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CLINICAL TRIALS (J BUTLER, SECTION EDITOR)

# Impact of Site Selection and Study Conduct on Outcomes in Global Clinical Trials

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**Abstract**
*Purpose of Review* There are over 25 million patients living with heart failure globally. Overall, and especially post-discharge, clinical outcomes have remained poor in heart failure despite multiple trials, with both successes and failures over the last two decades. Matching therapies to the right patient population, identifying high-quality sites, and ensuring optimal trial design and execution represent important considerations in the development of novel therapeutics in this space.
*Recent Findings* While clinical trials have undergone rapid globalization, this has come with regional variation in comorbidities, clinical parameters, and even clinical outcomes and treatment effects across international sites.
*Summary* These issues have now highlighted knowledge gaps about the conduct of trials, selection of study sites, and an unmet need to develop and identify "ideal" sites. There is a need for all stakeholders, including academia, investigators, healthcare organizations, patient advocacy groups, industry sponsors, research organizations, and regulatory authorities, to work as a multidisciplinary group to address these problems and develop practical solutions to improve trial conduct, efficiency, and execution. We review these trial-level issues using examples from contemporary studies to inform and optimize the design of future global clinical trials in heart failure.

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**Keywords** Heart failure · Clinical trials · Geographic variation · Site selection · Study design · Outcomes

**Abbreviations**
HF Heart failure

## Introduction

Heart failure (HF) has a tremendous impact on the population worldwide with prevalence of over 25 million globally and ~6.5 million in the USA [1]. Both in the USA and in Europe, there are more than 1 million hospitalizations for HF (HHF) annually [2]. The overall cost of HF in the USA has been projected to increase from $39.2 billion in 2010–2012 to $70 billion in 2030 [3–5]. Despite this heavy burden and some improvement in HF therapies, there is lack of therapeutic progress for a large group of patients with worsening chronic HF and those with HHF [6••, 7, 8]. The factors implicated in the failure of clinical trials in HF include inability to fully understand and match therapies to target patient subgroups, problems in study design and execution, and undue prioritization of short-term surrogate markers (e.g., dyspnea relief, natriuretic peptides) rather than long-term key clinical endpoints (e.g., mortality, rehospitalization) [6••, 9, 10, 11•]. Among these factors, study site selection is now being recognized as an important factor that may have a significant impact on background event rates and treatment effects [8, 12, 13], both of which may heavily influence the overall success of the trial. Heterogeneity across sites introduces issues with respect to quality and reliability of data from sites with issues in study execution and generalizability of data across various patient groups [14–16]. We highlight problems in trial conduct, efficiency, and execution; discuss the

importance of site selection; and identify practical solutions to improve the design of future global clinical trials in HF.

## Issues Facing Clinical Trials and Outcomes: an Overview

HF is a heterogeneous condition with multifaceted pathophysiology. Many patients, despite achieving standard treatment goals of improvement in exacerbating symptoms, fluid loss, and improved pulmonary pressures, still have poor post-discharge outcomes. At the trial level, there is a similar disconnect between positive early-phase trial experiences showing improvement in surrogate markers of treatment efficacy, followed by negative or neutral phase III trials testing definitive clinical endpoints [7, 17]. A focus on long-term treatment effects and prognosis may be especially important in patients with HHF [6••]. Interventions made around the time of hospital discharge and continued into the high-risk post-discharge period are therefore increasingly being evaluated [18, 19]. However, trials with this strategy have also failed to improve outcomes in some trials, e.g., EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) and ASTRONAUT (Aliskiren Trial on Acute Heart Failure Outcomes) [8, 20]. The complexity of the disease may also lead to problems in understanding the mechanism of action of the drug, matching it to the intended target, and selection of the right patient population [10, 21]. Key factors associated with problems in HF trials are discussed in Table 1.

