Equipoise, design bias, and randomized controlled trials: the elusive ethics of new drug development

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Abstract

The concept of 'equipoise', or the 'uncertainty principle', has been represented as a central ethical principle, and holds that a subject may be enrolled in a randomized controlled trial (RCT) only if there is true uncertainty about which of the trial arms is most likely to benefit the patient. We sought to estimate the frequency with which equipoise conditions were met in industry-sponsored RCTs in rheumatology, to explore the reasons for any deviations from equipoise, to examine the concept of 'design bias', and to consider alternative ethical formulations that might improve subject safety and autonomy. We studied abstracts accepted for the 2001 American College of Rheumatology meetings that reported RCTs, acknowledged industry sponsorship, and had clinical end-points ($n = 45$), and examined the proportion of studies that favored the registration or marketing of the sponsor's drug. In every trial (45/45) results were favorable to the sponsor, indicating that results could have been predicted in advance solely by knowledge of sponsorship ($P < 0.0001$). Equipoise clearly was being systematically violated. Publication bias appeared to be an incomplete explanation for this dramatic result; this bias occurs after a study is completed. Rather, we hypothesize that 'design bias', in which extensive preliminary data are used to design studies with a high likelihood of being positive, is the major cause of the asymmetric results. Design 'bias' occurs before the trial is begun and is inconsistent with the equipoise principle. However, design bias increases scientific efficiency, decreases drug development costs, and limits the number of subjects required, probably reducing aggregate risks to participants. Conceptual and ethical issues were found with the equipoise principle, which encourages performance of negative studies; ignores patient values, patient autonomy, and social benefits; is applied at a conceptually inappropriate decision point (after randomization rather than before); and is in conflict with the Belmont, Nuremberg, and other sets of ethical principles, as well as with US Food and Drug Administration procedures. We propose a principle of 'positive expected outcomes', which informs the assessment that a trial is ethical, together with a restatement of the priority of personal autonomy.