Published in final edited form as:

Am Heart J. 2014 August ; 168(2): 142–149. doi:10.1016/j.ahj.2014.05.009.

Designing effective drug and device development programs for hospitalized heart failure: A proposal for pretrial registries

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Abstract

Recent international phase III clinical trials of novel therapies for hospitalized heart failure (HHF) have failed to improve the unacceptably high postdischarge event rate. These large studies have demonstrated notable geographic and site-specific variation in patient profiles and enrollment. Possible contributors to the lack of success in HHF outcome trials include challenges in selecting clinical sites capable of (1) providing adequate numbers of appropriately selected patients and (2) properly executing the study protocol. We propose a “pretrial registry” as a novel tool for improving the efficiency and quality of international HHF trials by focusing on the selection and cultivation of high-quality sites. A pretrial registry may help assess a site’s ability to achieve adequate enrollment of the target patient population, integrate protocol requirements into clinical workflow, and accomplish appropriate follow-up. Although such a process would be associated with additional upfront resource investment, this appropriation may be modest in comparison with the downstream costs associated with maintenance of poorly performing sites, failed clinical trials, and the global health and economic burden of HHF. This review is based on discussions between scientists, clinical trialists, and regulatory representatives regarding methods for improving international HHF trials that took place at the United States Food and Drug Administration on January 12th, 2012.

Current worldwide epidemiological trends, including aging populations, improved survival after myocardial infarction, and decreased rates of sudden cardiac death, will translate into an increasing global burden of heart failure (HF) in the coming decades.^{1–4} The estimated lifetime risk of developing HF for Americans aged >40 years is 20%, and projections of associated direct costs will rise from \$21 billion in 2012 to \$70 billion in 2030.^{5,6} In Europe, the prevalence of HF is estimated approximately 1%, and HF is the cause for 5% of all hospitalizations.⁷ Unfortunately, our knowledge about the epidemiology and clinical characteristics of patients with HF in low- and middle-income countries is limited.^{8–11} These countries encompass most of the world’s population and make up a growing portion of phase III trial sites.^{12,13} However, data about the demographics, clinical characteristics, management, quality of care, and clinical course in many of these regions have not been systematically studied.

Although drug- and device-based therapies have favorably impacted survival for ambulatory outpatients with HF and reduced ejection fraction, there has been no such parallel progress in hospitalized heart failure (HHF), and outcomes remain persistently poor.^{14,15} Despite a decade of several large, costly, international randomized clinical trials, event rates for mortality and readmission remain >17% and >40%, respectively, within 1 year of discharge.^{16–19} The management of HHF remains largely unchanged from the 1970s.^{20,21}

Common across many failed HHF drug development programs has been a lack of high-performing clinical sites that efficiently and effectively enroll and monitor high numbers of appropriately selected study patients. This site selection problem has contributed to excessive trial costs and may influence study results.^{22,23} Accordingly, we must reevaluate how these sites are chosen. In this review, we propose one possible tool for improving the

quality of global HHF clinical trials: a “pretrial registry.” This article is based on discussions between scientists, clinical trialists, and regulatory representatives regarding methods for improving international HHF trials that took place at the United States Food and Drug Administration on January 12th, 2012.

Challenges in HHF trials

There is no single explanation for the failure of many past HHF trials. However, gaps in our knowledge of HHF have hindered our ability to find effective interventions or match a specific intervention to the appropriate patient subgroup. These limitations result in 2 notable problems for drug development. The first is challenges in “study design,” possibly due to gaps in our understanding of HHF (e.g., pathophysiology, clinical course, influence of comorbidities, and background therapies, regional, and global variations). The second is difficulty with “study execution” often resulting from the selection of study sites without capacity for proper patient selection, enrollment, and protocol execution. For instance, the proportion of study sites from one part of the world to another may vary dramatically between phase IIb and phase III studies. Table I summarizes factors contributing to unsuccessful phase III HHF trials.