Recently, HF trials have undergone marked globalization with concurrent decline in enrollment rates at sites in the USA and Western Europe [22]. There are multiple reasons for this shift, of which the important ones are highlighted in Fig. 1. Globalization of trials in HF has driven increased regional heterogeneity in enrolled populations, larger trial size, higher trial costs, issues with reliability and security of data, and challenges with characterizing global study sites [6••] (Fig. 2). A key factor is the problem in the execution of a study, where, despite experienced teams, avoiding issues with data collection can be a major obstacle towards approval of a new therapy by the regulatory authorities [23]. Hence, we attempt to better understand these trial-level issues with site selection and study execution and provide a mechanistic approach to minimize the impact of these factors on the future design of global clinical trials in HF.

**Table 1** Factors affecting the outcomes in HF clinical trials

| Complex pathophysiology of HF | Issues in novel therapy | Problems in study design | Execution of the study |
|---|---|---|---|
| - Multifactorial etiologies of HF syndromes<br>- Variability in patient population<br>-Influence of comorbid conditions on HF and their interaction with the investigational therapy<br>- Lack of understanding of underlying primary myocardial mechanisms contributing to HF<br>- Limited recognition of long-term, post-discharge events and their mechanisms | - Not understanding the exact mechanism of the drug<br>- Limited investment in clarifying the precise site of action and optimal dose of the tested drug<br>- Failure of majority of new compounds to show efficacy, leading to higher cost for developing a successful drug<br>- Failure to record the non-target effects on other organs | - Matching the drug to the "right" population<br>- Undue focus on short-term, surrogate outcomes<br>- Not evaluating long-term or post: discharge events<br>- Issues with site selection | - Wrong or suboptimal patient selection<br>- Significant loss to follow-up<br>- Substantial regional variability in patient enrollment and quality control<br>- High cost of conducting global phase III clinical trials prohibiting subsequent trials after lessons learned<br>- Enrollment barriers in the USA and longer processing times for new drug development |

*HF* heart failure

## Site Selection

Enrollment in global clinical trials is determined by the ability of individual sites to effectively enroll appropriate patients that fit the specific trial eligibility criteria [6••]. Although globalization in selection of sites may improve the generalizability of the trial findings to certain populations, there appears to be important site- and region-specific variation in enrollment patterns. For instance, in the EVEREST trial (4133 enrolled patients from 359 global sites with an overall enrollment rate of 0.41 patients/site/month), significant site- and region-based heterogeneity was observed in patient profiles, baseline comorbidities, and serologic markers of disease severity [8]. Similarly, there was variation in background event rates (HF hospitalizations and mortality), such that sites with lower recruitment rates (<10 patients/site/month) had worse outcomes compared to the sites with higher enrollment [8]. Regional heterogeneity may also impact the eventual success of the overall trial. In the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With and Aldosterone Antagonist) trial [24] of patients with HF with preserved ejection fraction, 3445 patients were enrolled from six countries that were divided into two regions (the Americas and Russia/Georgia). Region-specific analysis demonstrated clinically

