Reviewer's report

Title: Does Clinical Equipoise Apply to Cluster Randomized Trials?

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Reviewer: Benjamin Djulbegovic

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Does Clinical Equipoise Apply to Cluster Randomized Trials?
by Ariella Binik et al

General Comments

This is a well done paper by leaders in the field whose writings has also influenced my own thinking about ethics and science of clinical research. While I personally believe that equipoise is one of the most important concepts ever devised in the history of clinical research ethics-and, while in general agree with the authors that clinical equipoise is applicable to cluster randomized trials (CTR)- my own reasoning is somewhat different. The authors are at liberty to use or disregard it (see below) [if interested in details of my reasoning, please see: Djulbegovic B. Articulating and responding to uncertainties in clinical research. J Med Philosophy 2007;32:79-98, Djulbegovic B. Uncertainty and equipoise: at interplay between epistemology, decision-making and ethics. Am J Med Sc (in press)]

Several years ago I made the point that the key in these kind of debates is to start by acknowledging the important but a noncontroversial issue: the general requirement that trial should be undertaken only if there is existing uncertainty (about effects of competing treatment interventions, for example) has been pretty much universally accepted and has never been challenged by ethicists. The ethical dilemma arises from the question: “whose uncertainty is more morally relevant?” – the uncertainty of individual physicians (known as “theoretical equipoise”), patients (“indifference”), the treating physician and his patient (“uncertainty principle”), the community of expert practitioners, i.e. trialists (“clinical equipoise”), or the community of patients, advocacy groups, and lay people (“community equipoise”).

Hence, I disagree with the discussion implying that uncertainty is irrelevant in individually RCTs. (In fact, my main critique of the paper is that it does not clearly state that clinical equipoise also reflects underlying uncertainty- at the level of community of experts, however we define “the community”).

There is no doubt that trust is the key foundation of human experimentation. However, the paper implies, but never clearly explains, that investigators honor the trust only if they adhere to clinical equipoise but abuse the trust if they act according to individual beliefs (even if that mean acting honestly in patients’ best interests?) Clinical equipoise indeed provides resolution of an ethical dilemma for
individual practitioners who found themselves at the discrepancy between their individual beliefs and those of the group—under these circumstances “joining the crowd” may alleviate burden of personal decision-making. But, what if the individual investigators believe that his action is in the patient’s best interest even if it contradicts with the professional consensus? The authors have really not persuaded me that such individuals are morally obliged to adhere to clinical equipoise while violating their own individual equipoise. In the same vein, the trust is profoundly more felt at the individual rather than group (“state”) level, and I don’t see how violating individual while sticking with clinical equipoise promotes trust between researchers and participants?

However, I agree that clinical equipoise applies to CRT but for different reasons. The uncertainty level expressed as “indifference” or “uncertainty principle” affects patients’ willingness to enroll in trials, “community equipoise” influences a research agenda, but from the perspective of trial development to it is actually clinical equipoise that affects design of the trial. If there is no professional disagreement (uncertainties) about the effects of competing treatment interventions, it would be impossible to design the trial (including writing the protocol, obtaining funding etc). Without clinical equipoise the trial simply cannot go forward. Hence, clinical equipoise applies because a) articulates underlying uncertainty that need to be addressed in CRT, b) represents the only known mechanism that allows design and conduct of CRTs (if the latter are considered important public good).

However, there is one problem with clinical equipoise as it applies to CRT: reliability of results. Unlike in individual RCTs, if physicians/patients are not uncertain and do not want to be randomized, internal validity of trial is not affected since equipoise (or, uncertainty principle) relates to a pre-randomization phase of trial (i.e. the post-randomization phase of the trial is not affected). However, in CRTs, individual physician may choose to do completely opposite from what his/her group was randomized to. This may lead to contamination and hence affect internal validity of trial. This needs to be discussed.

Additional remark

Although I am personally a proponent of (clinical) equipoise, some very influential authors are not and call for its abandonment. However, the paper gives an impression that (clinical) equipoise is universally accepted moral requirement for clinical trials. In the interest of a fair and balanced exposure, please discuss briefly the critiques of equipoise (see, for example, Miller FG, Brody H. A critique of clinical equipoise. Therapeutic misconception in the ethics of clinical trials. The Hastings Center report 2003;33:19-28.)

Hope this helps.

Ben Djulbegovic

**Level of interest:** An article of importance in its field
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: None