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HEAD TO HEAD

Is the concept of clinical equipoise still relevant to research?

Spencer Hey, **Alex John London**, and **Charles Weijer** argue that there is no better framework for justifying patient participation in research. But **Annette Rid** and **Franklin Miller** say that it is a mistake to require clinical research ethics to align with the norms of clinical practice

Spencer Phillips Hey *faculty member*[1 2], Alex John London *Clara L West professor of ethics and philosophy*[3], Charles Weijer *Canada Research chair in bioethics*[4], Annette Rid *reader in bioethics and society*[5], Franklin Miller *professor of medical ethics in medicine*[6]

[1]Harvard Center for Bioethics, Boston, MA, USA; [2]Program on Regulation, Therapeutics, and Law, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [3]Center for Ethics and Policy, Carnegie Mellon University, Pittsburgh, PA, USA; [4]Departments of Philosophy and Medicine, University of Western Ontario, London, ON, Canada; [5]Department of Global Health and Social Medicine, King's College London, London, UK; [6]Medical Ethics in Medicine, Weill Cornell Medical College, New York, USA

Yes—Spencer Phillips Hey, Alex John London, Charles Weijer

Whether they are in their doctor's clinic or participating in a randomised controlled trial, patients have an interest in receiving competent medical care. Doctors also have a duty to provide patients with care consistent with professional standards. However, in a randomised trial a patient's interests and the doctor's duty seem to conflict with the scientific goals of the trial. How can it be in the patient's interest to leave the choice of therapy to chance? How can randomisation comport with the physician's duty of care?

Clinical equipoise was first proposed as a solution to the problem of randomisation 30 years ago. It is defined as a state of disagreement or uncertainty in the informed, expert medical community about the relative clinical merits of the intervention arms in a trial.[1] This state of equipoise may mean that there is insufficient evidence to warrant a judgment that one intervention in the trial is inferior to the others. It may also mean that some experts favour one intervention over the others, but different experts prefer different interventions for the same patients.[2] However, so long as one or both of these conditions apply to a trial, each of its arms is broadly consistent with competent medical care. This means that a patient can enrol in the trial without having to worry about being disadvantaged and a physician can refer patients without violating the duty of care.[3]

Scientific and social value

But equipoise does more than simply solve the problem of randomisation. It can also help to ensure that human and material resources are not wasted on low value trials. Indeed, if there is no uncertainty or disagreement in the expert community about which arm of a trial is superior, the scientific and social value of the study is questionable.[4] For example, Fergusson and colleagues conducted a systematic review and cumulative meta-analysis for trials that evaluated the serine protease inhibitor aprotinin to reduce perioperative bleeding and reduce the need for blood transfusion. They found 64 trials in total, but showed that the effect estimate for aprotinin had stabilised after 12 trials. Thus, they argued that clinical equipoise could have prevented the remaining 52 studies, which exposed thousands of patients to inferior care for little scientific gain.[5]

Before studies can recruit participants, research ethics committees must determine whether risks to participants have been minimised and the remaining risks are reasonable in light of either the prospect for participant benefit or the importance of the research. Equipoise clarifies each of these concerns. In this way, it helps to promote public trust in the research enterprise. For example, even when trials are not run by clinicians (as in public health) or patients find trials on their own initiative, equipoise ensures that they can participate without having to worry that their interests are being sacrificed at the altar of science.[3 4]

Ethical justification for trials

Equipoise does constrain medical research, since not all scientifically interesting questions will satisfy its requirements. But it is not as restrictive as some have assumed. Placebo controlled trials, for example, are consistent with equipoise when there is no standard treatment for the condition or if the

Correspondence to: S P Hey shey@bwh.harvard.edu, A Rid annette.rid@kcl.ac.uk

evidence supporting standard treatments is in doubt. Similarly, for sham surgery trials, if the existing evidence for the current procedure is weak or new evidence has called its efficacy or safety into question, equipoise not only permits a randomised trial, it explains why that trial is ethically justified.[6]

We acknowledge that equipoise is subject to ambiguity and limitations because it can be challenging to assess the state of uncertainty and balance of risks of benefits in a trial. However, other ethical frameworks that dispense with equipoise, such as the non-exploitation[7] or net risk[8] frameworks face similar challenges and offer none of equipoise's clarity. For example, they do not explain how a trial can be consistent with the duties of physicians or prevent patients in trials from being systematically and avoidably disadvantaged through withholding or withdrawing effective medical interventions in a way that is not necessary for scientific advance. These alternative approaches thus demand greater altruism from patients than clinical equipoise and compromise to the duties of care givers without clear, offsetting benefits. To modify a famous phrase: equipoise may be the worst ethical principle governing randomised trials, except for the alternatives.

