Equipoise: Integrating Social Value and Equal Respect in Research with Humans

Alex John London

The Oxford Handbook of Research Ethics
Edited by Ana S. Iltis and Douglas MacKay

Subject: Philosophy, Moral Philosophy Online Publication Date: Dec 2020
DOI: 10.1093/oxfordhb/9780190947750.013.13

Abstract and Keywords

The term “equipoise” refers to a state of uncertainty about the relative merits of a set of interventions, such as medical treatments for a particular disease or alternative policies for promoting economic, educational, or public health outcomes. This chapter discusses the role of equipoise in ensuring that research generates scientifically sound and socially valuable information while respecting the rights and welfare of the individuals whose interests are impacted by the conduct of the research. Alternative formulations of equipoise are distinguished, as are alternative ethical frameworks that provide a rationale for, and give content to, this appeal to uncertainty. It is argued that equipoise can be grounded in a general framework that applies to all research with humans that reconciles the imperative to produce socially valuable information with respect for the status of both participants and community members as free and equal persons.

Keywords: equipoise, risk, social value, uncertainty, standard of care, justice, integrative approach, equality, research with humans, adaptive trial

1. Introduction

Few concepts have played as critical a role in ethical decision-making while being the subject of such profound confusion as the concept of equipoise. The term “equipoise” refers to a state of uncertainty about the relative merits of a set of interventions. In the medical context, where studies test new vaccines, diagnostic tools, or therapies, the relevant merits consist in an intervention’s efficacy or effectiveness as a diagnostic, prophylactic or therapeutic agent. In public health, economics, or the social sciences, the relative merits of interventions might consist in their ability to remediate a hazard, promote beneficial behavior, or bring about an otherwise desirable outcome. The importance of equipoise as a concept in ethical decision-making stems from its role in reconciling a set of moral values that are potentially in conflict in any research study that involves human participants. These values include ensuring that research generates scientifically sound

and socially valuable information while respecting the rights and welfare of the individuals whose interests are impacted by the conduct of the research.

Confusion surrounding the concept of equipoise stems from protracted disagreements about a range of basic issues, including how to formulate the very question to which equipoise is supposed to offer a solution, whose uncertainty matters, what question those parties must be uncertain about, and under what conditions that uncertainty no longer obtains. The proliferation of competing conceptions of equipoise and confusion about the meaning of the term have prompted some to question the value of retaining this concept rather than simply abandoning it (Sackett 2000).

Despite the somewhat ironic persistence of uncertainty surrounding the value of the concept of equipoise, this chapter demonstrates that a framework employing this concept can be given a sufficiently general ethical grounding so that it applies to all research involving human subjects (i.e., research in medicine, public health, and the social sciences). This framework is capable of reconciling the imperative to ensure that research contributes to the public good of generating socially valuable information with respect for the status of study participants as free and equal persons whose rights and welfare should not be knowingly or intentionally compromised. As a result, equipoise has an important role to play in the ethical assessment of all research that involves human participants, whether in medicine, the social sciences, or elsewhere.

In the next section I articulate four key questions that must be addressed to construct a framework within which appeals to equipoise have substantive content. After that, I argue that the earliest articulation of the equipoise requirement, put forth by Charles Fried (1974), gives what might seem to be the most intuitive answers to those questions but that those answers are fatally flawed. The next section argues that any framework that appeals to uncertainty in the mind of the individual agent inherits this fundament flaw. The persistence of this intuitive but unworkable formulation has led critics to argue that appeals to equipoise are misguided. But such a charge erroneously assumes that every framework that appeals to equipoise locates uncertainty in the mind of some agent and, as a result, suffers from the same, or relevantly similar, set of defects.

In the fifth section I describe the most sophisticated early formulation of equipoise, provided by Benjamin Freedman (1987, 1990). What he called “clinical equipoise” has a number of advantages, but some have argued that it does not address the fundamental problem at the heart of research with humans. In the sixth section I argue that this objection is mistaken. However, in the seventh section I argue that even clinical equipoise retains a relatively narrow normative foundation that grounds the constraints on research in role-related obligations of physicians. This unduly narrow framework perpetuates the perception that frameworks that appeal to equipoise are not relevant to research with human participants that is conducted by non-physicians. This not only limits the scope of clinical equipoise to a subset of clinical research but renders it irrelevant to research conducted by economists, psychologists, public health practitioners, or other non-physicians.

In the eighth section I outline the "integrative approach" to risk assessment and management. This framework provides a unified, normative foundation for Freedman's focus on uncertainty in expert communities. Within this framework, the equipoise requirement reconciles the imperative to generate socially valuable information with a set of general moral values that are grounded not in any role-related professional obligation but in general ethical duties that free and equal persons owe to one another. This framework has the advantage of applying to the full range of research conducted with human participants, regardless of the professional or disciplinary background of the persons conducting the research. Section nine shows how this framework deals with the challenging case of response adaptive randomization (RAR). The final section examines how any framework for regulating risk in research should be relativized to a notion of community within which research can meaningfully contribute to strengthening the health system, or other social systems, on which individuals depend.

2. Competing Frameworks Involving Equipoise

It is useful to distinguish the concept of equipoise from the larger frameworks that give substantive content to the requirement that equipoise obtain. In particular, if we define "equipoise" as a state of uncertainty regarding the relative diagnostic, prophylactic, or therapeutic merits of a set of interventions, then a number of issues remain unspecified. Alternative frameworks that provide substantive content to the appeal to equipoise can be constructed from different answers to the following four basic questions (London 2007b).

1. *Normative Foundation*: What specific values are potentially in conflict in research involving human participants, and what is the normative basis for requiring research to be consistent with these values?
2. *Locus of Uncertainty*: Where is the relevant uncertainty located (i.e., whose uncertainty is morally relevant and why)?
3. *Model of Uncertainty*: How is uncertainty to be understood or modeled at a practical level?
4. *Epistemic Threshold*: At what point has the relevant uncertainty been disturbed such that it is not permissible to initiate or to continue a study?