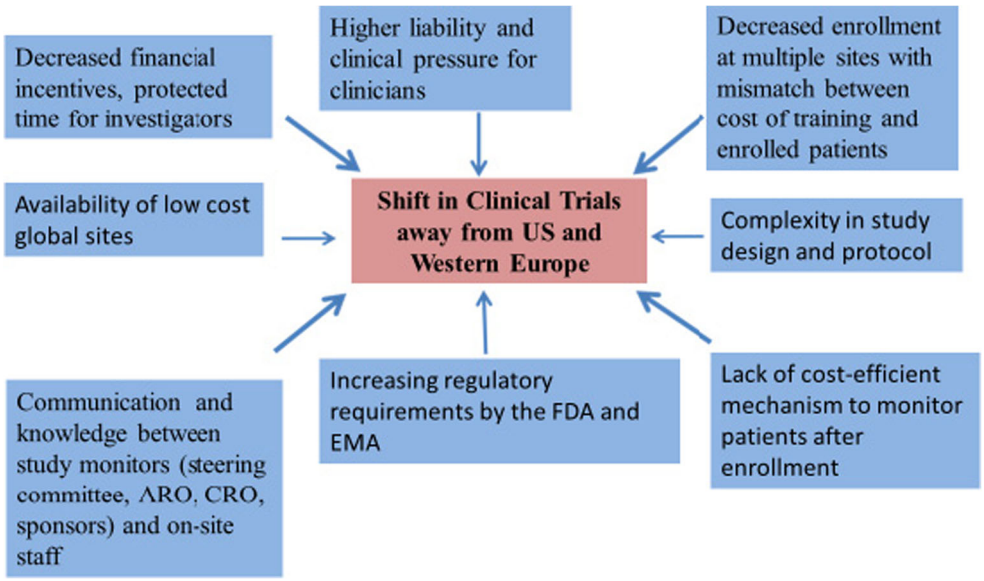


**Fig. 1** Factors influencing the state of HF clinical trials in the USA and Europe. *US* United States, *ARO* academic research organizations, *CRO* contract research organizations, *FDA* Food and Drug Administration, *EMA* European Medicines Agency. Permission to publish: not required as created by the authors

relevant variation in patient profiles, eligibility criteria, drug adherence, event rates, and treatment effects. In the overall trial, the primary composite endpoint of cardiovascular mortality, aborted cardiac arrest, and hospitalizations for HF was 18.6% in the spironolactone group and 20.4% in the placebo group ($p = 0.14$) [24]. However, when analyzing event rates by region, 31.8% ($n = 881$) of the patients in the placebo group in the Americas experienced the primary endpoint compared with only 8.4% ($n = 842$) of patients enrolled from Russia and Georgia. Furthermore, spironolactone reduced the primary endpoint in the Americas (hazard ratio 0.82, 95% confidence interval 0.69–0.98), but failed to impact the primary endpoint in Russia/Georgia when compared with placebo (hazard ratio 1.1, 95% confidence interval 0.79–1.51; treatment-by-region interaction $P = 0.12$) [24, 25].

Thus, sites with varying enrollment may play a significant role in the results of a study and make the true evaluation of an investigational therapy challenging. Analysis of trials conducted between 2001–2003 and 2009–2012 show that the trials conducted exclusively in North America have reduced in number compared to multiregional trials in recent years [11•]. Examples of lower participation of North American sites in recently conducted large multicenter international clinical trials in HF are shown in Table 2 [8, 12, 26–28].

Sites with low enrollment rates may lead to decreased exposure and inadequate training of the study investigators and

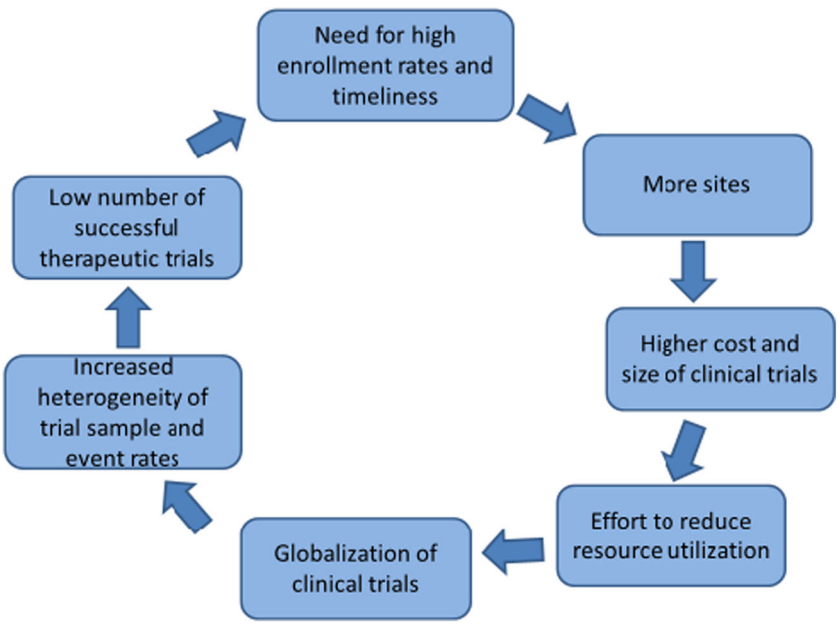


**Fig. 2** Factors driving globalization of clinical trials in heart failure. Permission to publish: not required as created by the authors