Limitations in study design

The description of HHF’s clinical course from prior registries is primarily limited to the inpatient phase or the initial weeks postdischarge; less is understood regarding long-term outcomes. The point in time at which a therapy is initiated and the duration for which it is continued are key design considerations that may significantly impact trial results.¹⁶ For example, early response to standard therapy is often not captured because of the retrospective nature of most inpatient registries and because patients are not enrolled early in their hospital course.

An intervention may be more effective in certain patient phenotypes defined by demographics, severity of presentation, etiology, background comorbidities and therapies, or biomarkers. Many of these patient factors vary greatly by geographic region.^{13,25} Our understanding of varying global profiles of HHF is predominantly from large multicenter registries in Europe, the United States, parts of the Middle East, and some Asian Pacific nations (Table II).^{8,17,26,27–39} Until recently, HHF registry data from South and Central America came largely from a few Argentinean registries.⁴⁰ Emerging data from ADHERE-international is adding essential information from Mexico and Brazil.⁴¹ There is only one multicenter registry of just >1,000 patients in Africa.³⁹ Otherwise, data regarding HHF in over half the world’s population (including South Asia and China) are based primarily upon small single-center case series.

These global disparities in registry data are particularly important given the predominance of non-North American patients in HHF trials. In 4 recent, large, randomized studies, only one-third of patients were enrolled in North America.^{42–45} Different regions have different medical practices, access to care, resources, risk factor prevalence, race, ethnic groups, culture, and social circumstances, which may result in geographic variation in treatment and outcome. For example, in the ATTEND registry of Japanese patients, the length of stay was

almost 5 times longer than patient in the ADHERE registry.³⁵ It is not clear whether this difference is a result of a sicker patient population, regional variations in perception of HF severity, or variation in reimbursement structure. Without increased consideration of global HHF patient profiles and management patterns, investigators will be limited in their ability to design optimal study protocols.

Limitations in study execution

Effective execution of a study protocol in phase III clinical trials is an equally important consideration. This step is reliant on a site's capacity to enroll the desired target population, administer the therapy at an appropriate time, and provide rigorous patient follow-up.

Recruiting the desired patient population presents unique challenges. A trial designed to study a therapy for patients with more advanced HF or severe presentations (e.g., low blood pressure) may not be appropriate for smaller sites with limited critical care resources. Similarly, evaluating a drug's ability to reduce dyspnea may require patients to be enrolled and receive the study drug within a few hours of presentation. Symptoms of pulmonary congestion often respond to diuretics and vasodilators within a few hours.^{44,46,47} Therefore, a novel intervention for acute breathlessness must either be introduced early to accelerate recovery or be administered late among patients who have failed to respond to therapy. For example, the success of the RELAX-AHF trial in randomizing patients within a mean 8 hours of presentation likely contributed to the investigators' ability to achieve a dyspnea-related primary end point in the subset of patients studied.⁴⁸ Such timely enrollment may pose a significant challenge at sites where there is limited collaboration with the emergency department, limited hours for a research coordinator to enroll patients (e.g., nocturnal enrollment), or limited pharmacy hours.

In studying end points such as mortality, contacting patients after hospitalization is crucial. Follow-up can be especially difficult in regions without well-established mechanisms for continuity of care. At some tertiary care centers, potential study participants may live far from the site or in areas with very limited access to health care, making effective study follow-up challenging. In addition, ensuring that new therapies are tested on optimal background therapy, consistent with current evidence and guidelines, requires participation of sites where this level of care is accessible and standard practice.

Globalization of clinical trials

Concerns regarding site quality and study protocol execution are especially relevant in the changing atmosphere for global HHF trials. In the last decade, there has been a trend toward globalization within studies, with fewer study sites in the United States and Western Europe, and an increasing number of sites that contribute few patients to the overall trial population (especially in the United States and Western Europe) (Figure 1).^{12,13} These trends require trials to include a large number of sites to recruit the necessary sample size and often result in a disproportionate number of patients from a select few high-enrolling centers, potentially at the cost of appropriate patient selection. The globalization and heterogeneity in study site performance generate a feedback loop: (1) the need for more patients requires more centers, (2) more centers require more countries, (3) more countries causes greater heterogeneity, (4)

greater heterogeneity introduces greater statistical uncertainty, and (5) this ultimately necessitates a larger patient population (Figure 2).^{22,49}