3. Fried's Equipoise: Intuitive and Unworkable

The term "equipoise" was introduced into research ethics by the noted law professor Charles Fried in his landmark book *Medical Experimentation: Personal Integrity and Social Policy* (1974). As Fried frames the problem, the goal of medical research is to generate information that will benefit large numbers of future people. Fried worried that the demands of sound science—in particular, procedures such as randomization, "blinding" researchers and participants to the identity of the intervention they are delivering or receiving, and adhering to a strict protocol—can conflict with the conscientious physician's

duty to provide personalized care that advances the medical best interests of the individual patient. In response to the first question from the end of section 2, Fried framed the concept of equipoise as a way of reconciling the demands of sound science that advances the common good with the physician's ethical and legal duty of personal care. The idea that the fundamental tension to be resolved is between the common good served by medical research and the role-related moral obligations of clinicians is so widespread it has been referred to as a dogma of research ethics (London 2007a).

Given this normative foundation for the appeal to equipoise, it is unsurprising that Fried answered the second question at the end of section 2 by locating the relevant uncertainty in the mind of the individual physician-researcher. As he puts it, "the traditional concept of the physician's relation to his patient is one of unqualified fidelity to that patient's health. He may certainly not do anything that would impair that patient's health and he must do everything in his ability to further it" (1974, 50–51). Only when the individual clinician is uncertain about the relative merits of a set of interventions for a particular patient would it be consistent with that clinician's duty of fidelity to allow that patient to be randomized to one of those alternatives.

Similarly, Fried modeled uncertainty (the third question at the end of section 2) as the judgment of the individual physician-researcher regarding the "balance of harms and benefits discounted by their appropriate probabilities" (1974, 52). Imagine two drugs, each of which has, on average, a 75 percent chance of helping a patient. If drug A would provide a larger benefit than B, then duty requires that the clinician provide the patient with A. In other words, Fried models the physician's duty of personal care as a duty to provide the intervention that, in the clinician's expert judgment, is most likely to best advance that person's health interests in expectation.

Together, these views entail a conception of equipoise that has a fragile epistemic threshold since the relevant uncertainty will only obtain in cases where the magnitude of benefit from one intervention, discounted by its appropriate probability, is the same as that of the other interventions in question. Only then is the clinician's judgment equally poised between the relevant alternatives.

Because the term "equipoise" evokes an image of equal balance of judgment, many stakeholders simply assume that the concept of equipoise is to be identified with a judgment that is balanced on a knife's edge (Lilford and Jackson 1995; Eyal and Lipstich 2017). The problem is that this conception of equipoise is fundamentally flawed, and several of these problems have been known for at least three decades. Canvassing these flaws will help to define a set of benchmarks that we can use to evaluate the relative merits of alternative frameworks that employ the general concept of equipoise.

4. Three Flaws with Individual Uncertainty

Two objections to the conception of equipoise were envisaged by Fried himself and voiced by its earliest critics. The first is that this conception of uncertainty is so fragile that it will rarely obtain (Marquis 1983; Gifford 1986). There may be many factors about which a clinician has some uncertainty, but when it comes to making a decision about what to do, the conscientious clinician will use all of the information available to weigh the likely benefits and burdens of each intervention and choose the one that is most likely to best advance the medical interests of the patient. Because it will rarely be the case that several interventions are believed to be of equivalent value once all things are considered, it will rarely be permissible to initiate a randomized controlled trial.

The second objection is that even if it is permissible to initiate a trial, a well-designed study will produce evidence that will disturb equipoise long before it reaches statistical significance (Hellman 2002; Saxman 2015). As soon as evidence emerges that supports one intervention, it would no longer be consistent with the physician's duty of personal care to allow a patient to be randomized. The clinician would be duty-bound to provide the patient with the intervention that they believe is most likely to advance the patient's welfare.

The upshot of these objections is that this conception of equipoise cannot resolve the dilemma between generating valuable social information and respect for the rights and welfare of individuals since, on this view, it will be almost impossible to initiate, or to complete, studies that are designed to generate such information.

A third objection holds that Fried's conception of equipoise also has the counterintuitive effect of permitting the conduct of studies that have no social value (London 2018). For simplicity, let us hold that a necessary condition for social value is that a study should generate information that leads stakeholders to alter their conduct in ways that improve the way care is provided or how scarce resources are utilized (Freedman 1987, 1990; Wenner 2017). In Fried's view, equipoise obtains between a set of interventions when the expert physician believes that they are equally valuable in expectation—that the expected benefits of each intervention are effectively equivalent. When this is the case, it is permissible to initiate a research study. So, it follows that if there is considerable medical evidence to support the claim that A and B are of equal clinical utility, it would be permissible to initiate a study of A and B. Moreover, if this evidence is accurate, then it will be permissible to continue such a study to the point that the trial reaches statistical significance. The problem is that such studies have little or no social value since they are initiated under conditions where judgments are supported by compelling medical evidence and run to completion only in cases where they confirm what is already known, namely, that the interventions in question are of equivalent value. In other words, this view permits research only in cases where it is expected to make no improvements to care delivery or clinical practice.

Together, this set of objections illustrates that modeling uncertainty as the belief of the individual clinician-researcher about the likely effects of a set of interventions discounted by the relevant probabilities does a poor job of capturing the distinctive role of research with human participants in resolving uncertainty. In this approach, research cannot be initiated or run to completion in cases where it is most needed, and it is most permissible in cases where it is least valuable.

In light of these objections, we might wonder whether the problem lies in locating uncertainty in the mind of the individual clinician or in adopting such a fragile epistemic threshold. Although there is some disagreement on this point, an insight from Benjamin Freedman provides compelling reason to believe that the problem lies in locating the relevant uncertainty in the mind of the individual clinician-researcher. As we will see, this point has important implications for other frameworks that employ the concept of equipoise.

