The questionable use of unequal allocation in confirmatory trials

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ABSTRACT

Randomization is the standard means for addressing known and unknown confounders within the patient population in clinical trials. Although random assignment to treatment arms on a 1:1 basis has long been the norm, many 2-armed confirmatory trials now use unequal allocation schemes where the number of patients receiving investigational interventions exceeds those in the comparator arm. In what follows, we offer 3 arguments for why investigators, institutional review boards, and data and safety monitoring boards should exercise caution when planning or reviewing 2-armed confirmatory trials involving unequal allocation ratios. We close by laying out some of the conditions where uneven allocation can be justified ethically.
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Randomization is the standard means for addressing known and unknown confounders within the patient population in clinical trials. Although random assignment to treatment arms on a 1:1 basis (i.e., "equal allocation") has long been the norm, many trials aimed at vindicating treatments ("confirmatory trials") use randomization schemes where the number of patients receiving investigational interventions exceeds those in the comparator arm (i.e., "unequal allocation ratios," such as 2:1). Recent examples include tests of endovascular therapy for treating stroke,[1] rituximab and glatiramer acetate for multiple sclerosis,[2,3] istradefylline for Parkinson disease,[4] and celecoxib for amyotrophic lateral sclerosis.[5]

All major codes of ethics require that human investigations address scientific questions using designs that minimize the total burden for study volunteers. Given this principle, as well as the fact that unequal allocation requires larger sample sizes to achieve the same level of statistical power, one would expect to find compelling arguments justifying the use of unequal allocation ratios. However, published reports rarely provide justification.[6]

What follows mainly concerns the use of uneven allocation in 2-armed confirmatory trials, which we define as trials aimed at demonstrating the clinical utility of a new drug (these are predominantly phase 3–like trials, though phase 2 trials sometimes have a confirmatory orientation but use surrogate endpoints). We offer 3 arguments for why investigators, institutional review boards, and data and safety monitoring boards should exercise caution when planning or reviewing such trials. We close by laying out some of the conditions in which the use of uneven allocation can be justified ethically.

UNDERPOWERED TRIALS AND THERAPEUTIC MISESTIMATION When a justification for unequal allocation in confirmatory trials is provided, investigators often claim it hastens recruitment or mitigates patient withdrawal. The assumption behind this justification is that patients are more likely to join placebo or sham-controlled trials when their odds of receiving active treatment are greater. However, if a confirmatory study is in clinical equipoise, then there are no scientific justifications for believing that patients in the active group will be better off than those in the placebo arm. The very aim of the trial is to make this determination.

Indeed, only a small fraction of new neurology drugs tested in trials prove safe and effective (for the 5 trials using uneven allocation trials mentioned in the introduction, 4 were unable to confirm therapeutic advantage for the

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treatment group). Given that the odds are stacked against medical advantage for patients receiving novel therapy, using unequal allocation to accelerate recruitment has 2 undesirable ethical properties. First, though patient-subjects may be able to appreciate that they are enrolled in trials,[7,8] it leverages what may be unreasonable expectations about therapeutic benefit ("therapeutic misestimation") to the advantage of investigators. Second, it provides no incentive for investigators to work with patients to dispel therapeutic misestimations.

Furthermore, we are unable to identify published findings showing that uneven randomization accelerates recruitment in confirmatory trials. Studies of patients with Alzheimer disease and their caregivers have consistently shown that although allocation to placebo is a concern for prospective subjects, the duration of treatment, travel time, home visits, and stringent inclusion/exclusion criteria are far more significant barriers to recruitment.[9,10] One cost-benefit analysis suggested that the gains in recruitment speed from unequal allocation would need to be substantial (~50%) to offer any operational benefits of reduced cost or faster study completion.[11]

INEFFICIENCY AND THE RESEARCH ENTERPRISE Unequal allocation also has consequences for statistical power. For example, a 2:1 allocation ratio requires 12% more patients than a trial using 1:1 to detect the same size effect with equivalent power; a 3:1 randomization scheme requires 33% more patients.[12] Trials using unequal allocation will therefore either have less statistical power or will be more expensive and entail exposing more patients than necessary to a novel intervention and research procedures. In light of the high failure rate of drugs entering randomized trials, unequal randomization misses an opportunity for investigators to minimize patient burden.