Combining variability in the number of patients enrolled across study sites with the aforementioned potential geographic variation in patient profile and management may strongly influence clinical trial results. The EVEREST and TOPCAT trials provide illustrative examples (although TOPCAT included ambulatory HF patients).^{42,50} Overall, a goal of HHF drug development programs should be to include fewer sites that enroll high numbers of appropriate patients. High enrollment at a given center must not be at the expense of misinterpretation of inclusion/exclusion criteria or increased protocol deviation.

Despite prespecified inclusion and exclusion criteria, recent analyses of EVEREST showed significant variation in patient characteristics, outcomes, and follow-up based on region or number of patients enrolled per site.²² EVEREST also highlights the poor recruitment rate that plagues contemporary HHF trials, with an individual site enrollment rate of 0.41 patients/center per month. Many sites enrolled 0 or 1 patient and did not justify investment of trial resources. Such a low enrollment rate prevents adequate representation of the study population for which the trial and drug were originally designed and further limits generalizability. Similarly, in TOPCAT, roughly 50% of the study cohort was enrolled in only 2 countries, Russia and the Republic of Georgia. The placebo group event rate among these patients was only 8.4%, compared with 31.8% among patients enrolled in the Americas.⁵⁰ Moreover, it appeared that the efficacy of the study drug differed across these 2 patient populations, with spironolactone reducing the rate of primary end point in the Americas and failing to do so in the lower risk cohort. These findings generate the hypothesis that the neutral results of TOPCAT were the direct consequence of geographic variation in patient characteristics, site enrollment, study execution, and/or interpretation of inclusion/exclusion criteria.

Potential solution: pretrial registry

With the goals of improving study design and execution for development of therapies that improve HHF outcomes, we propose a novel solution: a “pretrial registry” (Table III). A pretrial registry simulates the execution of a clinical trial but without the interventional component. It precedes patient enrollment for the study for a short period to serve as a “dry run” of the trial. Data are collected in a planned, systematic fashion, with (1) requisite procedures performed in a standardized manner, (2) routine surveillance by regular follow-up, (3) adjudication of outcomes, and (4) monitored reporting of results. The registry may have similar inclusion/exclusion criteria to the planned trial, although it may be prudent to include a somewhat broader population in case there is a need for subsequent modification of selection criteria. A pretrial registry would capture information on site-specific trial processes, in addition to patient characteristics and outcomes.

In contrast, existing “real-world” registries generally collect data as part of routine clinical practice that inconsistently reflect preplanned procedures, adjudicated outcomes, and/or patient follow-up. As a result, certain data are often missing and heterogeneous. Thus, results of “real-world” registries may not be representative of results expected in clinical

trials, as shown in the MAGGIC meta-analysis, where the type of study (observational versus trial) was found to influence observed outcomes in HF.⁵¹ In a pretrial registry, we propose data collection regarding a site's patient population and capacity for executing the protocol in the few weeks to months leading up to the potential enrollment of trial patients. These data would provide a streamlined registry of patients, detailing their demographics, comorbidities, background therapies, method of referral, severity of presentation, timing of enrollment relative to hospital presentation and initial treatment, and ability to follow-up. Data could be collected for consecutive or periodic consecutive patients (i.g., 1 day a week). At the end of the desired pretrial period, sites could be evaluated with regards to their ability to (1) recruit adequate numbers of appropriate patients, (2) execute the registry protocol (which may serve as a surrogate for the ability to complete enrollment and data collection in the subsequent randomized trial), (3) perform follow-up, and (4) communicate with the steering committee. This provides time for troubleshooting and identification of sites that are unlikely to perform adequately. It also allows ability to survey a center's institutional review board or ethics committee approval process to estimate the speed at which the center could be activated should other criteria for site performance be met. Undoubtedly, resources required for this stage would be substantial but likely significantly less than at the trial stage, as the focus of the pretrial registry is primarily data gathering as opposed to testing a specific intervention. Proposed requirements for a particular center to be included in a large multicenter trial, as gauged by a pretrial registry, are summarized in Table IV.