5. Clinical Equipoise and the Social Nature of Medical Uncertainty

Benjamin Freedman is perhaps the most important proponent of the concept of equipoise, and a major contribution of his work was to argue that the relevant uncertainty should be located not in the head of the individual clinician-researcher but in the larger medical community. In fact, Freedman's work can be seen as revealing a deep problem with Fried's approach, namely, that it simply cannot address a form of medical uncertainty that is common and of profound social importance. The seminal contribution of Benjamin Freedman was to recognize that the conflicting judgments of medical experts represent an important form of medical uncertainty and to define what he called "clinical equipoise" in these terms (Freedman 1987, 1990).

For brevity, consider a case in which expert clinicians are divided over the best way to treat a particular medical condition M. Some experts regard the current standard of care (call it "A") as the best alternative available. But others believe that a new intervention, "B," has shown great promise in some of the sickest patients with M and that it, therefore, is a superior alternative. Imagine further that neither group of experts is uncertain in the sense defined by Fried: when each reviews the available medical evidence, each arrives at an informed, all things considered judgment in favor of one medical intervention for patients with M. It is just that whereas some regard A as superior to B for M, others regard B as superior to A for M.

On Fried's view, equipoise does not exist in this situation because each individual expert has a strict preference in favor of one intervention. So nobody thinks that each intervention is likely to be of roughly equivalent value in expectation. Therefore, on Fried's view, it would not be permissible to initiate a trial. But this view is self-defeating: it prevents patients from being randomized to A or B so that we can quickly and clearly determine their relative merits, but it permits different camps of medical experts to continue to pro-

vide A to some patients and B to others (London 2007a, 2007b). Moreover, although who gets A or B outside of a trial might not be determined by explicit use of a random process, it is fundamentally influenced by arbitrary circumstances, such as whether people live closer to physicians who support A rather than B, whether their insurance includes providers of A rather than B, or simply who is on call when they present for care (Freedman 1987). As a result, preventing the study does not make anyone better off—but it prevents a range of stakeholders from generating the information they need in order to discharge some of their professional responsibilities and moral obligations (London 2019).

Freedman argued that uncertainty is a property of the expert medical community. When experts disagree about the best way to address a particular problem, clinical research represents an important tool for resolving that uncertainty—for generating the information the medical community needs to determine the relative merits of the available alternatives. About this, Freedman was surely correct—resolving this type of uncertainty can have significant social value since arbitrary variations in care can result in some providers utilizing practices, procedures, or interventions that are less effective than an available alternative. Clarifying the relative merits of these interventions not only enables clinicians to improve their practice; it enables health systems to direct funds and scarce resources away from practices, procedures, and interventions that are worse than a feasible alternative. It also provides patients with the information they need to make more informed medical decisions and to better safeguard their own medical interests.

6. Does Clinical Equipoise Address the Wrong Problem?

Although Freedman rejects Fried's model of uncertainty, he accepts Fried's view of the central problem to be solved. Both see the central dilemma as squaring research participation with the role-related obligations of physicians. Recently, two of the most prolific proponents of clinical equipoise, Paul Miller and Charles Weijer, have argued that, although clinical equipoise may offer a better conception of uncertainty at the social level, it does not address the core question to be resolved, namely, "when may physicians, consistent with their duty of care to patients, offer the [*sic*] them enrolment in an RCT [randomized controlled trial]?" (2006b, 542). Because these critics hold, along with Fried and Freedman, that this is in fact the correct problem to be solved, they argue that clinical equipoise must be supplemented with what is effectively a revised version of Fried's equipoise.

Miller and Weijer note that clinical equipoise is applied by research ethics committees (RECs) to determine whether it is permissible to initiate a research study (2003; Weijer and Miller 2004). Because RECs carry out their work prior to the enrollment of any particular participants, they argue, clinical equipoise can establish only that the medical community is uncertain about the relative clinical merits of an intervention for patients with a particular medical condition. But this doesn't mean that it is permissible for any particular patient to participate in a study because individual patients, with their specific

medical histories, may face different risks from the same interventions. As a result, they claim, “clinical equipoise does not contemplate the particular circumstances of individual patient-subjects. Therefore, it is not, and indeed cannot be, considered to be an adequate specification of the duty of care of doctor-researchers, because they are bound to protect the [individual] welfare interests of the patient-subjects” (2006b, 546).

To safeguard the medical best interests of individual patients, Miller and Weijer propose a framework called “component analysis” in which RECs use clinical equipoise to evaluate study protocols and then require, in addition, that, if a protocol is approved, the individual physician-researcher must agree that study participation does not contravene the medical best interests of the individual patient. In other words, component analysis requires both that RECs find that clinical equipoise exists and that study participation is consistent with the moral duties of the individual researcher. Miller and Weijer think component analysis can avoid the problems that plague Fried’s view by holding that the epistemic threshold on the individual clinician researcher’s uncertainty is less fragile than Fried thought. They argue that individual researchers are subject to the “clinical judgment principle,” which holds that “the physician may offer patients enrolment in a trial unless (1) they believe that it would be medically irresponsible to do so and (2) this belief is supported by evidence that ought to be convincing to colleagues” (2006b, 546).

For our present purposes it is sufficient to raise three problems for this aspect of component analysis. First, either the clinical judgment principle is weaker than the clinician’s morally and legally recognized professional duty to the individual patient or it is not. If it is weaker, then Miller and Weijer’s own view can be rejected for not addressing what they assert to be the central problem to be resolved, namely, reconciling research participation with the clinician’s duty of personal care. If it is not weaker, however, then it is unclear how their position on this question differs from Fried’s and therefore avoids the deep problems that his view faces. After all, the clinical judgment principle is supposed to address the same fundamental problem that Fried was addressing in his work, namely, how to square the interests of individual participants with the individual clinician’s duty of personal care. And within component analysis, if the individual researcher does not regard study participation as consistent with the clinical judgment principle, then they cannot allow a patient to participate in a study. This dilemma has not previously been articulated, but it poses a major problem for component analysis.

