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Debate

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Choosing a control intervention for a randomised clinical trial

Howard Mann*[1] and Benjamin Djulbegovic[2]

Address: [1]Department of Radiology 1A71 University Hospital 50 North Medical Drive Salt Lake City UT 84132 and [2]H. Lee Moffitt Cancer Center & Research Institute University of South Florida Department of Interdisciplinary Oncology 12902 Magnolia Drive Tampa FL 33612

Email: Howard Mann* - howard.mann@hsc.utah.edu; Benjamin Djulbegovic - djulbebm@moffitt.usf.edu

* Corresponding author

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Abstract

Background: Randomised controlled clinical trials are performed to resolve uncertainty concerning comparator interventions. Appropriate acknowledgment of uncertainty enables the concurrent achievement of two goals : the acquisition of valuable scientific knowledge and an optimum treatment choice for the patient-participant. The ethical recruitment of patients requires the presence of clinical equipoise. This involves the appropriate choice of a control intervention, particularly when unapproved drugs or innovative interventions are being evaluated.

Discussion: We argue that the choice of a control intervention should be supported by a systematic review of the relevant literature and, where necessary, solicitation of the informed beliefs of clinical experts through formal surveys and publication of the proposed trial's protocol.

Summary: When clinical equipoise is present, physicians may confidently propose trial enrollment to their eligible patients as an act of therapeutic beneficence.

Background

Randomised clinical trials (RCTs) are performed to resolve uncertainty concerning the relative efficacy of comparator interventions. They are conducted as "pivotal" trials in support of an application for marketing of an investigational agent, to evaluate the relative effectiveness of a novel treatment strategy, or the relative merits of commonly used interventions. Each year, thousands of human participants are recruited for RCTs in the context of established patient-physician relationships, in which patients seek medical care and physicians are bound by a duty of therapeutic beneficence. How is the latter to be reconciled with the need to recruit patients for trials?

Uncertainty in RCTs may be considered at three levels : the community of "expert" practitioners and trialists, who propose a trial for its resolution; the individual practitioner, who has to decide whether to participate in a trial, and whether to offer enrolment to particular patients; and the patient, who has to decide whether to accept an offer of enrolment [1] The concept of *clinical equipoise* [2] denotes the level of community uncertainty, and has been proposed as a moral requirement for the recruitment of patients.[3] The presence or absence of community uncertainty is thus of particular interest to research ethics committees which must approve the conduct of clinical trials. If one of the interventions in a proposed trial is known to be superior, considering both effectiveness and adverse effects, a proposed RCT cannot be justified. The appropriate acknowledgment of uncertainty enables the concurrent achievement of two objectives : the acquisition of valuable scientific knowledge (the trialist's primary goal), and the best *treatment* choice (the patient's primary goal) under conditions of uncertainty.[4]

If a trial is to evaluate an unapproved drug or biological agent (available only in the context of a trial), or novel intervention, positive evidence of efficacy and safety from preliminary non-clinical and clinical testing must be sufficient to support the conduct of a RCT. If so, then from the point of view of trial design the ethical requirement of clinical equipoise is expressed as an appropriate choice of a control intervention. Appraisal of this choice should explicitly be made by research ethics committees.

In proposing the imperative of clinical equipoise for the conduct of a RCT, Freedman [2] also emphasized the need for designing and conducting the trial in a manner that ensures that equipoise will be disturbed if one of the comparator interventions is indeed superior. Thus, the trial must meet the requirement of scientific (internal and external) validity.[5] With respect to scientific validity, there is substantial guidance for the trialist, including the CONSORT statement [6] applicable to the reporting of RCTs. The CONSORT statement's checklist of items comprehensively addresses the notion of internal validity (avoidance of bias in the form of systematic error). However, a trial may be judged methodologically valid, but may not address uncertainty of clinical relevance to the patients being recruited, or, by extension, the health of future patients, similarly situated [7] The choice of a control intervention is a critical design feature in a RCT – factors that should inform the appropriate choice of a control intervention are summarized in panel 1. The first factor – existent knowledge concerning the relative efficacy of the proposed experimental and control interventions – is a principal focus of the ensuing discussion.

Panel 1: Factors that determine the proper choice of a control intervention for a trial

- Existent knowledge concerning the relative efficacy of the proposed experimental and control interventions
- The dose (for drugs) and mechanism of control intervention application
- Appreciation of the range of interventions available for the condition being evaluated (drug versus non-drug therapies)
- Current medical practice in the setting in which the trial is conducted

Discussion

In a scheme for the ethical analysis of risk of harm in a proposed randomized controlled trial by research ethics committees, Weijer [8] describes three determinations necessary to consider a trial approvable: therapeutic research components must be justified by the direct prospect of health-related benefits (a harm-benefit calculus); non-therapeutic research components must be justified by the prospect of acquiring valuable knowledge (a harm-knowledge calculus); and clinical equipoise must be present. With respect to the latter, Weijer describes how a research ethics committee may, in selected cases, "require a search of the medical literature or consultation with relevant experts who have no connection with the study or its sponsor."

