Evidence-based medical practice depends on randomized controlled trials. The number, size, and complexity of trials has increased enormously over the past 40 years. We have learnt much about the conduct and analysis of trials but, surprisingly, there has been little focus on the most fundamental component of the clinical trial machine, the investigative site responsible for patient enrollment.1,2 Yet, it is the study site that directly determines many of the metrics of trial quality, including treatment adherence rates and completeness of follow-up. As Greene et al3 also report in this issue of Circulation: Heart Failure, the rate of occurrence of trial efficacy outcomes may also vary by center, as evidenced in their analysis of the ASCEND-HF database (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure). Specifically, the authors found that that there was a relationship between event rates and the number of patients recruited, whereby high volume recruiting centers appeared to have lower rates of death and rehospitalization than centers enrolling fewer patients. However, the full picture is more complicated because patient recruitment is also closely intertwined with geographic region, reflecting the increasing globalization of clinical trials. In turn, there are race and ethnicity differences related to geography, as well as other important considerations, such as background therapy, availability of and access to care, and medical practice patterns, which also vary by country. Some illustrations of these issues in the present trial include the much younger age of patients in high enrolling centers (patients with heart failure outside North America and Western Europe are generally younger) and the much lower use of β-blockers and implanted cardiac devices in these centers, despite a similar proportion of patients with reduced ejection fraction.4–6 Clearly, disentangling all of these factors is extremely complex. Greene et al have attempted to do so using multivariable analysis to adjust for geographic region, as well as additional prognostic variables and background therapy to evaluate the independent role of site enrollment volume. In keeping with another trial in patients hospitalized with acute heart failure, these differences diminished in the adjusted models, especially for longer-term mortality.7 Uniquely, the present report also includes data on dyspnea, although the pattern found is hard to interpret. Specifically, dyspnea persisting at 6 hours was more frequent in larger volume sites, while the opposite was true at 24 hours.

See Article by Greene et al

What are we to make of all this? Were higher volume sites enrolling a more complete and representative cohort of patients or more liberally interpreting the inclusion and exclusion criteria? The latter seems unlikely because it would probably have led to inclusion of a higher proportion of patients with preserved ejection fraction, which was not the case (indeed the opposite was observed). Overall, the adjusted differences in all outcomes examined were small, with only 1% to 2% relative increases or decreases per 10-patient higher enrollment, and probably should not be of great concern. To the contrary and probably of more importance, trial quality metrics, such as rates of withdrawal of consent and loss to follow-up, showed a trend to be higher (worse) at smaller sites. This is consistent with the data from chronic heart failure trials (Figure) but may not have been significant in view of the relatively short-term follow-up in the present trial and because patients were not required to take an investigational product on a daily basis.8 The even bigger question of whether site enrollment volume modifies the effect of the experimental therapy under investigation cannot be answered because neither trial for which we have data on patient recruitment tested a successful treatment.3,4 Although the interpretation of the data provided by Greene et al may be uncertain, these authors are to be applauded in tackling a highly relevant subject that has been overlooked for too long but is of critical importance to the efficient conduct of future clinical trials, especially because these already often enormous human endeavors get bigger and more expensive. It is remarkable how little scientific understanding we have of one of the most fundamental aspects of the trials we undertake, that is, site selection. Better insight into study-site characteristics and performance is long overdue.9–13

Disclosures

None.

References


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Site Selection and Performance in Clinical Trials: The Need for Better Understanding
John J.V. McMurray

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