Some commentators downplay the loss of power or increased sample size.[13] However, trials draw on scarce resources—e.g., a limited pool of eligible volunteers, public and private sources, time, as well as the talent and focused attention of clinical investigators. In an era of scarce research budgets—and in the absence of robust evidence showing efficiency gains with unequal allocation—the levy associated with even a 12% increase in sample size could be better spent on pursuing other research avenues.

VALIDITY Finally, investigators should consider whether unequal allocation has implications for the internal validity of trials. Assuming successful masking, a 1:1 allocation ratio has the virtue of producing postrandomization agnosticism about allocation in patients, caregivers, and outcome assessors. A 2:1 ratio, on the other hand, produces a justified postrandomization belief regarding allocation to the investigational treatment.

How this justified belief interacts with treatment observations is not well-understood.[14] However, the express purpose of double-blinding is to mitigate any alterations in patient, caregiver, or assessor behavior due to beliefs about allocation. It is at least plausible that in studies where outcome assessors are not agnostic about allocation, the attention to events—both positive and negative—might be altered. Indeed, there is some evidence that unequal allocation for placebo-responsive conditions like Parkinson disease and depression elevates placebo effects in the comparator arm, dampening the ability of studies to detect clinical response.[15,16]

EXPLORATORY TRIALS, COST, AND SAFETY INFORMATION Nevertheless, unequal allocation can be scientifically advantageous and consistent with ethical study design. First, it may have substantial advantages in early phase trials, where the aim of investigation is to explore treatment dimensions—like dose, schedule, or cointervention—needed to effectuate clinical utility.[17] As numerous commentators have observed, the standard 2-arm, hypothesis-testing trial is not well-suited to exploring and optimizing this combination of variables.[18,19] Insofar as the ratio of total patients receiving an active intervention vs a placebo is not 1:1, such early-phase trial designs utilize unequal allocation ratios. However, such trials often maximize their statistical efficiency by implementing equal allocation across cohorts.

A second circumstance where uneven allocation may be justified is where study treatments are especially costly. However, this justification is rarely relevant for studies involving placebo or sham comparators, since these are almost always less expensive than investigational agents.

The need for additional safety information may also justify unequal allocation. A larger sample size in the active treatment group confers a gain in statistical power for monitoring certain adverse events. Importantly, this is useful only in cases for toxicities where causal relationships can be assigned in the absence of a comparator. This might be the case where anticipated safety signals are easily attributable to the intervention (i.e., immediate or signature events).

This justification can also be compelling where there are grounds for believing that—even in the absence of efficacy—safety information about an intervention is vital. For example, when evaluating novel therapeutic platforms that are likely to be varied in subsequent investigations, additional safety information from early studies may be valuable to collect. However, in such circumstances, investigators must design and report studies in ways that enable

interpretation and aggregation of safety information. Moreover, the strength of this justification diminishes as the research community acquires greater experience with a given intervention platform.

DISCUSSION As with any decisions in clinical trial design, ethical considerations intertwine with good scientific and operational judgments. Investigators often justify the use of unequal allocation in 2-armed confirmatory trials by appealing to patient demand or recruitment facility. These are neither scientifically nor ethically compelling justifications. Equal allocation is the most efficient approach: it offers the best risk-benefit ratio for subjects, it incentivizes conscientious informed consent discussions, and it minimizes certain threats to internal validity. When proposing or reviewing confirmatory trials involving unequal allocation ratios, investigators, sponsors, and institutional review boards should provide scientific and ethical arguments that overcome the disadvantages associated with the practice.

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