Clinical equipoise may be considered a state of *reasoned* epistemic uncertainty in the clinical community concerning a body of factual evidence about treatment effects – a claim susceptible to critical appraisal. Our core argument is that the choice of a control intervention should be supported by the application of one or more of the activities in panel 2. The methods used to choose a control intervention should be included in the published report of a trial's results.

Panel 2: Justifying the choice of a control intervention for a trial

- Systematic review of the relevant literature
- Cumulative meta-analysis of completed trials
- Formal survey of expert clinical practitioners
- Publication of the trial's protocol to solicit critical appraisal

Systematic review of the literature

The conduct of clinical research should be informed by existent knowledge. This will ensure that certain requirements for the ethical conduct of clinical research are met : social and scientific value, a favorable harm-benefit ratio, and respect for potential or enrolled participants [5]. With respect to clinical trials, Herxheimer [9] cogently expressed this need as follows: "...a proposal for a trial should be accompanied by a thorough review of all previous trials that have examined the same and closely related questions. Only in the light of such a review can a sound opinion be given on whether the proposal is ethical." Reliance on the opinions of one or two "experts" only – a common strategy in research ethics committee deliberations – to assess whether clinical equipoise is present is unsatisfactory. Previous work has shown dissonance between the opinions of experts and the state of existent knowledge as revealed by a systematic review or meta-analysis of the relevant literature.[10] The factors in Panel 1 applicable to the proposed trial should be addressed in relation to a systematic review.

The systematic review should be conducted, reported and submitted to research ethics committees by a principal trialist(s) in accordance with well established procedures [11], or a claim of clinical equipoise may be supported by reference to an up-to-date systematic review(s) published in the peer-reviewed literature, or produced under the aegis of organizations like the Cochrane Collaboration.

Members of research ethics committees need to understand the essential components of a systematic review (an appropriate literature search strategy in particular), and be able to assess the general quality of a review submitted in support of a trial. Committee members with special expertise in the medical area under investigation should confirm the adequacy of the systematic review in light of their personal knowledge.

We anticipate an argument that the requirement for an up-to-date systematic review is unjustifiably stringent – too demanding of investigators' time, may necessitate additional financial resources, and will delay the completion of important trials. These are relevant concerns, but we do not find them persuasive. Any delay in initiating a clinical trial will be offset by greater confidence in the value and relevance of the research. More investigators and ethics committee members will acquire valuable skills relative to the conduct and appraisal of research synthesis. The consequences of a limited or selective review of the published literature may be severe as indicated by the tragic death of a research volunteer in research involving hexamethonium. A systematic literature search using explicit methods would have uncovered 16 relevant papers concerning pulmonary complications associated with its use.[12] Evidence from recently completed trials (controlled and uncontrolled) may either disturb existent community equipoise, or may further support a state of community equipoise, justifying the conduct of a RCT. Finally, as Chalmers has described, an up-to-date systematic review will also be of substantial value in two other important ways: to enhance interim results monitoring of an ongoing trial, and to facilitate the informative reporting of a trial's results in relation to existent knowledge.[13]

Cumulative meta-analysis of completed trials

The state of knowledge concerning treatment effects changes as evidence is cumulated and synthesized. Uncertainty exits in degrees along a continuum – evidence supportive of a treatment option may vary between "tentative or preliminary" and "robust or convincing." This notion is particularly relevant when the place of new interventions is being considered.

The statistical technique of cumulative meta-analysis is applicable to the assessment of treatment effects as they are revealed by the outcomes of successively completed clinical trials. It may be considered the product of performing a new meta-analysis every time a new trial is added to a series of trials.[14] The use of this technique is illustrated in an analysis of trials evaluating streptokinase in myocardial infarction.[15] Lau and colleagues found 33 relevant trials, and concluded that uncertainty about its efficacy had been resolved after the completion of 15 trials, and long before its ultimate approval by the U.S. Food and Drug Administration. Half of the 32,660 participants in the 18 succeeding trials were randomized to a no-treatment or placebo arm, and the authors made the salient observation that "Against the need for replication to learn more about subgroups [from large trials] must be weighed the propriety of assigning patients to a control group instead of giving them a treatment shown to be effective by the meta-analysis of a number of small trials."

More recently, Clark and colleagues performed a cumulative meta-analysis of placebo-controlled trials evaluating the efficacy of erythropoietin in cancer-related anemia.[16] They concluded that uncertainty about its efficacy could conservatively have been considered resolved after the results of 6 of the19 trials found had been reported.

Investigators and research ethics committees need to be aware of situations when a cumulative meta-analysis should be done in support of a proposal to conduct a RCT. This necessitates a preliminary systematic search for published and unpublished results of completed trials, the methods and results of which should be submitted for committee review.

Formal survey of clinical practitioners

Trialists may need to evaluate novel interventions in areas of clinical care in which there are no or only a few completed trials to guide the design and conduct of a proposed RCT. Because a RCT is performed to address uncertainty about comparator interventions, the choice of control intervention should adequately reflect, to the extent possible, "current standard medical practice." We show the difficulty of defining the latter in certain circumstances with an example.