Second, set aside the dilemma and imagine that the disagreement in the medical community is so polarized that each side regards the intervention championed by the other side as violating that principle. In that case, no clinician regards participation as consistent with their duty of personal care, so Miller and Weijer would be required to agree that although a REC can approve such a study, no clinician can permit their patients to participate in it. But this position is self-defeating for the same reasons—it prohibits a trial in a situation in which individuals in that community will continue to receive the interventions in question without the possibility of learning about their relative merits.

Third, Miller and Weijer motivate their appeal to the clinical judgment principle because they regard the principle of clinical equipoise as incapable of being applied to individual study participants and therefore as incapable of ensuring that no study participant is exposed to unreasonable risk. But this is a mistake. Other frameworks do apply clinical equipoise at the level of the individual patient (Kadane 1996; London 2006, 2007a, 2007b), and the example below involving RAR illustrates how this is done. As a result, it is simply false to claim that clinical equipoise must be supplemented by a form of uncertainty that resides in the head of a particular individual in order to ensure that individuals do not participate in studies where everyone would agree that they face unreasonable risks.

7. Physician Obligations: The Wrong Normative Foundation

Clinical equipoise represents a major advance in conceptualizing the relationship between ethics and uncertainty in research with humans. Nevertheless, almost all frameworks that appeal to equipoise face two critical problems arising from the dogma that the fundamental tension in research derives from a conflict between producing information that will advance the common good and the narrow role-related obligations of particular professionals.

The first problem is that Fried, Freedman, and others were preoccupied with a specific formulation of a problem that is far more general than they envisioned. In particular, research with human participants is not the sole or exclusive province of physicians. Non-physician experts in public health, psychology, economics, and other social sciences routinely carry out RCTs involving human participants. In these studies, participants are frequently exposed to risks for the purpose of generating valuable information. If we assume that the core problem in research is to reconcile the production of such information with the physician’s duty of personal care, then it would turn out that the same study protocol, involving the same risks, would be governed by different ethical standards depending on whether the principal investigator is a physician. If, as seems more reasonable, like cases should be treated alike and the relevant criteria for treating research studies as ethically similar revolve around the effect of a study on the rights and interests of participants, then we should reject as unduly narrow the idea that the core problem is reconciling research participation with the specific moral and legal duties of physicians (London 2006; Kukla 2007; MacKay 2018).

Although the proponents of component analysis have argued that clinical equipoise can be grounded in a trust relationship between the state and citizens, they retain the clinical judgment principle because they cling to the view that the fundamental dilemma in this area arises “because offering patients enrolment in RCTs imperils the doctors’ duty to act in their interests” (Miller and Weijer 2006b, 542). As such, component analysis remains vulnerable to the objections presented here.

The proposal to reject this narrow foundation receives support from a second, independent consideration. In particular, if the central problem to be solved hinges on the potential for conflict between the rights and welfare of study participants and the moral obligations of clinicians, then no conception of equipoise can fully resolve this problem. The reason is simply that participants in medical research are often exposed to tests or procedures that are included solely for research purposes. Yet these purely study-related procedures pose some affirmative risk to participants, and no expert is uncertain about that. In particular, no expert is uncertain about the fact that those tests expose recipients to risks that are justified not by the prospect of direct benefit to recipients but by their scientific value. But if, as Fried claims, the conscientious physician "may certainly not do anything that would impair that patient's health and he must do everything in his ability to further it" (1974, 50–51), then allowing patients to participate in any study that includes purely research-related procedures would violate the physician's duty of personal care.

In response to this problem, the proponents of component analysis argue that equipoise is limited to the evaluation of interventions that are provided to study participants because of the prospect that they may confer a direct benefit to recipients. For such potentially "therapeutic" interventions, clinical equipoise must obtain, and then the individual clinician must ensure that it is consistent with the clinical judgment principle. Purely research-related procedures are not governed by this ethical framework at all. Rather, they are subject to the very kind of calculus that Fried wanted to avoid, namely, "standards that weigh the welfare interests of patient-subjects in protection from harms of research against the interests of the public and others in the benefits of research" (Weijer and Miller 2004; Miller and Weijer 2006b, 544).

Bifurcating the moral foundation for clinical research has led critics to charge that component analysis is arbitrary in the way that it regulates research risks. Such critics argue that if the interests of individuals can be weighed against the interests of society when it comes to purely research-related risks, the same considerations should apply to every other aspect of research as well, and the equipoise requirement can simply be dispensed with (Miller and Brody 2003; Rid and Wendler 2010).

Miller and Weijer's reply to this is that when persons are sick, they are owed a duty of care (2006a, 2006b). I am sympathetic to this reply. But it is not clear why this fact entails a distinction between therapeutic and non-therapeutic *procedures*, rather than a moral distinction between obligations owed to people whose interests are threatened or already set back in some way (e.g., by sickness or disease) and what is owed to people whose interests are not threatened or set back in some way. For instance, if physicians owe a special duty of care to sick patients, then exposing already sick patients to the risks of purely research-related interventions seems to contravene that duty. The point of these remarks is to drive home the extent to which component analysis retains a foundational commitment to the moral duties of physicians while embracing an approach to evaluating

different risks (those offered with a therapeutic purpose versus those offered for purely research purposes) that seems difficult to reconcile with that fundamental commitment.

Third, it has been argued that any framework that appeals to the physician's duty of personal care to limit research risks faces a fundamental dilemma (London 2006, 2007a, 2007b). As that duty is understood by Fried, Freedman, Miller and Weijer, and others, it is a duty to advance the medical best interests of study participants. To the extent that this duty has determinant content, it is objectionably paternalistic. For example, when Fried says that the conscientious physician can't do anything that would impair the patient's health, it looks like the conscientious physician cannot allow the patient to donate a kidney or a portion of their liver to another person. The reason is that such a procedure poses significant risks to the health of the donor for benefits that accrue not to the donor but to another individual. Understood in this way, the physician's duty is clear, but it is more restrictive than the way physicians' duties are understood in clinical medicine, where clinicians expose patients to affirmative risks in the course of procedures that primarily benefit other persons.