**Table 2** Enrollment from North America in contemporary global clinical trials in HF

| Trial name (year) | Total number of patients enrolled | Number of patients enrolled from North American sites |
|---|---|---|
| PARADIGM-HF [26] (2014) | 8399 | 602 (7%) |
| TOPCAT [12] (2014) | 3445 | 1151 (33%) |
| RELAX-AHF [28] (2013) | 1161 | 114 (10%) |
| ASTRONAUT [27] (2013) | 1615 | 124 (8%) |
| EVEREST [8] (2007) | 4133 | 1251 (30%) |

reduced support from the administration, both of which are keys to developing research protocols and structure at the participating sites. Limited trial participation and volume would also not justify the cost of trial-related training and infrastructure at the participating sites [8].

As such, mechanisms to identify high-quality, reliable, and efficient sites are needed. The development of large patient registries may help in identifying sites with sufficient quantity and quality [29]. However, an obstacle in developing a pre-trial global HF registry may come from the sites themselves, where the performance of the study site is presented to the accessible registries in a non-anonymous way and hence, exposing the site-specific data to the public. Data regarding the efficiency of the sites that have participated in prior trials may also be available to the trial execution organizations including academic research organization and contract research organization networks. This information can be used to create a separate repository of sites which may be utilized to enroll patient populations with desired characteristics for the trial with acceptable performance metrics. Leveraging novel methods of natural language processing of electronic health records and quantifying hospital volume for specific conditions may be further used to identify optimal sites [30]. For instance, the number of HF visits in US emergency departments in 2012 showed that out of 130 million total visits, 1.3 million were for acute HF and 1.04 million led to hospitalization [31]. Site-specific ED volume may be an indicator of the ability of the site to effectively participate in a given trial and may help differentiate whether low enrollment rates at a site are a function of low site performance or inadequate volume of patients with HF.

**Table 3** Problems in site selection, enrollment, and study design with proposed solutions

| Obstacles | Interventions |
|---|---|
| - Non-anonymous reporting in the registry<br>- Cost of pre-trial infrastructure | - Pre-trial registry<br>- Identify sites with patient quality and quantity |
| - Absence of substantial institutional incentives (financial reimbursement, protected time, and recognition) for trial participation<br>- Less clinician-patient interaction, especially at enrollment which is replaced by research coordinators<br>- Inadequate coordination at various levels between departments, investigators, on-site personnel, and administrators<br>- Challenges with efficient enrollment at individual sites<br>- Complex healthcare policies<br>- Conflict of interest policies<br>- Complex protocol procedures | - Aligning financial incentives with trial participation<br>-Steps to encourage and integrate clinical trial participation in academic and healthcare systems<br>- Leveraging emergency department data to identify high-volume sites<br>- Sites with HF clinicians and electronic health records to identify qualifying patients<br>Site-efficiency data from ARO and CRO networks<br>- Sites with integrated healthcare and good coordination between departments<br>- Site verification visits |
| - Growing number of patient comorbidities with aging HF population making it harder to recruit patients that fulfill the trial requirements<br>- Complex and time-consuming consent process for patient enrollment | - Inclusion and exclusion criteria must be closer to the characteristics of real-world patient population<br>- Public awareness about HF—feasibility protocol and questionnaire for site managers<br>- Follow-up visits and investigation schedule that is easier and pragmatic for the patient<br>- Simple and easier consent process |

*ARO* academic research organizations, *CRO* contract research organizations, *HF* heart failure

## Aligning Interests and Incentives

Developing a protocol or questionnaire for the study sites to match the goals and expectations of the study administrators with that of the site managers may also represent a step in improving coordination and detecting trial-level issues early. This may be followed by verification visits of selected sites that may prove to be expensive, but invaluable and cost-effective in the long-term in minimizing errors at later stages.