The ARDS Clinical Network performed a multi-centre clinical trial between 1996 and 1999 evaluating two tidal-volume strategies (6 ml/kg versus 12 ml/kg) in patients with ARDS. [17]The trial result published in 2000 provided evidence in support of the relative superiority of the lower tidal-volume strategy. This trial has informed subsequent clinical practice. Concerns about the choice of the control intervention have been raised, most recently by Eichacker and colleagues [18], who argue that the 12 ml/kg tidal volume strategy was inappropriately high, and did not reflect "current clinical practice" at the time the trial was conducted. It is not our purpose here to evaluate the relative merits of the opposing arguments.()[18,19], but note that both parties refer, in part, to a practice survey conducted in 1992, and published in 1996 [20], in support of their respective positions. The survey solicited opinions regarding several factors important in the diagnosis and treatment of ARDS, including the application of

ventilator therapy. Although the survey was not conducted in support of the ARDS trial, and is not cited in the trial's protocol [21], it revealed a division of opinion in the expert clinical community concerning the choice of tidal volumes: 45% and 48% of respondents thought tidal volumes of 5–9 ml/kg and 10–13 ml/kg, respectively, most appropriate in patients with ARDS.

A survey conducted expressly to evaluate practitioners' beliefs concerning a set of clinical questions may support a claim of clinical equipoise for a particular trial. For example, a survey was conducted, *and reported* [22], in support of a proposed trial comparing early and delayed delivery of preterm fetuses. The results revealed that the respondents did not agree about the benefit of delivery for preterm infants that were failing to thrive. The formal measurement of clinical belief revealed collective uncertainty, providing impetus and justification for a related RCT. Responses by practitioners to survey questions may also represent statements of prior beliefs concerning treatment effects, used expressly when Bayesian methods are used for interim results monitoring and final analysis of outcome measures.[23] Parmar and colleagues reported the monitoring of two RCTs (lung, and head and neck cancer) by Bayesian methods after establishing "sceptical" and "enthusiastic" prior distributions through a survey of participating physicians.[24]

A formal survey of relevant experts is also consistent with the views of potential trial participants on the implication of expert opinion on their decisions to enroll in a trial. A study conducted by Johnson et al. [25] showed that half the respondents perceived a trial as unethical when clinician equipoise was disturbed beyond 70:30, and less than 3 percent would consider trials morally justifiable when clinician equipoise is disturbed beyond 80:20.

We propose that, in the appropriate clinical circumstances, trialists should adopt a low threshold for conducting a formal survey in support of a RCT, and present the results to research ethics committees and prospective participants. The survey should be conducted as close to the anticipated start of the trial as feasible to ensure that the assessment of clinical equipoise is informed by the current practice of relevant practitioners.

Publication of the proposed trial's protocol

Trialists should strongly consider soliciting critical appraisal of a proposed RCT by publishing the trial protocol before it is finalized, and prior to its submission to research ethics committees for review. Godlee [26] has summarized reasons to publish protocols : readers may submit critical comments leading to improvements in trial design; publication should be coupled with trial registration; readers may compare what was declared in the protocol with what was subsequently done; and investigators will more easily appreciate what research is being conducted in their areas of interest. The first of these is particularly relevant to this discussion – trialists should devote a section of the protocol to the rationale for the choice of experimental and control interventions.

An argument will be made that trialists or sponsors will generally be unwilling to publish their protocols because of perceived adverse academic, proprietary or commercial implications. But this argument places the interests of trialists and sponsors ahead of those of potential participants and the public's health, without justification. As one of us (HM) has proposed [27], research ethics committees should make research approval contingent on trial registration, and the latter should provide summary details of the trial's objectives, comparator interventions and design, sufficient to permit a preliminary judgment concerning clinical equipoise.

Concluding comments

RCTs should produce results that resolve or diminish uncertainty concerning the relative merits of comparator interventions. Randomization of patients among comparator interventions should promote patient-participants' interests in securing the best treatment under conditions of epistemic uncertainty. Assurance of clinical equipoise and the proper choice of a control intervention is critical to these ends. If evidence were to emerge that results of RCTs consistently and significantly favor experimental over control interventions, *in aggregate*, this form of biomedical research would be jeopardized. At present, there is evidence, albeit limited, that this is not the case, [28–31] although concern has been expressed about preservation of the uncertainty principle in an analysis of RCTs in multiple myeloma sponsored by industry.[31] More research of this type is needed.

Trialists and research ethics committees should verify a state of reasoned uncertainty in relation to an up-to-date synthesis and appraisal of existent knowledge and the informed beliefs of colleagues. Physicians may then confidently propose trial enrollment to their eligible patients as an act of therapeutic beneficence.

Competing interests

None declared

Authors' statement and contributions

HM and BD are members of their respective institutional review boards. The authors jointly conceived the concepts in this essay. HM produced the first draft. Both authors provided additional content during subsequent revisions, and approved the final version submitted.

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