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EDITOR'S PAGE

Politically Correct Heart Failure Research in America to Avoid Geographic Variation

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Conducting research in North America remains a challenge. Recent large-scale clinical trials have continued to show that North America lags behind other regions of the world with regard to the recruitment of patients with heart failure. We face significant barriers and limitations to optimal recruitment. Most of the large phase III programs require global participation to recruit enough patients and have enough clinical events to answer the question at hand. Unfortunately, in 3 recent clinical trials, TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist), TRUE-AHF (Trial of Ularitide Efficacy and Safety in Acute Heart Failure), and GENETIC-AF (A Genotype-Directed Comparative Effectiveness Trial of Bucindolol and Toprol-XL for Prevention of Symptomatic Atrial Fibrillation/Atrial Flutter in Patients With Heart Failure), important geographic variation might have resulted in the attenuation of the discovery of a positive signal (1-3).

To address this, many initiatives have been set forth through academics, patients, government agencies, and multiple stakeholders such as the Heart Failure Collaboratory (4). Despite these efforts, while quality of conduct remains high, recruitment lags behind most other regions of the world, at unacceptable rates. To this end, while we continue to address recruitment in North America, we have to be proactive and screen for geographic variation. Geographic variation now has been seen as an important determinant in several trial outcomes, and it must be identified early and prevented if possible.

Several approaches should be taken into consideration to reduce the problems associated with geographic variation: 1) Steering committees must be attentive to these issues and must work together with clinical trial organizations to collect data regarding the reporting of serious adverse events that need clarification, as well as to collect data on dropouts, lost to follow-up randomization errors, and violations of inclusion and exclusive criteria by region. 2) Steering committees should have access to blinded aggregate event rates by region, in order to understand whether the correct population is being enrolled and whether there is under ascertainment or under-reporting of the clinical trial events. 3) The data safety monitoring board should actively review quality of trial conduct by region. This includes patient characteristics, background therapy, and reporting of adverse events and clinical events. In addition, any trends toward unusual unblinding activities should be identified. 4) Pharmacosurveillance of drug therapy should be considered in drug trials. One can confirm whether there are issues with randomization, adherence, and unexpected interruption by conducting an evaluation of drug levels in the patients enrolled in the trial. By doing this, we can ensure that there is adequate administration of and continued adherence to therapy by region. This should be hardwired into the data safety monitoring board's activities, for it is imperative that all clinical trials report geographic variation of the results.

In this capacity, we can learn whether there are trends, specific reasons, and identifiable ways in which surveillance, adherence, and understanding can be enhanced in our journey to provide the relevant conduct of clinical research that our patients deserve, while invigorating enrollment in North America. Until that time, we have to ensure the very best care and conduct occurs across the world, and therefore, monitoring surveillance of geographic variation is indeed politically correct.

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