On the other hand, if medical procedures such as living organ donation are consistent with the physician's duty of personal care, then we should apply the same standard to clinical research. Doing so eliminates the objectionable paternalism, but it also deprives the resulting framework of a clear standard for limiting risk. After all, like organ donation, research participation involves accepting some risk to one's health to advance a meritorious social end. At what point do such risks become inconsistent with the clinician's duty of personal care? Once we reject the claim that the physician's duty is to optimize the patient's health interests, narrowly construed, then we are left with no independent criteria to set limits on reasonable risks. The appeal to clinicians' duties is effectively an unexplained explainer.

For our present purposes there are two possible responses to these worries. The first is to reject any appeal to equipoise as misguided and to look to a different approach to managing research risk and promoting socially valuable research (Brody and Miller 1998, 2003; Miller and Brody 2003; Rid and Wendler 2010). The second response is to reject the appeal to the role-related obligations of clinicians and to provide a more general foundation for research ethics that applies to all studies involving human participants and in which clinical equipoise plays a meaningful role. It is to this second option that we now turn.

8. The Integrative Approach and Clinical Equipoise

Returning to the four basic questions outlined at the end of section 2, the integrative approach to risk assessment and management provides a framework within which clinical equipoise is grounded not in the role-related obligations of any profession but in the general ethical and political obligation to respect individuals as free and equal persons (Lon-

don 2006, 2007a, 2007b). In response to the first question, the normative foundation for this framework, the integrative approach begins with the following principle:

> *Principle of Equal Concern*: As a necessary condition for ethical permissibility, research with human subjects must be designed and carried out so as not to undermine the standing of any research participant as the moral and political equal of other study participants and the members of the larger community whose interests that research is intended to serve.

In any society where people have access to information and enjoy basic liberties of expression and association, individuals will invariably cultivate and embrace diverse conceptions of the good life. Within these conceptions of the good life, individuals are likely to value different ends and to pursue different goals. A consequence of this diversity in "personal interests" is that there may be a wide range of disagreement about the value of health relative to other goals (helping others, for example, or achieving a physical ideal of strength or beauty) and the relative disvalue of risks to health that might come from the pursuit of these various ends (by donating a kidney, for example, or undergoing a purely cosmetic medical procedure). This legitimate diversity in life plans was partly responsible for the charge that frameworks that ground the equipoise requirement in role-related obligations are either unjustifiably paternalistic (because they adopt the professional's valuations of various risks or outcomes as authoritative) or lacking in content (because they eschew this paternalism but then offer no independent guidance about the boundary between reasonable and unreasonable risk).

The integrative approach borrows a distinction from the philosopher John Rawls to define the "space of equality" for regulating what individuals with such different life plans owe to one another. In particular, although individuals may differ in their first-order life plans, they share a higher-order interest in having the physical and mental capabilities and social freedoms necessary to formulate, pursue, and revise a first-order life plan (Rawls 1982; London 2003). The basic social institutions in a decent society must be justifiable to that society's members as working to safeguard and advance the basic capacities that each needs in order to be able to formulate, pursue, and revise a life plan of their own—consistent with the ability of every other member of that community to do the same.

At its normative foundation, therefore, the integrative approach holds that research with human participants should be justifiable on these same terms—it should be designed to generate socially valuable information while ensuring that the basic interests of all study participants will be safeguarded in the process. To sharpen the operational content of this general moral commitment, the integrative approach articulates three operational criteria for respecting the principle of equal concern.

> The first operational criterion for equal concern is as follows:
>
> *No Unnecessary Risk*: To be consistent with the principle of equal concern, the risks to both the basic and the personal interests of participants should be reduced to those that are necessary to generate information expected to bridge a

> gap in the ability of a social system—such as a health system—to safeguard and advance the basic interests of the people it serves.

This criterion applies to both the basic and the personal interests of individuals because it is disrespectful to the standing of persons to expose them to risks that are gratuitous or not necessary to accomplish some meritorious social end. The arbitrary interference with a person's life plan also constitutes a form of domination from which individuals have an interest in being free.

The second operational criterion is applied after the first and reflects the special importance of the basic interests of individuals:

> *Special Concern for Basic Interests*: If the basic interests of research participants are threatened or impaired (e.g., by sickness, injury, or disease), participants must be provided a level of care and protection for their basic interests that does not fall below what at least a reasonable minority of experts in the relevant community (e.g., clinical medicine for a medical condition, public health for a public health hazard) would regard as the most beneficial method of response.

This operational criterion focuses on the basic interests of persons because those define the space of equal regard. When a person's ability to formulate, pursue, or revise their life plan is threatened by sickness, injury, disease, or disability, they are not able to function as an equal with their compatriots. In that case, respect for their status as free and equal persons requires that they have access to established effective means of restoring, preserving, or advancing those basic interests.

It follows from this principle, however, that it is permissible to ask study participants to modify or sacrifice some of their personal interests in order to advance socially valuable research. This includes enduring unpleasant experiences, exposing themselves to transient sickness, or undergoing the burdens of study-related procedures that are necessary to advance scientifically sound and socially valuable research. It is then up to individuals to decide whether the risks offered to them are acceptable, in light of their own goals and commitments, during the process of informed consent.

Within the integrative approach, this second criterion is operationalized by a version of clinical equipoise. This provides the content to the second of the four basic questions outlined at the end of section 2, namely, that the locus of uncertainty is not the individual researcher but the experts in the relevant expert community.

> *Equipoise as Practical Test*: A specific intervention *s* is admissible for an individual *i* just in case there is either uncertainty among, or conflict between, experts in the relevant domain (e.g., expert clinicians in the case of medical research) about whether *s* is dominated by any other intervention or set of interventions that are recognized as options for treating individual *i*. For each individual in a study, the care and protection afforded to that individual's basic interests satisfy the principle of equal concern just in case each intervention to which that individual might

be allocated within the trial is admissible for that individual (adapted from London 2006).

