

## Event

In a traditional, two-armed randomized controlled-trial (RCT), patients are equally likely to be assigned to the experimental or the control treatment arm. Recently, trials have begun employing outcome-adaptive randomization (OAR)<sup>1</sup>, an approach that dynamically adjusts treatment assignment as the a study progresses. As interim data becomes available over the course of a study, OAR increases the likelihood that a patient will be assigned to the 'better performing' treatment arm. Proponents of this design argue that it is more ethical than the traditional RCT. However, closer analysis suggests otherwise<sup>2</sup>.

## Significance

Advocates of OAR argue that it is more ethical than the traditional RCT because it limits patient-participant exposure to what is assumed to be sub-optimal care in the 'poorer performing' treatment arm. This claim has been widely accepted and assumed sufficient for incorporating OAR, particularly in the realm of biomarker diagnostic development<sup>3</sup>. However, in practice OAR promotes (rather than dispels) longstanding research ethics concerns regarding participants' therapeutic misconceptions. It may also threaten the internal validity of clinical trials, thus increasing the overall societal cost of research.

## Analysis

An ethical trial demands a state of clinical equipoise—that is, there must exist genuine uncertainty in the clinical community as to the relative therapeutic merit across all arms of a trial. Thus, insofar as every intervention arm in a trial is consistent with competent medical care, the physician's duty of care and the researcher's scientific goals are consistent<sup>4</sup>. Nevertheless, many patients enter trials erroneously believing they will be allocated to the most favourable treatment arm. While OAR does indeed weight treatment assignment in favour of the better performing intervention, it does not resolve such therapeutic misconceptions. Instead, it simply concentrates such misunderstanding to patients in the flagging treatment arm, and further blurs the research-treatment distinction by asking researchers to address the purview of care systems.

Moreover, it is only at the final stages of clinical testing that an experimental intervention can be considered a rival for the standard of care. Therefore, the use of OAR designs in the earlier phases of testing cannot be assumed to minimize patient research burden. Given that the vast majority of experimental interventions do not prove to be clinically useful, the 'better performing' arm in an early-phase OAR study is actually more likely to be inferior to the standard of care.

Further, even during the final stages of testing, OAR remains ethically problematic. Since patient-participant assignment likelihoods are adjusted over time, OAR introduces a systematic disadvantage for those enrolling earlier in the study. This systematic difference between early and late-enrolling populations represents an injustice for patient-participants. Furthermore, it increases the risk of biased effect estimates, threatening the scientific validity of the study as a whole and its capacity to deliver evidence that will support clinical decision-making<sup>2</sup>.

## Conclusion

Clinical translation is an expensive and time-consuming process, fraught with risk and failure. Innovations in study design are therefore an attractive prospect. OAR represents the cutting edge in study design. Unfortunately, its purported ethical advantages over the traditional RCT do not stand up to scrutiny.

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