria for the RELAX-AHF (The Relaxin for the Treatment of Acute Heart Failure) trial to the ADHERE-U.S. (Acute Decompensated Heart Failure National Registry) and ADHERE-International registries and found that only approximately 2 in 10 patients with AHF in the United States, Latin America, or Asia-Pacific would have been eligible for enrollment.¹⁷ Finally, AHF trials often include a

Box 1**Advantages of pretrial registries for appropriate site selection***Understand the disease characteristics in the intended study population*

- Demographic variables (ie, age, gender, ethnicity)
- Distribution of heart failure causes and precipitating factors
 - Coronary artery disease versus other causes
 - Precipitating causes (ie, acute coronary syndromes, hypertension, atrial fibrillation, infectious causes, noncompliance)
- Heart failure treatment
 - Adherence to guidelines for medical treatment
 - Adherence to for device implantations
- Clinical course of the disease
 - Presentation (ie, signs, symptoms, clinical parameters)
 - Speed of symptom control and acute therapy that was administered to achieve this effect
 - Length of the hospital stay (including intensive care unit stay)
 - Procedures (ie, right or left heart catheterization, echocardiogram, balloon pump)
 - Discharge to rehabilitation/palliative care/other structures
- Event rate and general outcomes
 - Mortality, readmission, health care resource utilization rates
 - Causes of death and readmission: cardiovascular versus noncardiovascular

Estimate the power requirements of the study with respect to outcomes

- Estimate event rate to ensure study is adequately powered
- Ensure that the planned effect-size is clinically relevant
- Estimate variability in biomarker levels and other potential surrogate end points (ie, variation in laboratory cut-offs, comparability of assays, or genetics of patient population)
- Assess potential impact of protocol implementation on outcomes (ie, following a protocol might improve outcomes compared with institutional practice even in the placebo arm)

Improve protocol execution

- Center training: Allow time for better understanding of the process and terminology, including data recording and sample collection, detecting issues with language barriers and translation, and improving communication with coordinators
- Identify underperforming centers: Detect inadequate follow-up or compliance issues; corrective efforts can be used or center might be excluded from participation
- Predict enrollment rate in trial: Help guide whether enrollment rate will be adequate to achieve desired power within planned timeline
- Decreases chances of missing effective therapy

From Greene SJ. Designing effective drug and device development programs for hospitalized heart failure: a proposal for pretrial registries. Am Heart J 2014;168(2):146; with permission.

more prolonged duration of follow-up requiring a greater number of postdischarge visits and/or telephone contact. As a result, for all of the aforementioned reasons, patient recruitment and protocol adherence for many AHF trials may be an onerous undertaking at the site level for principle investigators and study coordinators.

In response to these concerns, several prominent clinical investigators have called for pragmatic trials to streamline recruitment and facilitate data collection. The prototypical example of this concept is the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial, which was conducted to evaluate the efficacy

Box 2**Optimal center characteristics for successful participation in a multicenter trial***Proper patient enrollment*

- Center achieves and maintains a high enrollment rate
- Patient characteristics conform to the enrollment criteria of the trial

High quality in protocol implementation and data collection

- Adherence to protocol process with minimal violations
- Adequate quality of collected data (minimal rates of missing data, verifiable from original sources with high fidelity of transcription, and so forth)

Good clinical practice in heart failure management

- Management of heart failure adheres to the current guideline-driven standards
 - Optimal medical treatment
 - Evidence-based device implantation (with consideration of regional variations in guidelines)
- Adequate documentation of diagnostic and therapeutic procedures

Patient follow-up procedures

- Established follow-up process
- Little or no loss to follow-up
- High-quality data on outcomes and adverse events (adjudication of outcomes)

From Greene SJ. Designing effective drug and device development programs for hospitalized heart failure: a proposal for pretrial registries. *Am Heart J* 2014;168(2):146; with permission.