Information gathered through such pretrial registries can be added to larger registries maintained by those involved in clinical research. By accessing information from previous trials and pretrial registries, new trials can be set up and run more efficiently. Similar efforts are already being directed through a newly incorporated nonprofit organization, TransCelerate BioPharma (King of Prussia, PA, USA) (<http://transceleratebiopharmainc.com>), whose global initiatives include standardization of clinical trial protocols and forms, and establishment of a global investigator registry. Other specific organizational goals involve efforts to qualify and train sites, standardize data collection, develop a shared investigator portal for communication between sponsors and sites, and improve patient safety monitoring. Such efforts to gauge and improve study site quality in concert with global registries may work synergistically to improve HHF trial quality.

Two recent innovative and efficient percutaneous coronary intervention trials have already modeled how registries, by using systems already in place, can be used to streamline processes for establishing trial sites, enrolling the appropriate patients, and maintaining adequate patient follow-up. The SAFE-PCI for Women trial was able to use an existing registry infrastructure to identify centers with sufficient transradial percutaneous coronary intervention volume, thus significantly increasing the likelihood that local site investigators and operators would feel comfortable with patient randomization to this less common access site compared with traditional femoral access.⁵² Moreover, data regarding patient demographics, medical history, medications, and index hospitalization clinical outcomes already routinely coded into the registry database were electronically captured from consenting patients and autopopulated into an electronic case report form. This feature led to an estimated 65% decrease in site coordinator workload. Similarly, the TASTE trial leveraged a preexisting registry infrastructure to rapidly and cost effectively enroll high

numbers of patients.^{53,54} In fact, TASTE investigators recruited >6 times more patients than a previous randomized trial of thrombus aspiration in acute myocardial infarction.⁵⁵ Taken together, SAFE-PCI for Women and TASTE demonstrate the potential of registry-based clinical trials and provide optimism that a similar strategy can be used in an HHF study population.

Challenges for creating a pretrial registry

Although a pretrial registry may allow improved estimation of the capacity of prospective trial centers, there are specific challenges associated with implementation. These challenges can be broadly categorized into 3 domains: cost, time, and selection bias.

Upfront additional costs will be significant. There are additional costs associated with personnel training, data collection, data storage, and analysis. However, these costs may be a small fraction of the expense of maintaining poorly performing study sites in a “mega-trial.” In addition, costs can be consolidated by providing training for both the registry and full trial protocol concurrently. The “fixed cost” of a new trial site is on the order of \$30,000 to \$50,000 with significant monthly maintenance costs. In the aforementioned example of the EVEREST trial, 77 of 436 sites enrolled 0 patients, 62% of sites enrolled 10 patients, and the median enrollment per site was only 6 patients.²² Upfront costs for improving the capacity of sites to enroll quality patients and identify poorly performing sites may be offset by more efficient utilization of resources during the upcoming clinical trial. Thus, trial sponsors should have an incentive to properly execute a pretrial registry as part of a cost-effective drug development strategy.

A second consideration is the additional time needed for pretrial data collection and analysis. However, considering that the follow-up and outcomes assessment time frame for HHF is relatively short (6 months in many cases), the time for pretrial data collection should not take more than a few months. Furthermore, not every patient would need to be enrolled; consecutive patients may be enrolled every few days to help generate a representative sample.

A third concern is selection bias. By using a pretrial registry as a “screening tool” for centers, additional selection biases beyond those intrinsic to most clinical trials could be introduced. For example, eliminating centers with poor follow-up rates may also eliminate centers representing patients of differing socioeconomic status. However, using the pretrial screen as a tool for enhancing follow-up strategies at lower enrolling centers by providing additional training or resource allocation during trial protocol implementation might help mitigate this risk. Furthermore, information from pretrial profiles of centers can demonstrate how sites’ patient profiles and outcomes compare, perhaps serving as impetus for quality improvement initiatives.