Current systems, especially in the USA, poorly incentivize trial participation by investigators. Incentives, both for study sites and investigators, have become more relevant as healthcare institutions have linked financial incentives to performance goals in clinical care. Participation by investigators in clinical trials must often be integrated into usual clinical care, which is often challenging and burdensome. Performance of study investigators and coordinators can be improved by linking incentives into their performance metric. The support and resources for these incentives are further diminished as concerns for liability and ethical consequences from funding agencies and regulators come into play, resulting in almost no incentive for the teams involved in clinical trials [6••].

## Study Design

With development of effective therapies, improvements in care of coexisting comorbidities, and increases in the relative prevalence of HF with preserved ejection fraction, patients with HF are expected to be older with greater comorbidity burden. Trial designs, on the other hand, incorporate strict inclusion and exclusion criteria and most require the patients to be on an optimal medical therapy. While this may increase the chances of a positive effect of an investigational therapy, it makes recruitment more difficult and narrows the patient population likely to benefit from the novel therapy. For instance, the eligibility criteria applied to the PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor-Neprilysin Inhibitor] with ACEI [Angiotensin-Converting-Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure [HF]) trial was significantly narrower than the target population with approved use by the US Food and Drug Administration [32]. As such, eligibility criteria in future HF trials should be expanded to be more representative of a general "real-world" HF population, especially in the face of low enrollment patterns [33]. SPIRRIT (Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction) trial (ClinicalTrials.gov Unique Identifier: NCT02901184) is a planned, registry-based randomized clinical trial which aims to test spironolactone in HF with preserved ejection fraction in a broader target population, in light of the uncertain results of TOPCAT [34].

Simplification of the study protocol and consent process is important for the site investigators and patients. Complex consent forms are prohibitive [35], especially in patient populations with low health literacy. Lengthy consent processes may present another barrier for enrollment, especially during time-sensitive periods such as early during hospitalization for HF [36]. Extensive and unnecessary data collection requires more time and increase the cost of trial conduct, while data collection that is restricted to regulatory requirements and pertinent to the immediate clinical question will improve the consumption of site resources [33]. Most large multicenter trials have large committees and there is extensive input from the members which make the protocols more complex. The committees responsible for study design need to be smaller and if needed, the study protocol can be subsequently reviewed by a larger supervising committee [6••].

With growing national focus on reducing hospital length of stay, there is limited research coordination between various departments (for example, emergency and hospital medicine departments), potentially impacting the ability of sites to efficiently enroll patients in a timely manner. In trials of HHF patients, this is especially problematic given focus on short-term surrogate endpoints (largely based on improvements in symptoms), which require timely assessment early during hospitalization [28]. In order to optimize patient enrollment, sufficient administrative staffing should be available during key periods (based on site-specific historical emergency department visit records) including the nights and weekends. Furthermore, study personnel should not only establish contact with patients in emergency departments, but also in short stay and observation units. Outside the USA, most investigators have more time to enroll and evaluate patients early, owing to longer hospital length of stay from 7 to 21 days [37] and a different healthcare system than the USA. It is essential to establish an efficient multidisciplinary structure to identify these key problems and address them in a mechanistic way (Table 3).

## Conclusion

Patients with HF constitute a large population at high risk for morbidity and mortality. The future design of trials in this population requires special consideration by the clinicians, investigators, industry, and regulators. In recent years, the globalization of HF trials and widening disparities between geographical regions, associated with intrinsic heterogeneity and lack of HF site information, have introduced significant variability of the trial population. Marked heterogeneity in the trial sample has posed unique challenges to the efficient development and testing of novel therapies. Hence, it

is imperative to recognize and address these trial-level issues to inform and optimize the design of future global clinical trials in HF.

**Compliance with Ethical Standards**

**Conflict of Interest** Chaudhry MS Sarwar and Muthiah Vaduganathan declare no conflicts of interest.

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**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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