Controversy

Why Sackett's analysis of randomized controlled trials fails, but needn't

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ß *An invited response from Dr. Sackett appears on page 835.*

Randomized clinical trials play a pivotal role in answering questions about the superiority of competing treatments. They are initiated not because a particular investigator is unsure of the treatment of choice, but because there is sufficient uncertainty in the medical and scientific community to warrant mounting a trial. Of course, the commitment of enrolling physicians and patients in a trial is critical to its success, and we agree with Dave Sackett's recent comments[1] about the importance of "coal-face commitment."

The idea that an individual physician must be in a state of complete indifference with regard to two alternative treatments in order to randomly assign patients to those treatments was challenged years ago as untenable by Benjamin Freedman.[2] Sackett makes that observation again, although the solution he proposes is not consistent with Freedman's.

Sackett and others[3] take the view that a physician must be substantially uncertain about the merits of a treatment to ethically recommend enrolment for a patient. We do not contest the physician's obligation to serve the best interests of each patient; comorbidity or other reasons might make enrolment in one or both of the trial arms undesirable for any particular patient. However, fulfilling that obligation requires not only clinical skill and an understanding of each patient's situation, but up-to-date knowledge of the best therapeutic strategies available. Physicians cannot develop this knowledge in isolation, but must rely on the collective judgement of the medical community as a whole.

The uncertainty or certainty of any individual physician about the relative merits of a treatment is irrelevant to the moral basis of a trial. Rather, the ethical basis for a clinical trial arises from the uncertainty that rests with the expert clinical community as a whole: this is the state of clinical equipoise described by Freedman.[4] Consider a situation in which there was no individual physician uncertainty, with half the physicians considering treatment A preferable, and half preferring B. A consequence of Sackett's position would be that a randomized trial could not move forward: physicians could not, in good conscience, enrol any patients. Yet it is just this state of (un)certainty that calls out for evidence as to which is the better treatment. It is important for the individual physician to set aside his or her opinion, bias or "certainty" in deference to the reasoned uncertainty that exists within the larger community of experts. When clinical equipoise exists one could argue that physicians have an obligation to inform patients of the existence of relevant clinical trials.

A trial that is in clinical equipoise does not sacrifice the welfare of current patients for the sake of future patients. Neither investigators nor enrolling physicians should ask patients to forgo what is known to be a better or more appropriate treatment to enter a clinical trial. Clinical equipoise ensures that the physician's obligation to the patient is not breached because it requires that the only trials that go forward are those for which the superior treatment is unknown; that is, there is a lack of consensus in the expert community as to the superior treatment. It provides a basis for assessing whether a trial is ethical, with regard to both its initiation and its continuation. That decision is not idiosyncratic, but collective. Although the decision as to whether to offer enrollment in a trial will of course rest with the enrolling physicians, they need not feel that they can only maintain "coal-face commitment" if they personally are uncertain as to the preferred treatment for an individual patient. To the extent the uncertainty principle promotes that view, it does a disservice by creating unnecessary tension.

In arguing that equipoise is incapable of application, Sackett confuses theoretical equipoise (which requires that the evidence supporting 2 treatments be exactly balanced) with clinical equipoise (which requires only a lack of consensus within the expert community). His claim that equipoise is almost never possessed by investigators or explored by ethics committees is surprising from one who has spent so much time advancing an evidence-based approach. The Tri-Council Policy Statement[5] begins its section on clinical trials with a discussion of clinical equipoise, and most research ethics boards that we are familiar with consider clinical equipoise an integral part of the ethics review process.

Giving undue weight to a physician's possibly uninformed views, as the uncertainty principle allows, is not consistent with an evidence-based approach to health care. The collective judgement of the medical community relies on the informed views of its members as a whole. Sackett's analysis takes into account the individual physician, but fails to locate that individual within the larger community of which he or she is a part. He briefly considers a group version of the uncertainty principle. However, this seems to be a bit like trying to reinvent the (clinical equipoise) wheel.

Although there is much of value in Sackett's discussion of randomized controlled trials, his comments on equipoise perpetuate misconceptions rather than helping to remedy them.

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