Future of Intensive Care Research

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Abstract.

In clinical research, randomisation among alternatives is central to progress because associations and inferences from observational studies may not prove causative. Unfortunately, as currently conducted, our large randomised trials often conflict and generally have proven disappointing in the critical care setting (1, 2). The most likely explanations include imprecise definitions, inexact or inappropriate controls, and an inability to control or account for all influential variables, as important synergistic interactions produce emergent phenomena that are not accounted for in the trial design. Inability to recruit sufficient numbers of appropriate candidate patients over a reasonable time drags out the data collection process (often attenuating relevance to current practices) or terminates many such investigative efforts.

One innovative approach to randomized trial design is to depart from rigid one-to-one randomization and into adaptive allocation to the study limbs in accordance with relative response as the study progresses(3). Under this paradigm, if a subgroup starts to do better with one treatment, more future patients are allocated to that limb to confirm or refute that trend and accelerate the pace of the investigation. Frequent looks at the developing data are implicit when taking this approach.

The platform trial, an efficient strategy for simultaneously and sequentially evaluating numerous treatments within the framework of a single study, has been proposed by Berry and colleagues as a tool with which to determine their relative worth among a heterogeneous population(4). This approach recognizes the imprecision of our current definitions and classifications, as it explicitly recognizes that targeted populations and treatment responses may be heterogeneous, even when careful measures are taken to be appropriately selective. Such a strategy departs from that of the traditional trial, which assumes itself to

be testing the efficacy of a single intervention in a generally homogeneous population. A unique aspect of this particular “adaptive” approach is that the platform trial can be carried out over the long-term—even perpetually, so long as there are suitable treatments requiring evaluation(5). The number of treated groups or specific treatments may change over time, with specific individual treatment groups removed for demonstrated efficacy or harm. Such capability departs from our current “fixed randomization” approach in which the entire trial is stopped for success, futility, or harm based on the effects of a single experimental treatment. We must change our clinical trial paradigm so that we recognize current limitations. Should we embrace the principle

that most major public health problems should be the subject of perpetual global adaptive trials(6)?

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