Lessons Learned from Clinical Trials in Acute Heart Failure: Phase 3 Drug Trials

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KEYWORDS

• Acute heart failure • Phase 3 clinical trials • Endpoints
• Efficacy • Safety

Phase 3 clinical trials in acute heart failure (AHF) are conducted to allow safety and efficacy data to be collected for the evaluation of treatment strategies, including drugs, devices, diagnostics, or nonpharmacological interventions. Phase 3 trials occur after there has been satisfactory information gathered on animal studies and early phase studies, such that the safety, pharmacokinetic, and dosing profiles have been adequately ascertained. The phase 3 study is then designed to test the efficacy and safety of the intervention in a larger sample size. There are several important features regarding the conduct of phase 3 clinical trials in AHF. This article describes in detail these important aspects of conducting phase 3 clinical trials in an AHF population.

STUDY DESIGN

In the planning of an AHF trial, one of the most important determinants of the scope of the trial is the question being asked. Stating the question clearly and in advance allows the investigative team to properly design the study. Each clinical trial has a primary question, which should be clearly defined in advance and stated as such in the protocol. Numerous secondary questions are often asked, and these should be put in descending order of importance. Primary and secondary questions should be important and relevant to the field of acute decompensated heart failure. As always, patient safety and well being should be considered in evaluating the importance of the questions asked.

The key to developing the question is to have a clear understanding of the type of intervention, including the dose, frequency, and duration of administration of therapy, whether it is a drug, device, or behavioral intervention. In acute decompensated heart failure trials, aspects such as timing of initiation, duration of the intervention, logistics of blinding, and location of study patients pose particular challenges in the design of phase 3 studies. For example, it is highly unlikely to expect that a therapy could be administered routinely within 1 hour of presentation to the emergency room, given the challenges in ascertaining the diagnosis of the patient, unlike a patient with ST segment elevation myocardial infarction (STEMI) or a patient in cardiogenic shock.

One of the most important aspects of phase 3 studies in AHF is the study population. Defining the population in advance and stating very clearly the inclusion and exclusion criteria are important as one draws conclusions at the end of a trial. This aspect also impacts recruitment. As often seen, the study population is truly a subset of the general population of the disease state being studied. How this differs from registries is important in the generalizability of results. Careful characterization of the study population is essential for the proper interpretation of the trial. In general, subjects who have the potential to benefit from the intervention are the candidates for participation in the study. If the mechanism of action of the intervention is precisely known, then a more homogenous population can be studied. For

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example, patients with acute decompensated heart failure who have a wide QRS interval may be candidates for a randomized controlled study of biventricular pacing versus usual care. However, if the mechanism of action of the intervention is not known or multifactorial in its potential for benefit, a broader, more heterogeneous population may participate in the study. The degree of homogeneity or heterogeneity may evolve over time. As the underlying disease process is better understood, more targeted interventions to subpopulations may be more prudent for determining a greater response.

Additionally, the safety profile is important in determining the patient population of a study. Subjects such as pregnant women or the very elderly (ie, >age 90) may be excluded from studies. However, the broader the population, the more one can generalize the results. Recently, it has been very important to identify and enhance the enrollment of patients of special populations such as the elderly, women, and minorities, and from different geographic regions, enhancing one's ability to draw conclusions in these subgroups.

RANDOMIZATION AND BLINDING

Fundamental to phase 3 clinical trials in AHF is randomization. This ensures that patients are equally likely to be assigned to either the intervention or the control group. The advantages of randomization are multifactorial.

First, it removes potential bias in the allocation of patients to either group. Second, it provides comparable groups in the intervention and control group. Third, it allows to the validity of statistical testing. When randomization is not used, assumptions regarding the comparability of the groups and the types of statistical tests in models must be made, which increase the difficulty of interpretation. Randomization can be done with several methods. Fixed allocated randomization allows an equal allocation of the probability of receiving the intervention or the control, which is not altered as the study is conducted. Some advocate unequal allocation such as 2:1 or 3:2 randomization interventions in the control. Simple randomization is usually conducted by development of a random number generated by algorithm, and allocating patients to 1 treatment group or the other. Block randomization technique is used to avoid large imbalances in the number of patients assigned to a group. Patients have equal probability to treatment assignment, and are allocated in blocks of even size such as 6 or 8. Stratified randomization is another way to prevent imbalance. These variables are factors that correlate with a subject response or outcome in an attempt to balance randomization within each stratum, to prevent an imbalanced response at the end of the trial. There are also methods of adaptive randomization; that is, to adjust the randomization based on information as the trial is ongoing. In general, large phase 3 studies generally use block randomization. Stratified randomization is generally not necessary in trials in which there are over several thousand patients enrolled, because the balance of randomization is usually guaranteed among the important prognostic variables. For smaller studies, randomization could be blocked or stratified based on a few important factors. Adaptive randomization strategies are also used in smaller-sized studies.

In phase 3 AHF trials, blinding is also an important component of the study design. To avoid potential issues of bias during data collection assessments, particularly subjective assessments such as dyspnea or physician global assessment, a double-blind design should be instituted. In studies where such a design is not possible, a single-blind approach should be used with independent core laboratories for primary and secondary endpoints.

SAMPLE SIZE

Sample sizes should have sufficient statistical power to detect differences between groups; therefore, issues regarding sample size calculations are extremely important. One of the most important challenges is the adjustment of sample size to compensate for noncompliance to intervention and low event rates. Patients in the active treatment group who do not comply are often termed dropouts. Similarly, a controlled patient who begins to take active therapy is considered a drop-in. Therefore, attention must be made with estimates of the potential dropout rate. A simple way to estimate this is to multiply the sample size by $(1\text{-}R^2)$. For example, a dropout rate of 25% would increase the sample size by greater than 75%. Sample sizes for testing equivalency of interventions are even more difficult. These often require sample sizes of much greater than those of superiority trials, and can be significantly influenced by drop-in and dropout rates.

CLINICALLY RELEVANT ENDPOINTS IN AHF TRIALS

Response variables are the outcomes being measured during the course of the trial, and define and answer the questions being asked. In general, a single response variable should be identified to