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Designing better, not just bigger, multicenter critical care trials

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To the editor

Dr. Landoni and colleagues report their assessment of multicenter trials that have reported mortality effects in adult critically ill patients and make suggestions that we respond to as follows (1).

First, they argue that future trials should enroll more patients. Certainly, underpowered trials are too common and problematic (2) and there are indeed merits to large and simple trials. Yet the costs and tradeoffs of pursuing bigger trials in terms of delay in results, expense, and temporal change that can influence results are large. Though not offered as a recommendation, there is also considerable room for innovation in critical care medicine using adaptive trial designs, especially when examining limitedly understood interventions (2, 3). One promising design is a seamless phase II/III trial that begins with several treatment arms and then, based on observed patient outcomes during the trial's progress, algorithmically prunes inferior or harmful arms (e.g., doses of drug) and proceeds directly into phase III with the promising arm(s) retained (3). These adaptive designs can complete years before separate phase II and III trials. Further, they will enroll considerably fewer patients at a lower cost and terminate faster in situations of null or harmful effects.

Second, the authors promote a greater number of participating trial centers (1). While the multicenter design increases the likelihood of attaining adequate sample sizes, the diverse characteristics that vary across ICUs, such as intensivist practice patterns, protocols, or the acumen of trainees and staff can exert a powerful influence on patient outcomes. As the goal is to decrease the mortality of a broadly defined syndrome (e.g., sepsis or ARDS), the resultant patient population in multicenter trials comprises an admixture of heterogeneous patients across a range of acuity treated diversely across centers and providers. Due to such great patient heterogeneity, mortality should be adjusted, at a minimum, for patient acuity and center effects. This is especially important when the contribution of enrolled patients differs across centers, and failure to do so can lead to complex and unpredictable type I or II errors when comparing trial arms (4–6).

Finally, we suggest that some often-missing specific data is needed at the patient and provider levels such as information on patient and physician preferences to use life-sustaining therapy because those preferences can affect time of and rates of death in the critically ill (7). To assume that only an intervention can impact mortality in a trial gives too much credence to the power of randomization. Deeper understanding of all trials is essential to assess any evidence base.

Multicenter trials are paramount to examine the external validity and generalizability of intervention(s). Before making our trials bigger, we argue that there is considerable opportunity to first better leverage novel trial designs, trial data and empirical tools during analysis that could provide increased insight into the observed results while optimizing finite patient, time and financial resources.

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