Conclusion

Pretrial registries have the potential to bridge our current knowledge gaps in HHF and provide site-specific and region-specific information for improving efficiency and quality of clinical trials. The data collected could substantially increase the probability of success for

large phase III programs through appropriate selection of (1) the target HHF subpopulation and (2) trial centers that match the needs and standards of the trial protocol. Although such registries would require additional upfront resource investment, the expense may be modest in comparison with the costs associated with unsuccessful large phase III studies. Trial sponsors may have an incentive to properly execute a pretrial registry as part of a cost-effective drug development strategy. Considering the high mortality, morbidity, and direct costs associated with HHF care throughout the world, improving HHF patient outcomes should remain a critical concern for all parties involved, including patients, clinicians, academicians, regulators, and industry sponsors. Accordingly, the utilization of a pretrial registry for optimization of HHF drug and device development programs warrants strong consideration.

Acknowledgments

The authors thank Ms. Fumiko Inoue for organizing the meeting that prompted this manuscript.

Author disclosures

S.D.A. has received honoraria from Vifor Pharma, Bayer, CardioMems, ThermoFisher, St Jude Medical, Novartis, and Cardiorentis and received research support from Vifor Pharma, Bayer, and Novartis; O.C. has received research support from Abbott, Servier, and Vifor and served as a consultant for Philips, Novartis, and Janssen; S.P.C. has received research support from NIH/NHLBI, Medtronic, Radiometer, Cardiorentis, and Novartis and served as a consultant for Medtronic, Trevena, Novartis, Janssen, and Radiometer; W.D. and L.R. are employees of Bayer Pharma AG; G.C.F. has received research support from NHLBI, AHRQ, and Gambro and has served as a consultant for Novartis, Medtronic, Bayer, Johnson & Johnson, and Medicines Company; N.S. has received honoraria from Otsuka Pharmaceuticals, Daiichi-Sankyo, Novartis Pharma, Eisai, Bayer, Boehringer-Ingelheim, Bristol-Myers, Philips Respironics, Ono Pharma, Kyowa-Hakko-Kirin, and Astellas and served as a consultant for Novartis and Bayer; B.P. has received modest speaker honoraria or served as a steering committee member for Bayer Healthcare, Novartis, Stealth Peptides, Boehringer Ingelheim, Bristol Myers-Squibb, Daiichio Sankyo Medtronic, and Biotronik; M.G. has served as a consultant or received honoraria from Abbott Laboratories, Astellas, AstraZeneca, Bayer Schering Pharma AG, Cardiorentis Ltd, CorThera, Cytokinetics, CytoPhex, Inc, DebioPharm SA., Errekappa Terapeutici, GlaxoSmithKline, Ikaria, Intersection Medical, INC, Johnson & Johnson, Medtronic, Merck, Novartis Pharma AG, Ono Pharmaceuticals USA, Otsuka Pharmaceuticals, Palatin Technologies, Pericor Therapeutics, Protein Design Laboratories, Sanofi-Aventis, Sigma Tau, Solvay Pharmaceuticals, Sticares InterACT, Takeda Pharmaceuticals North America, Inc, and Trevena Therapeutics.

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Figure 1.

Mechanisms for the globalization of clinical trials in HF. Abbreviations: *US*, United States; *WE*, Western Europe. Reprinted, with permission, from Gheorghiade et al.²³

Figure 2.

