JAMA Guide to Statistics and Methods

Equipoise in Research
Integrating Ethics and Science in Human Research

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The principle of equipoise states that, when there is uncertainty or conflicting expert opinion about the relative merits of diagnostic, prevention, or treatment options, allocating interventions to individuals in a manner that allows the generation of new knowledge (eg, randomization) is ethically permissible.[1,2] The principle of equipoise reconciles 2 potentially conflicting ethical imperatives: to ensure that research involving human participants generates scientifically sound and clinically relevant information while demonstrating proper respect and concern for the rights and interests of study participants.[1]

Related article page 483

In this issue of *JAMA*, Lascarrou et al[3] report the results of a randomized trial designed to investigate whether the "routine use of the video laryngoscope for orotracheal intubation of patients in the ICU increased the frequency of successful first-pass intubation compared with use of the Macintosh direct laryngoscope." Intubation in the intensive care unit (ICU) is associated with the potential for serious adverse events, and video laryngoscopy in the ICU has gained support from some clinicians who believe it to be superior to direct laryngoscopy. Such practitioners may therefore regard it as unethical to randomize study participants to direct laryngoscopy because they consider it to be an inferior intervention. But requiring uncertainty of individual clinicians to conduct a clinical trial gives too much ethical weight to personal judgment, hindering valuable research without providing benefit to patients. Therefore, it is important to understand the role of conflicting expert medical judgment in establishing equipoise and how this principle applies to the trial conducted by Lascarrou et al.

What Is Equipoise?

Two features of medical research pose special challenges for the goal of ensuring respect and concern for the rights and interests of participants. First, to generate reliable information, research often involves design features that alter the way participants are treated. For example, randomization and blinding are commonly used to reduce selection bias and treatment bias.[4] Controlling how interventions are allocated and what researchers and participants know about who is receiving which interventions helps to more clearly distinguish the effects of the intervention from confounding effects. But randomization severs the link between what a participant receives and the recommendation of a treating clinician with an ethical duty to provide the best possible care for the individual person. In the study by Lascarrou et al,[3] patients were randomized to undergo intubation with the video laryngoscope or the direct laryngoscope, independent of the preference of the treating physician.

Second, medical research involves exposing people to interventions whose risks and potential therapeutic, prophylactic, or diagnostic merits may be unknown, unclear, or the subject of disagreement within the medical community. In the present case, some clinicians may maintain that video laryngoscopy is the superior strategy for orotracheal intubation in the ICU, others may disagree, while others judge that there is not sufficient evidence to warrant a strong commitment for or against this approach.

The principle of equipoise states that if there is uncertainty or conflicting expert opinion about the relative therapeutic, prophylactic, or diagnostic merits of a set of interventions, then it is permissible to allocate a participant to receive an intervention from this set, so long as there is not consensus that an alternative intervention would better advance that participant's interests.[1,2,5-7]

In the present case, there is equipoise between video vs direct laryngoscopy because experts disagree about their relative clinical merits. These disagreements are reflected in variations in clinical practices. If it is ethically permissible for patients to receive care from expert clinicians in good professional standing with differing medical opinions about what constitutes optimal treatment, then it ordinarily cannot be wrong to permit participants to be randomized to those same treatment alternatives.[5] Although randomization removes the link between what a participant receives and the recommendation of a particular clinician, the presence of equipoise ensures that each participant receives an intervention that would be recommended or utilized by at least a reasonable minority of informed expert clinicians.[1,5,6] Equipoise thus ensures that randomization is consistent with respect for participant interests because it guarantees that no participant receives care known to be inferior to any available alternative.

Why Is Equipoise Important?

Ensuring equipoise helps researchers and institutional review boards (IRBs) fulfill 3 ethical obligations. First, to "disturb" equipoise studies must be designed to generate information that resolves uncertainty or reduces divergence in opinion among qualified medical experts. Such studies are likely to have both social and scientific value. Second, any risks to which participants are exposed must be reasonable in light of the value of the information a study is likely to produce.[5,6] IRBs must make this determination before participants are enrolled.

Third is the obligation to show respect for potential participants as autonomous decision makers. Explaining during the informed consent process the nature of the uncertainty or conflict in medical judgment that a study is designed to resolve allows each individual to decide whether to participate by understanding the relevant uncertainties, their effects on that person's own interests, and how their resolution will contribute to improving the state of medical care.

What Are the Limitations of Equipoise?

Since its introduction, the concept of equipoise has received numerous formulations, creating the potential for confusion and

misunderstanding[2,7] and spurring criticism and debate. One criticism holds that the version of equipoise described here is too permissive because it allows randomization even when individual clinicians are not uncertain about how best to treat a patient.[8] The trial conducted by Lascarrou et al[3] represents a case in which some clinicians have strong preferences for one modality of treatment over others. Requiring individual clinician uncertainty entrenches unwarranted variation in patient care by preventing participants from being offered the choice of participating in a study in which they might be allocated to interventions that would be recommended or utilized by other medical experts. If it is ethically acceptable for patients to receive care from informed, expert clinicians who favor different interventions, then it ordinarily cannot be unethical to allow patients to be randomized to the alternatives that such clinicians recommend. Legitimate disagreement among informed experts signifies that the clinical community lacks a basis for judging that patients are better off with one modality over the other.

An interpretation of equipoise that requires uncertainty on the part of the individual clinician is not ethically justified because it prevents studies that are likely to improve the quality of patient care without the credible expectation that this restriction will improve patient outcomes.

Another criticism is that equipoise is unlikely ever to exist, or to persist for long.[9] This objection applies most directly to the view that equipoise only exists if the individual clinician believes that the interventions offered in a trial are of exactly equal expected value.[10] On this view, equipoise would often disappear even though different experts retain conflicting medical recommendations. It therefore appears poorly suited to the goals of promoting the production of valuable information and protecting the interests of study participants.

How Is Equipoise Applied in This Case?

Lascarrou et al did not explicitly discuss equipoise in their study. However, the consent process approved by the ethics committee reflects the judgment that the interventions in the trial "were considered components of standard care" and patients who lacked decisional capacity could be enrolled even if no surrogate decision maker was present.

Ensuring that a study begins in and is designed to disturb a state of equipoise provides credible assurance to participants and other stakeholders that patients in medical distress can be enrolled in a study that will help improve patient care in emergency settings without concern that their health interests will be knowingly compromised in the process.

How Does Equipoise Influence the Interpretation of the Study?

In the past, strongly held beliefs about the effectiveness of treatments ranging from bloodletting to menopausal hormone therapy have proven to be false. Intubation in the ICU is associated with the potential for serious adverse events. Because video laryngoscopy is increasingly championed as the superior method for orotracheal intubation in the ICU, careful study of its relative merits and risks in comparison to conventional direct laryngoscopy addresses a question of clinical importance. The findings of Lascarrou et al[3] suggest that perceived merits of video laryngoscopy do not translate into superior clinical outcomes and may be associated with higher rates of life-threatening complications. This result underscores the importance of conducting clinical research before novel interventions become widely incorporated into clinical practice, even if those interventions appear to offer clear advantages over existing alternatives.

ARTICLE INFORMATION

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