Letters

Correspondance

Uncertainty about clinical equipoise

It is not surprising that David Sackett[1,2] disagrees with Stanley Shapiro and Kathleen Glass;[3] they are talking about different things.

A clinical trial involves decisions at 3 distinct levels: that of society, the individual physician and the patient.

The decision on whether a proposed trial should be carried out is formally taken by a research ethics board (REB), which, in effect, must decide whether asking patients to consent to participate is consistent with the standards of society as a whole. The concept of clinical equipoise is an essential part of the REB's decision; the REB must be confident that expert clinical opinion regards the trial as valid.

Individual clinicians must decide whether they should enter patients into the trial. The concept of uncertainty addresses this decision.

The consent of the patient is requested by the uncertain physician on a case-by-case basis if he or she believes that the uncertainty for a population of patients applies to the specific case.

The term "clinical equipoise," though perhaps ungainly, effectively captures the valuable concept of collective expert uncertainty and differentiates it from individual uncertainty, which may be insufficient justification for a trial.

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In a rebuttal to Stanley Shapiro and Kathleen Glass,[1] David Sackett[2] argues that a term such as "clinical equipoise" is useful only if it has a consistent meaning for everyone, describes something real and is in common currency. With regard to the latter, he states that because "uncertainty" yielded 292 860 hits on a MEDLINE PubMed search whereas "equipoise" yielded only 52, "uncertainty principle" would be a better term to use. However, "uncertainty" has many meanings and a search of "uncertainty principle" using PubMed (1966–present) yielded only 41 articles, of which only 8 were related to Sackett's use of the term. In comparison, a search of "clinical equipoise" yielded 29 articles, all of which were directly relevant to the topic. The term "uncertainty principle" therefore fails the tests of consistent meaning and of frequency of use.

Sackett also argues that bioethicists don't grasp the importance of the trust between individual patients and clinicians, and that the patient and clinician are often reasonably certain of which treatment is needed. This implies, I think inadvertently, that a patient should simply trust his or her clinician and never seek a second opinion. As a clinician and a researcher, I would suggest that in many areas of medicine different expert clinicians often have different opinions as to the most appropriate treatment. Indeed, in life- or limb-threatening conditions, or when a treatment has many side effects, patients should be encouraged to seek a second opinion. In essence, the concept of clinical equipoise as originally articulated by Benjamin Freedman[3] simply suggests that where second opinions are likely to disagree, physicians should be willing to include their patients in a randomized controlled trial. Rather than prohibiting the clinician from informing the patient of his or her personal beliefs,[2] clinical equipoise simply asks the clinician to be honest, letting the patient know that a different but equally competent clinician might decide on a different course. Of course, whether a randomized controlled trial should be done will also depend on the size of the patient population at risk and the cost, but this is an economic argument, not an ethical one. Understood in this light, I cannot agree with Sackett's conclusion that clinical equipoise is inconsistent with the "patient's autonomy and right to refuse to be randomized on the basis of their opinion, bias or certainty."

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[The author responds:]

In conducting, participating in and teaching about randomized clinical trials, I've found it useful to recognize that uncertainty exists at 3 levels. Because the levels each have unique properties, problems and solutions, they must be clearly distinguished.

The first level is community uncertainty, where sufficient numbers of clinicians, methodologists and ethics committees must become sufficiently uncertain whether an intervention is beneficial for a randomized clinical trial of the intervention to be judged both necessary and appropriate; the trial's data safety and monitoring board later resolves this community uncertainty in light of the emerging results.

The second level is the uncertainty of individual clinicians who are deciding whether to join a randomized clinical trial and then, if they join, whether or not to offer trial participation to any of their patients (for example, some clinicians were certain that endarterectomy was beneficial in symptomatic carotid stenosis and refused to join the North American and European trials in

which only half their patients would undergo this operation).

The third level is uncertainty at the level of the individual partnership between patient and clinician, where unless *both* of them are uncertain which arm of the trial is better for the patient, the patient doesn't join the trial.

I think Francis Rolleston has both nicely described these 3 different levels of uncertainty and correctly pointed out that my original essay was concerned primarily with the third level of uncertainty, that within the individual patient–clinician partnership.[1] Alas, he then proposes retaining the term "clinical equipoise" to denote the first level, community uncertainty. The disutility of his proposal is immediately revealed in the letter from Ian Shrier, who evokes clinical equipoise in addressing the third level of uncertainty.

I thank these 2 correspondents for making my point.

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Reference

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The value of industry-sponsored studies of initial antihypertensive therapies

Despite serious concern,[1,2] James Wright continues to dismiss a body of evidence from actual practice that newer classes of antihypertensive drugs may improve adherence to therapy and therefore blood pressure control.[3–5] We believe that it is he who has "misse[d] the point."[6] The issue here is not that observational data should replace data from clinical trials, but simply that results from real-world studies are also worth considering in the initial choice of antihypertensive therapy.

Wright's summary dismissal of this evidence is based on the contention that the results of observational studies are contradictory and that those showing worse compliance with diuretics reflect the vested interest of the sponsoring companies. The clincher, he avows, is that such studies are irremediably biased anyhow whereas blinded randomized trials are not. His first and third points are clearly incorrect. All studies of adherence in patients with newly diagnosed hypertension have produced similar results, demonstrating greater adherence to angiotensin-converting-enzyme inhibitors.[7] The observational studies that have not shown these results[8,9] are about patients with chronic hypertension, that is, patients who already have established prescription therapy; the findings of the latter studies are thus irrelevant in this debate.[10] Although observational studies are clearly more prone to confounding, randomized trials are by no means immune to bias. More importantly, randomized trials severely aggravate the Hawthorne effect, and blinding of patients precludes proper study of the question of the relation of compliance to drug characteristics: the method Wright advocates will *not* answer this question.

Funding by drug manufacturers should always be taken into account when interpreting results, but it does not justify summary dismissal of the findings. Apart from disclosing the funding sources for our study, we reported our methodology in detail: neither our data source (Saskatchewan Health) nor our straightforward methods were in any way influenced by the company that partly funded the study (the company was interested in irbesartan, a drug that was not included in our report).[11]

Wright's own position on these matters would have been more widely communicated if he had addressed the studies of actual practice, not just presented arguments against their validity. We remain convinced that proper assessment of first-line antihypertensive therapy means looking at all available evidence, including the observational studies. Wright's failure to acknowledge these data is a serious and misleading omission and discourages a deeper understanding of the reasons for our poor performance in managing hypertension.

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[The author responds:]

I am pleased that Jaime Caro and Krista Payne have kept this discussion alive, thus allowing me to explain my position at greater length.[1,2] The objective of scientific research is to minimize bias as much as possible, which is why the double-blind randomized trial is the gold standard. In a perfect world, observational studies of adherence to dispensed drugs might be valid. However, the real world is far from perfect.

In my opinion, the studies mentioned by Caro and Payne[3,4] are predominantly a measure of the effect of