This test is similar to clinical equipoise to the extent that it relies on uncertainty or conflict among experts to determine which interventions are admissible for each participant in a study. Contrary to Miller and Weijer (2006), however, this principle can be applied both at the stage of protocol development and during study enrollment. In the former case, the question concerns whether there is disagreement among experts about the relative merits of different means of responding (i.e., different treatments or policies to be tested) to a particular problem, such as a disease or injury. In the latter case, the question is whether, for the particular person and for each intervention in question, there is at least a reasonable minority of experts who would recommend that intervention for that individual. We can ascertain what experts would recommend for each individual in a trial by asking representatives from these different expert communities to determine whether it is permissible to provide the intervention they favor to the individual in question. Alternatively, Kadane (1996) created decision models of such experts and used those to determine which interventions were admissible for each study participant.

As a result, the integrative approach answers the third of our four basic questions by an appeal to the state of the expert medical community. The relevant uncertainty exists under several conditions. The first is if there is conflict among experts. In this case, some fully informed experts from the relevant community believe that one intervention (A) is superior for a particular individual, while other fully informed experts regard another intervention (B) as superior for that same individual. In this case, as long as there is no other option that all regard as superior to both A and B, then both A and B are admissible for that individual. Second, a weaker form of conflict exists if some experts regard one intervention as the superior option for a given individual while others do not regard any intervention from some set of alternatives (e.g., the set including A and B) as inferior to any other options. Third, the relevant uncertainty would also exist if all of the experts in the relevant community regard the relative merits of some set of interventions (e.g., A and B) as not having been established and regard these options as not inferior to any other alternative.

Unlike component analysis, which classifies interventions as therapeutic or non-therapeutic and then applies different standards to interventions in each class, the integrative approach focuses instead on ensuring that the basic interests of study participants are not neglected or knowingly compromised in the course of study participation. To see why this focus on basic interests matters, consider a trial in which researchers want to test a new treatment for male pattern baldness or mild symptoms of seasonal allergies against a placebo. In both cases effective treatments already exist, so allowing a participant to be randomized to a placebo would seem to violate the clinician’s duty of personal care. Weijer and Miller (2004) resist this conclusion by arguing that in such cases providing no treatment is “consistent with competent medical care” (p. 571). But this resolves one difficulty by raising another. In particular, why is it the case that the provision of an established effective treatment is required in some cases but optional in others? Component

analysis appeals to the standard of competent medical care to determine whether or not it is acceptable to withhold established effective alternatives from participants in the control arm. But, presumably, clinicians do recommend these treatments to patients experiencing these conditions, just like they do recommend standard therapies to patients suffering from more severe medical problems; and in both cases, competent patients can consent to treatment or withhold their consent and refuse care. If there is a moral difference in these cases—if the clinician's duty differs in these two cases—it is not grounded in a fact about current medical practice. It is grounded in the kind of consideration that the integrative approach highlights, namely, that more severe conditions threaten the basic interests of individuals, whereas these minor conditions primarily affect an individual's personal interests.

Instead of dividing components of research into therapeutic and non-therapeutic, the integrative approach focuses attention on the basic interests of participants and requires that the level of care and protection provided to those interests must not be known or credibly believed to be inferior to any available alternative. Because these interests are so critical to being able to formulate, pursue, and revise a life plan, they constitute the space within which free and equal persons have a just claim to equal treatment. As a result, the integrative approach formulates equipoise as a practical test that ensures that the basic interests of study participants are respected by ensuring that every study participant receives a level of care and concern for their basic interests that would be recommended by at least a reasonable minority of experts.

In the integrative approach, the use of a placebo control can be justified, in principle, even in cases where established effective treatments exist as long as the risks of non-treatment are effectively limited to the personal interests of participants. If those risks implicate the basic interests of participants, then there must be conflict or uncertainty in the expert medical community about whether provision of the placebo makes recipients worse off than they would be if they were provided any available alternative.

Finally, the integrative approach recognizes that when individuals pursue their particular life plan, they often willingly accept risks to their basic interests. Not only is it not possible to live a fulfilling life without accepting risks to those interests, but it would not be desirable since avoiding all risks to one's basic interests would eliminate most meaningful life plans from consideration. As a result, in order to treat study participants as free and equal persons, it must be permissible for them to accept some affirmative risks to their basic interests that are not offset by the prospect of direct medical benefit and that stem from research participation. The ethically difficult question lies in determining what the threshold for such risks should be.

The integrative approach adopts a third operational criterion for equal regard that seeks social consistency between the limits on such risks in research studies and the limits on such risks in other relevantly similar social activities:

> *Social Consistency*: In all cases, the cumulative incremental risks to the basic interests of study participants that are not offset by the prospect of direct benefit to the participant must not be greater than the risks to the basic interests of individuals permitted in the context of other socially sanctioned activities that are similar in structure to the research enterprise.

To count as relevantly similar, such activities should involve public service, they should be subject to sufficient regulation that the risks they involve are not regarded as independently objectionable or unreasonable, and the risks associated with those activities should not contribute to the value of that activity for those who pursue it. Given these criteria, paramedics, volunteer firefighters, lifeguards, and other "first responders" may provide benchmarks for activities that are structurally similar to the research enterprise.

In each of these comparator cases, the level of permissible risk may change in relation to the urgency of the need in question or in relation to the different kinds of values that are at stake. So, for example, the threshold on permissible risks for a paramedic might depend on the immediacy and severity of the danger others are facing, just as the level of acceptable risks for firefighters may change depending on whether they are attempting to save property or a human life or whether they are trying to avert a risk that might in the future endanger a person. Similarly, in research, the degree to which individuals might be allowed to accept risks to their basic interests that are not offset by the prospect of direct benefit can vary according to the social value of the information a study is likely to generate.

