Different meanings of equipoise and the four quadrants of uncertainty

The widely cited principle of ''equipoise'' generally asserts that a randomized clinical trial (RCT) is ethically justified only if there is uncertainty around the interventions being tested [1], although many kinds and quantities of uncertainty would appear to be considered acceptable [2]. This imprecision has the potential to create an important ethical dilemma: if ''equipoise'' can refer to any of several forms of uncertainty, then researchers may be free to pick the version of ''equipoise'' they prefer, and with it, the ethical standards that govern their RCTs. This would be a clear conflict of interest.

Therefore, we sought to test whether different meanings of ''equipoise'' could be observed in the real world. We asked 15 clinician-researchers, 15 institutional review board chairs, and 15 bioethicists/philosophers of medicine to define ''equipoise.'' They offered 7 different definitions, and 2 respondents could not define ''equipoise'' at all. The most frequently provided definition related ''equipoise'' to uncertainty at the level of a community of physicians, although this definition was offered by fewer than one-third of respondents. Multiple definitions were offered within each group, and there was no consensus about how much uncertainty was required to justify an RCT or how this should be demonstrated.

These results support our concerns about ''equipoise,'' and have led us to consider how the uncertainty used to justify RCTs could be standardized. We propose an approach based on four quadrants of RCTs—α, β, γ, δ—each of which would have its own logically distinct standard of uncertainty (Fig. 1). In α quadrant RCTs, two approved treatments are compared for relative efficacy. The relevant evidence base will be large and clinician experience, significant; as such, the uncertainty necessary to justify an RCT could be demonstrated through a systematic review or by gathering physician opinion. In a β quadrant trial, a novel treatment is tested against standard of care; there will be little relevant evidence and thus clinicians will have no scientific basis for a preference, suggesting that different methods for demonstrating uncertainty will be necessary. In a γ quadrant trial, a novel treatment is compared with a placebo where no effective treatment exists for that condition. In this case, the uncertainty required to conduct a trial would be more closely tied to the seriousness of the condition and the potential risks of the treatment. Trials in the δ quadrant test a standard of care that has developed without good evidence. In these cases, the uncertainty threshold should be high (but not insurmountable), and should relate to available evidence rather than to the opinion of physicians who will likely strongly support the *status quo*.

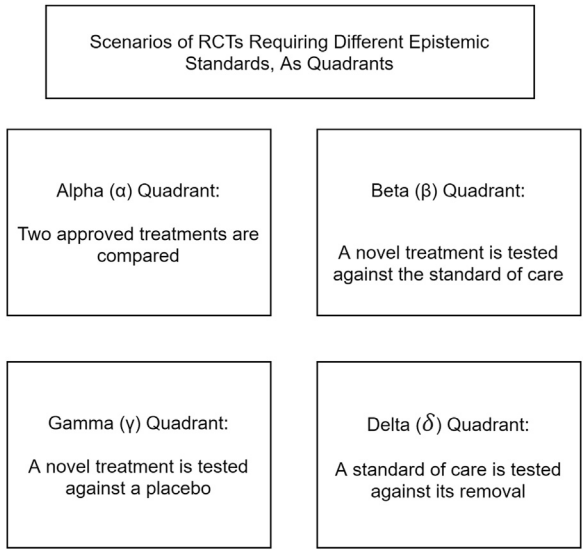

Fig. 1. The quadrants of uncertainty. RCT, randomized clinical trial.

These examples show how the available evidence and structure of an RCT can be used to formulate different standards of RCT-justifying uncertainty, or what has come to be called ''equipoise.'' Using the four quadrants to better locate what we mean when we say ''equipoise'' may be a helpful step toward standardizing the ethical justification of RCTs and preventing opportunities for conflicts of interest arising from references to ''equipoise''.

CRediT authorship contribution statement

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