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Letter to the Editor

Dear Madam: In her article alleging the failure of equipoise to resolve the ethical tension in a randomized clinical trial, Professor Deborah Hellman misconceives the nature of equipoise in relation to the design and conduct of such trials ("Evidence, Belief, and Action: The Failure of Equipoise to Resolve the Ethical Tension in the Randomized Clinical Trial," *JLME*, Fall 2003). Conceptually, equipoise relates to evidential uncertainty concerning the relative merits of comparator interventions, and is directly relevant to the scientific validity and value of randomized clinical trials, and the ethical recruitment of patients.

Uncertainty may be considered at three levels: (1) the community of "expert" clinical practitioners and trialists, who propose a trial for its resolution; (2) the individual physician, who must both decide whether to participate in a trial and whether to offer enrollment to particular eligible patients; and (3) the patient, who must decide whether to accept an offer of enrollment.[1] The first level is that of "clinical equipoise" as proposed by Freedman.[2]

With respect to data produced by research, including the results of randomized clinical trials, Professor Hellman makes distinctions between evidence obtained in trials (Q1), one's belief given the evidence (Q2), and action taken in regard to such evidence (Q3): "the question that is of interest to the patient is *what should I do?* It is a question directed at decision-making and action. The concept of equipoise relates to a very different question; it relates to the question *what should I believe?*"

The notion that clinical equipoise is irrelevant to an action decision is puzzling. The action required of a patient is a choice among available medical interventions for her condition. A patient is surely interested in the reasoned beliefs of physicians expert in her condition. The notion of equipoise is well-recognized in utility theory, the basis of the strategy of clinical decision analysis,[3] commonly used by physicians and their patients when making treatment choices in clinical care. Utility theory takes account of a patient's values and preferences in decisions about treatment options. If, after being apprised of community uncertainty concerning the relative efficacy of the comparator interventions, and the nature of the interventions and their harms, a patient is also "maximally uncertain" (in equipoise) about their relative merits, enrollment is a rational option.[4] Indeed, randomization will offer the patient-participant the best odds (50 percent) of getting the best treatment, if one is subsequently shown to be superior. Thus, equipoise enables the best *treatment* choice under conditions of uncertainty: the trial.[5] The notion of leaving the choice of treatment to chance, the flip of a coin, is seemingly at odds with the notion that "care requires that patients get the treatment that is best suited to the action-oriented question—*given the data, what should I do*[?]" However, it is best to remember that the "casting and drawing of lots" is a time-honored method of dealing with uncertainty.[6] 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

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treatment choice (the patient's primary goal) under conditions of uncertainty.[7]

Professor Hellman states that "[i]f a patient (or the parents of a patient) is offered a choice between likely death from disease or an experimental therapy that holds a small but better chance of success than no therapy or current standard treatment, that is a tragedy we can all lament...." and "[f]rom that patient's perspective, the most rationale choice may well be the new therapy — uncertain though it is." This argument follows a discussion of the Gelsinger case, which did not involve a randomized clinical trial, and is thus not pertinent to the relation between comparator interventions in randomized clinical trials, when clinical equipoise is present. In a phase one or phase two trial, a formal technique for the resolution of uncertainty (akin to randomization) does not exist. Here, the patient's dilemma concerns acceptance of a standard treatment with generally known outcomes, compared with an innovative therapy that carries the hoped-for benefits, but also the unknown risks of harm of any inadequately tested intervention.

Professor Hellman cautions that we "ought not to mouth adherence to ethical standards that put the patient's interest first while pursuing clinical research methods that routinely compromise patients' health-related interests in order to acquire information that will benefit future patients." This sentiment is expressed in several other locations in her essay, but is a statement of belief unsupported by evidence. Rather, there is no evidence that the outcomes of clinical trials, ***in the aggregate***, consistently and predictably favor innovative over control interventions, in spite of trialists' hopes that the new interventions are better. Indeed, there is limited evidence to the contrary.[8] Finally, there is accumulating evidence that patients treated in the context of randomized clinical trials have better outcomes than similar patients receiving treatments outside of trials.[9]

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