Setting these risk thresholds in practice will require judgment, but the moral goal of such judgments is clear—the point is to ensure that there is a publicly available justification for the claim that each study participant is treated as the moral equal of every other participant within the study and of the community members in whose name research is conducted and who are likely to be its future beneficiaries. Together, these conditions ensure that those who participate in research are free to contribute to a valuable social undertaking without being subject to arbitrary risks and burdens and without having their status as a free and equal person compromised in the process.

As a result, when effective interventions exist for conditions that impact the basic interests of persons, a placebo would only be permissible if there were no feasible alternative design that could answer the relevant question and any risks to participants' basic interests can be reduced to the point that they are consistent with the risks to a person's basic interests that are permitted for other social groups who voluntarily accept personal risks for the common good.

Finally, the integrative approach regards the relevant uncertainty as having been eliminated or resolved (the fourth of our basic questions) when sufficient evidence has been generated to substantially reduce or eliminate the conflict or uncertainty in the relevant expert community. As a result, research that satisfies these conditions has a strong prima facie claim to generating socially valuable information because that information directly addresses an uncertainty or conflict in the expert community regarding how to best safe-

guard or advance the basic interests of persons. Resolving that conflict provides information that clinicians, policymakers, and other stakeholders, including patients or other individuals, need in order to make more efficient use of scarce resources for the purpose of safeguarding interests that every community member has an equal claim that the basic institutions of their community respect and advance.

9. The Integrative Approach and RAR

The integrative approach is grounded in a fundamental concern for the basic interest of each person in being able to formulate, pursue, and revise a life plan of their own. It thus gives specific operational content to the observation of Hans Jonas that "Human experimentation for whatever purpose is always also a responsible, nonexperimental, definitive dealing with the subject himself and not even the noblest purpose abrogates the obligations this involves" (1969, 220) and Kukla's claim that "the research enterprise gives investigators no license to compromise citizens' moral entitlements to justice, respect, and welfare protection" (2007, 184).

This fundamental concern for the basic interests of individuals provides a social foundation for Freedman's social conception of uncertainty. To illustrate the power of this combination, it is useful to consider how the integrative approach deals with the most difficult case for any conception of equipoise, namely, trials that use RAR.

In designs that use RAR, the probability that an individual will be randomized to one of n interventions in the trial changes dynamically as the trial progresses. An initial block of participants is randomized with a $1/n$ probability of receiving each of the n interventions in the study. After outcomes are observed from individuals in this initial block, the probability of being allocated to an intervention is updated in light of the outcomes observed in participants who received each intervention. Imagine that individuals who received intervention A had slightly better outcomes than individuals who received intervention B, who fared slightly better than those who received C. In this case, the randomization weights would be updated to give a slightly greater chance of allocating the next patient to A than to B than to C. The randomization weights are updated again after the next block of outcomes are observed until prespecified cutoff points are met for dropping underperforming interventions or accepting one intervention as superior to the others.

It has been argued that studies using RAR violate equipoise because as evidence accrues that one intervention is outperforming others, some participants are still allocated to other interventions (just with a lower probability). It is tempting to treat the trial as a kind of group agent whose beliefs about the relative merits of the interventions in question are represented by the randomization weights that reflect the relative performance of these different interventions. Conceived of in this way, it would violate the duty of care to allocate anyone to an intervention other than the one that is best performing (Saxman 2015). However, intuitive as it may be, this view suffers from all of the problems outlined for views that model uncertainty as a property of the beliefs of a single agent (London 2018).

In contrast, the integrative approach treats such trials as modeling an idealized health system in which the randomization weights of the trial represent the relative proportion of experts in this idealized community who favor each of the *n* interventions. Treatment recommendations for participants are generated in this model by drawing an expert at random from the diversity of experts in the community to which the interventions under study are most relevant (London 2018).

This is an idealized health system in two respects. First, as evidence emerges from the trial, these various experts update their judgments using clearly specified rules. Second, participants are allocated to experts at random. When a trial models the diversity of expert judgment in the medical community, randomization weights do not reflect the views or beliefs of any agent; they model the relative proportion of experts who favor each intervention. As evidence emerges that favors A, for example, some members of the B-favoring or C-favoring communities may become agnostic about the merits of B or C or may begin to favor A. This change in judgment means that there are slightly more A-favoring experts now than B-favoring or C-favoring experts. Nevertheless, as in the real world, there remain well-informed experts who continue to favor B or C and who would thus recommend B or C as the best intervention for the problem in question. As experts update their judgments in light of evidence and, for example, the A-favoring community increases in relative size, randomly drawing an expert whose judgment will determine which treatment an individual receives entails that there is a higher likelihood that the next participant will receive what an A-favoring expert would recommend for them.

Those who treat the trial as though it is a single agent whose beliefs are being updated in light of evidence would be required to stop it after the initial block of data is seen. While that evidence would change the mind of some experts, it would not fundamentally alter the treatment practices and judgments of other clinicians or of policymakers in the relevant community. Hence, that position is self-defeating—it stops the trial without fundamentally altering the disagreement in the expert community.

When studies using RAR reflect the diversity of fully informed expert judgment in the relevant community, they can satisfy the practical test that has been outlined because every individual is guaranteed to be allocated to an intervention that would be recommended as best for them by at least a reasonable minority of experts. When this is the case, such trials also satisfy the requirement to show special concern for the basic interests of participants, as defined. Study participants are not knowingly treated in ways that are inferior to any other study participant or to anyone in the community the study is designed to benefit. As long as the study satisfies No Unnecessary Risks and cumulative risks of study participation satisfy Social Consistency, studies involving RAR are capable of generating socially valuable knowledge while respecting the Principle of Equal Concern (London 2018).