and safety of nesiritide in AHF.^{18,19} Enrollment criteria were broadly applicable including patients greater than or equal to 18 years of age hospitalized for an objective episode of AHF and primarily excluding patients with other life-limiting comorbidities or high-risk features and/or concomitant therapies precluding the provision of nesiritide. Study participants were randomized to a continuous infusion of nesiritide or placebo with or without an initial bolus for a minimum of 24 hours and a maximum of 7 days. Coprimary end points were dyspnea at 6 or 24 hours after study drug initiation and the composite of HF rehospitalization and death at 30 days. Thus, although nesiritide was ultimately found to be safe but no more efficacious than placebo, the ASCEND-HF trial, the largest conducted in AHF to date, is particularly noteworthy for taking a practical approach to trial design and conduct. These features may have contributed to the robust North American representation, with almost 50% of enrollment occurring in the United States and Canada.

BARRIER: INADEQUATE INFRASTRUCTURE FOR RECRUITMENT OF PARTICIPANTS AND STUDY CONDUCT

Few SBR organizations have a full-time research team. More commonly, principle investigators

participate *ad hoc* in clinical trials based on interest and availability. In addition, study coordinators may include part-time or shared staffing models and clinical research activities are carried out simultaneous in the same physical space as standard of care. Study protocols may also have to go through the same cumbersome local institutional review board approval procedure at every single site. This slow and inefficient startup process occurs at a substantial premium and must be absorbed by the study sponsor and/or participating center. In addition, whether enrollment goals are met or not there are ongoing costs associated with keeping sites active.

A potential work-around is to establish permanent clinical trial networks with shared administrative overhead and dedicated research staff. In the purest form, industry and other sponsors would be able to approach a fully integrated academic or contract research organization with the authority to negotiate and make decisions on behalf of the entire network to simultaneously open enrollment across many individual and geographically diverse sites. In-network centers would be expected to have expedited start-up time and support staff with superior research training and specialized competency within various CVD states. There are many examples of existing multicenter research

collaborations including the National Institutes of Health Heart Failure Network and the Duke University Cooperative Cardiovascular Society yet there are no large-scale, fully integrated clinical trial networks with the capacity to independently conduct pivotal studies across the spectrum of CVD on demand for potential sponsors.

BARRIER: UNDERDEVELOPED RELATIONSHIPS BETWEEN CARDIOLOGISTS AND OTHER PHYSICIANS CARING FOR THE CARDIAC PATIENT

There are more than 1 million admissions annually in the United States accounting for nearly 6.5 million hospital days.¹ It has been estimated that approximately 80% of patients with AHF initially present to the emergency room.²⁰ As a result, emergency physicians make all of the early decisions regarding diagnostic work-up and treatment. Emergency providers are also ultimately responsible for deciding disposition (ie, discharge vs admit) and triage (ie, observation, floor, telemetry, intensive care unit). In addition, with the growth of hospital-based medicine many patients admitted for AHF are being treated exclusively by internal medicine-trained hospitalists or in consultation with specialists in general cardiology and/or HF. However, despite the prominent role played by emergency physicians and hospitalists in the care of patients with AHF, these providers have traditionally been excluded from leadership roles at the site level, and clinical trials have historically relied on cardiology-based research teams to enroll patients up to 24 to 48 hours after hospital admission.

Thus, by excluding emergency physicians and hospitalists from participation in AHF trials, a significant number of potential participants may be outright missed and the enrollment of many more patients may be substantially delayed.^{21,22} However, trial experience in such diverse diseases and conditions as ACS, sepsis, stroke, and trauma suggest that it is practical to enroll patients in the emergency room. In addition to direct referrals from emergency room staff, the research team may review admission logs, screen the electronic medical record remotely, or activate via automated alerts (ie, chief complaint, diagnosis, symptoms, laboratory values, and so forth). Although establishing a definitive diagnosis of AHF may theoretically be challenging in an urgent/emergent setting, several small-scale multicenter registries and trials have shown that it is feasible to diagnose and treat AHF within 6 to 12 hours of initial presentation.^{15,23} Hence, it is imperative to build a collaborative relationship

with emergency room physicians and hospital-based physicians at the site level to shift enrollment to the emergency department and the acute phase of hospitalization. This early enrollment may be critical to trial success depending on the study drug mechanism of action and the study end point. For example, in the URGENT-dyspnea study, greater than 75% of patients with AHF reported dyspnea improvement with standard therapy within 6 hours of emergency room presentation. Thus, for trials including dyspnea improvement as a primary end point, early recruitment in the emergency department may be critical to trial success.