Interaction between trial site selection, geographical differences, and trial enrollment.
Reprinted, with permission, from Gheorghiade et al.²³

Table I**Contributors to unsuccessful phase III HHF trials**

Incomplete understanding of pathophysiology

- Poor understanding or evaluation of the cardiac substrate (ie, importance of echocardiographic measurements in addition to ejection fraction)
- Uncertain relationship between hemodynamic measurements, renal, and biomarker data and clinical outcomes
- Unclear interactions among cardiac and noncardiac comorbidities, therapies, and outcomes

Incomplete understanding of patients and their clinical course

- Heterogeneous patient population in terms of etiology, clinical presentation, and social factors
- Inadequately studied postdischarge course
- Significant regional variation in patient profiles, management, and outcomes

Incomplete understanding of the investigational therapy (experimental drug or device)

- Transition from animal to clinical studies without comprehensive understanding of the properties of the drug in target population and specific patient subgroups (ie, not really “knowing” the drug)
- Inadequate dosing regimens
- Possible variation of drug efficacy and safety with time: (given fluctuations in symptoms, hemodynamics, neurohormonal activation, renal function, and myocardial injury during the course of hospitalization and postdischarge, efficacy and/or safety of drug/device may be dependent on time of intervention)
- Most drugs tested thus far reduce systemic blood pressure, which may decrease coronary and renal perfusion, thereby contributing to myocardial and/or kidney injury

Suboptimal protocol design

- Patient selection: inappropriate selection of target population and timing of intervention
- Surrogate end points in phase II trials do not predict the results of phase III trials
- Clinical outcomes in small number of select centers in phase II trials do not predict the results of large, phase III trials with wider, international center participation
- Inappropriate selection of end points
- Signs and symptoms improve with standard therapy in most patients: adequate power is needed to prove that investigational therapy produces incremental improvements if dyspnea is the primary end point

Suboptimal protocol implementation

- Nonadherence to patient selection criteria
- Protocol violations
- Suboptimal follow-up procedures
- Varying quality of study sites
- Varying HHF trial experience and ability to recruit patients

Adapted from Gheorghiade et al.²⁴

Table II

Geographic distribution of international HHF registry data

Registry	n	North America	South America	Europe	Asia	Africa	Australia	Middle East
ADHERE ²⁷	105388	X						
OPTIMIZE-HF ¹⁷	48612	X						
GWTH-HF ²⁸	110621	X						
EHFS-I ²⁹	11327			X	X			X
EHFS II ³⁰	3580			X				
ESC-HF Pilot ³¹	1892			X				
IN-HF Outcome ³²	1855			X				
EFICA ³³	581			X				
RO-AHFS ²⁶	3224			X				
AHEAD ³⁴	4153			X				
ATTEND ³⁵	4842				X			
National HF Audit ³⁶	6170			X				
ADHERE-AP ³⁷	10171				X			
ALARM-HF ³⁸	4953	X	X	X			X	
THESUS-HF ³⁹	1006					X		

Table III**Advantages of pretrial registries for appropriate site selection**

Understand the disease characteristics in the intended study population
<ul style="list-style-type: none"> • Demographic variables (ie, age, gender, and ethnicity) • Distribution of HF causes and precipitating factors: <ul style="list-style-type: none"> - Coronary artery disease versus other causes - Precipitating causes (ie, acute coronary syndromes, hypertension, atrial fibrillation, infectious causes, and noncompliance) • HF treatment: <ul style="list-style-type: none"> - Adherence to guidelines for medical treatment - Adherence to guidelines for device implantations • Clinical course of the disease: <ul style="list-style-type: none"> - Presentation (ie, signs, symptoms, and clinical parameters) - Speed of symptom control and acute therapy that was administered to achieve this effect - Length of the hospital stay (including ICU stay) - Procedures (ie, right or left heart catheterization, echocardiogram, and balloon pump) - Discharge to rehabilitation/palliative care/other structures • Event rate and general outcomes <ul style="list-style-type: none"> - Mortality, readmission, and health care resource utilization rates - Causes of death and readmission: cardiovascular versus noncardiovascular
Estimate the power requirements of the study with respect to outcomes
<ul style="list-style-type: none"> • 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, a protocol might improve outcomes compared with institutional practice even in the placebo arm)
Improve protocol execution
<ul style="list-style-type: none"> • Center training: allow time for better understanding of the process and terminology, including data recording and sample collection, 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 the identification of an effective therapy

Abbreviations: *ICU*, intensive care unit.

Table IV**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, etc)

Good clinical practice in HF management

- Management of HF 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)
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