10. Social Value for Whom?

Rebecca Kukla has rightly noted that formulating the equipoise requirement in terms of the narrow relationship between physicians and patients isolates that requirement from the larger social, cultural, and economic context in which health services are delivered and research is carried out (2007). From the fact that some intervention is known to bring about a beneficial effect in one context, it does not follow either that it will have the same effect in another context structured by different resource constraints or that all persons have an equal claim to receive that same intervention no matter where they reside (London 2001). For example, during the 2014 Ebola outbreak in West Africa, patients with Ebola virus disease in the United States were treated in state-of-the-art intensive care units (ICUs) with robust staffing and access to a wide range of supportive care and containment measures. Such facilities are relatively scarce even in high-income countries and virtually unknown in the West African countries that experienced the largest Ebola outbreak in history. It cannot be the case, therefore, that any treatment strategy designed to be implemented in a context such as that in West Africa—a large-scale outbreak in a context with relatively weak infrastructure—must be expected to perform at least as well as the best possible care that could be provided to the individual patient in the world's best ICU.

At the same time, the amount and kind of health resources available in different countries often depend on a wide range of circumstances, some of which relate to the extent to which political authorities and other powerful actors use their power, authority, or resources to advance the basic interests of its citizens or for purposes that frustrate this goal (London 2000). The mere fact that an intervention is not currently available in a place does not address the deeper and more relevant question of whether it could be used in a sustainable way within that country to achieve important health objectives (London 2001, 2005; Kukla 2007). This insight also generalizes beyond medical interventions as we recognize that a wide range of stakeholders in different fields are involved in research with humans to study the effects of a diverse set of interventions or policies that affect the welfare and rights of participants (MacKay 2018).

As it is framed here, the Principle of Equal Concern requires equal treatment of study participants and members of the larger community whose interests that research is intended to serve. As a result, different formulations of this principle are possible, depending on how the boundaries of the relevant community are determined. On the human development approach, the relevant community is defined by shared basic structures and institutions that affect the ability of individuals to formulate, pursue, and revise a reasonable life plan. Such structures and institutions include individual and public health systems, social welfare programs, and institutions for political participation (London 2005, 2008). Because the shared social institutions that structure the lives and opportunity of individuals are usually regulated at the national level, this creates a default presumption that study participants have a right to receive treatment equal to that of their compatriots —the other residents and citizens of their country—recognizing that equal treatment is

relative to the de jure baseline of the level of care that is attainable and sustainable in the social, political, and economic contexts of that nation (London 2000; Kukla, 2007).

In a similar way, MacKay has argued that it is governments that "have duties of justice to provide their residents with access to particular types of goods, and/or to realize particular outcomes" (2017, 3). As such, he argues, study participants in a wide range of research are entitled to a baseline that is practically attainable and sustainable, where this means (a) that it is "consistent with residents' rights" and (b) the "government could implement it long-term, given a just system of resource procurement and allocation" (2017, 4).

In contrast, Wenner is reluctant to identify the relevant community with national boundaries, in part because there can be substantial inequality within nations. Instead, she has argued that research should be required to generate social value at the local community level, where this is operationalized in terms of the knowledge needed to alter the decisions of policymakers, funders, or aid agencies (2017). This raises the prospect that one response to a health inequality within a nation might be to conduct the research necessary to convince local stakeholders to alter their policy decisions. This potentially creates a tension between the claims of residents of a nation to equal treatment from their basic social institutions, including access to existing resources—such as healthcare or public health resources—and the value to local policymakers from answering a particular research question. However, Wenner has recently defended what she calls the basic structure model of stakeholder obligations in research. Within this model, the relevant community may be larger than the state. In particular, that view emphasizes that the knowledge produced in medical research can impact the treatment practices or decisions of stakeholders in a wide range of venues, and, as such, "all individuals have moral standing to claim consideration in the determination of which questions are studied and how those studies are used to benefit themselves, their communities, and the health systems within which they participate" (Wenner 2018, 30–31).

For our present purposes, it is sufficient to emphasize that the question of how to determine the relevant baseline or care and protection that a study must not fall below—the standard of care that sets the minimum requirements to which all study participants are entitled—is not unique to the topic of equipoise. Rather, it is a question that must be answered by any framework for assessing and regulating risk in research. It might appear to be a new complication encountered by frameworks that reject the narrow conception of equipoise as grounded in role-related professional obligations, but this appearance is deceiving. Rather, the fact that this was not a topic of debate at the inception of the equipoise requirement reveals the extent to which that discussion was isolated from the larger social and political context in which research, healthcare, and other social services are carried out.

As a wider range of players, from local, state, and national governments to nonprofits and international organizations, begin to use randomization to evaluate interventions outside of clinical medicine in areas like public health, aid programs, nutrition, educational poli-

cy, and beyond, it is important that ethical frameworks for regulating research are grounded in normative requirements that are sufficiently general that they are seen as appropriate for, and binding on, these different players in these different areas. The principle of equal concern provides such a foundation, linking the ethics of research with humans to moral values that ought to regulate the conduct of private individuals as well as the operation of important social institutions. Demonstrating the compatibility of equipoise with this principle is, therefore, critical to ensuring that as more players in a wider range of social institutions move to evidence-based practice, they do so in a way that does not denigrate, harm, exploit, or dominate individuals or groups in the process.

11. Conclusion

Critics of the concept of equipoise fasten onto the numerous flaws that plague any framework that locates the relevant uncertainty in the mind of the individual medical professional. Critics are correct in holding that such frameworks are overly narrow and ultimately unworkable. But they are incorrect in holding that these defects mar every framework that relies on uncertainty to ensure that research has a strong, prima facie claim to generate social value while also respecting the rights and interests of study participants.

As a result, the strongest defense that can be made of a framework that employs the concept of equipoise is to show how well it can integrate these desiderata. It is an advantage of the integrative approach that it provides a framework that advances socially valuable science while giving clear, operational guidance for ensuring that study participants are not subject to neglect, abuse, or arbitrary treatment in the process.

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Alex John London

Alex John London is Clara L. West Professor of Ethics and Philosophy and Director of the Center for Ethics and Policy at Carnegie Mellon University. His book, For the Common Good: Philosophical Foundations of Research Ethics is forthcoming from Oxford University Press and he is co-author of Ethical Issues in Modern Medicine, now in its 8th edition (McGraw-Hill, 2012).