BARRIER: MISALIGNMENT OF INCENTIVES BETWEEN PRINCIPLE INVESTIGATORS AND PARENT CLINICAL FACILITY

It is hard to make generalizations regarding the incentives for performing SBR because there is so much potential diversity in the relationship between the principle investigator and the parent clinical facility. For instance, the principle investigator's relationship with the parent clinical facility may range from being the sole proprietor or part of an ownership group to being a salaried employee. However, as a result of health care reform legislation and market trends, most clinical providers are now employees of academic or community-based hospitals and health care systems and they are often compensated for clinical services using formulas based on relative value units. Although the operating facility is often reimbursed at a premium for participating in clinical trials (ie, sponsor payments exceed normal payer mix, which would otherwise include lower payments from Medicaid and Medicare programs), clinician-investigators are often not compensated for time spent on research. Thus, clinician-investigators may paradoxically be compensated less for participating in SBR, whereas clinical trials may increase facility revenues directly by favorably changing the payer mix and indirectly by increasing the volume of patients seen and services rendered (ie, diagnostic testing, procedures, and so forth associated with study participation). A practical solution to realign incentives between site-based investigators and the parent clinical facility is to develop a research relative value unit to properly compensate providers for time and effort spent on clinical research. Furthermore, achievements in SBR may also be recognized by the institution for overall career advancement including promotions and consideration for tenure.

BARRIER: LIMITED UPFRONT TRAINING AND ONGOING SUPPORT FOR STUDY COORDINATORS AND OTHER STAFF

Although clinical trials are often led by a steering committee of academic and industry experts with substantial experience in the design and conduct of global research studies, most enrollment takes place at community-based, nonacademic hospitals and clinics. The local principle investigator and study coordinator usually are only able to devote part of their effort to SBR and may have variable prior experience and training. The research team is often provided with educational materials including background information, such as guideline-based recommendations for management and the rationale for the study. In addition, in some instances there may be in-person investigator meetings and/or telephone or World Wide Web conferences.

Industry sponsors often do not have the available personnel and infrastructure to manage the day-to-day aspects of a conducting a pivotal trial and must therefore rely on the assistance of academic research organizations or contract research organizations for site support, data collection, event adjudication, and data and safety monitoring. However, following a trial launch there may be very little contact between the study sponsor/academic leadership and site-based researchers. Furthermore, study coordinator may have little external or internal support to excel at SBR. It is obligatory for study sponsors, academic leaders, and academic research organizations/contract research organizations to monitor enrollment and prioritize the early troubleshooting of potential problems a priority. The sponsor may also further engage the local principle investigator and study coordinator by recognizing recruitment meeting or exceeding benchmarks with leadership roles in the trial and/or involvement in subsequent scientific publications.²⁴

SUMMARY

AHF is a growing public health problem of pandemic proportions and there is currently an unmet need to expand the available therapeutic armamentarium. However, nearly every clinical trial conducted in AHF to date has been neutral in terms of efficacy and/or safety. In addition, SBR in North America is currently in a state of crisis with many trials being conducted predominantly or entirely in Eastern Europe, South America, and Asia-Pacific where patient characteristics, background therapy, and event rates may differ tremendously therefore limiting the

generalizability to US patient populations. Although there is not a single panacea for remedying the decline in SBR in the United States, a combination of improving awareness of AHF and clinical trial opportunities, using registry data to preview patient characteristics and protocol adherence, designing and conducting pragmatic trials, establishing permanent clinical trial networks, building multispecialty collaborations to care for the cardiac patient, aligning financial incentives between clinician-investigators and hospital administrators by compensating for time and effort spent on research, and expanding start-up and ongoing site-based support may facilitate enrollment. Despite these global recommendations, improving the provider and patient experience in SBR in North America will ultimately require a more nuanced approach that implements changes at the site level and accounts for the uniqueness of each individual participating center.

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