No—Annette Rid and Franklin Miller

Clinical equipoise—defined as the "honest, professional disagreement among expert clinicians" about which treatment best promotes patients' clinical interests—is generally seen as "an ethically necessary condition for all cases of clinical research."[1] However, the equipoise requirement was a mistake when it was first introduced 30 years ago and remains a mistake in today's research environment.

Wrong ethical foundation

The equipoise requirement rests on the wrong ethical foundation. It was primarily introduced in response to the question: when can clinicians conduct controlled clinical trials without violating their "obligation to provide … the best medical treatment"?[1] The main concern was that participants in the control arm might receive substandard care—including no treatment or a placebo control—for scientific purposes. The equipoise requirement ensures that trials are conducted only when expert clinicians disagree about the relative merits of standard care and the investigational or control treatment, meaning that all treatments in a trial are consistent with competent clinical care.

Yet conducting clinical trials is ethically different from providing clinical care. Clinicians are obligated to treat patients in their best clinical interests. By contrast, clinical investigators may perform procedures that do not promote participants' clinical interests if this is necessary for generating clinically valuable knowledge. This fundamental difference shows that the equipoise requirement is a misguided attempt to align clinical research with the norms of clinical practice.[9]

Alternative approaches to equipoise attempt to escape this objection. For example, the equipoise requirement has been reframed as a way for the state to protect the interests of research participants,[10] or as a way of showing equal regard for the basic interests of all members of society—those who are participating in research as well as those who are intended to benefit from it.[11] However, just like the clinical approach,[1] these alternative approaches do not escape a major inconsistency in equipoise based ethical frameworks for clinical research.[12] Many clinical trials include procedures with some level of "net risk" to participants, meaning that the procedures are done purely for research purposes and hence do not promote participants' best clinical interests. Equipoise proponents justify them by virtue of being necessary to conduct a scientifically valuable study.[10 11] Yet they preclude the provision of substandard care for the same reason. For example, in a trial evaluating drug eluting stents to treat angina,[13] proponents of equipoise would not object to using follow-up cardiac catheterisation if this is necessary to measure restenosis rates—although this research catheterisation would not be clinically indicated. By contrast, in a trial evaluating a novel drug to treat angina, they would object to the methodologically justified use of a placebo control because it would not be consistent with providing competent clinical care to participants during the trial.[14]

Why should it matter whether investigators set back participants' clinical interests by withholding competent care or performing a research cardiac catheterisation, as long as the associated risks are acceptable? None of the existing ethical justifications for the equipoise requirement[1-11] provide an adequate answer.

Unnecessary and problematic

The equipoise requirement is also unnecessary for ensuring ethical research. There are well established frameworks for acceptable research risks that do not require equipoise. For example, the net risks framework demands that researchers ensure the given trial's social value; reasonably reduce risks to participants; ensure that the risks to participants are justified by potential clinical benefits for them or by the social value of the research; and respect absolute upper risk limits to participants.[8-15]

Finally, the equipoise requirement has negative consequences. It can prevent valuable and acceptable trials from being conducted, such as placebo-controlled trials of conditions with high rates of placebo response, where short term withholding of competent care does not pose undue risks.[16] Additionally, some trials are stopped early because equipoise has been disturbed, even when continuing the trial would be valuable for obtaining definitive results and other frameworks suggest that the risks to participants are acceptable.[7-15]

Of course, if investigators can conduct valuable trials without setting back participants' clinical interests, they should do so. But requiring equipoise is a mistake today as much as it was 30 years ago.

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