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CHAPTER 24

# CLINICAL EQUIPOISE: FOUNDATIONAL REQUIREMENT OR FUNDAMENTAL ERROR?

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A PROFOUND moral tension lies at the heart of research ethics (Jonas 1969; London 2003). On the one hand, medical research is an important and socially valuable activity whose goals are to advance our limited understanding of health-related issues by utilizing scientific and statistical methods to investigate clinically relevant questions. By pushing forward the boundaries of knowledge, medical research ultimately aims to improve the standard of medical care available to future patients. On the other hand, medical research requires the participation of individuals, each of whom has his or her own interests and needs. As high-profile scandals in research ethics powerfully illustrate, the pursuit of sound science and statistical validity may require research activities that diverge from—or which are simply antithetical to—the best interests of present participants. One of the fundamental challenges of research ethics, therefore, has been to articulate a framework for advancing

scientifically meritorious research without also sacrificing the interests of research participants to the greater good of scientific progress.

One of the most promising frameworks holds that as a necessary condition for ethically acceptable human-subjects research, clinical trials must begin in and be designed to disturb a state of equipoise. The concept of 'equipoise' was first articulated by the philosopher Charles Fried in the mid-1970s. Fried claimed that physicians owe a 'duty of personal care' to their individual patients, a duty that may be in tension with important features of the gold standard for medical research, the randomized clinical trial (RCT). According to Fried, it would be consistent with the duty of personal care to enroll a particular patient in a clinical trial only as long as the physician was uncertain about the relative therapeutic merits of the interventions to which the patient could be randomly assigned in the trial (Fried 1974). He referred to this state of uncertainty—being equally poised between the available options—as 'equipoise'.

Perhaps the clearest and most ambitious use of the concept of equipoise appeared roughly a decade later in the work of Benjamin Freedman (Freedman 1987, 1990). Freedman argued that equipoise is a necessary—though not always a sufficient—condition for ethical human-subjects research, but he rejected Fried's formulation of equipoise. Since that time, the equipoise requirement has played an important role in research ethics and subsequent thinkers have gone on to offer a variety of interpretations or refinements of the concept. From its inception, however, the equipoise requirement has also been the subject of searching criticism and vociferous debate. The turn of the new millennium has brought what may be the most concerted and far-reaching criticisms of this approach. As a result, research ethics may now be at a critical juncture as the field struggles to clarify issues that touch on its very foundations (Kaebnick 2003).

The most prominent and critically significant criticisms of the equipoise requirement can be grouped under three general headings. Objections from *indeterminacy* point to proliferating conceptions of equipoise and question the extent to which the concept has a determinate meaning. In the first section below I clarify important features of competing conceptions of equipoise to reveal a *set* of well-formed conceptions of equipoise. In order to assess the merits of these various formulations, I turn to objections from *utility*. These objections hold that the equipoise requirement does not resolve the inherent tension between advancing science and safeguarding the interests of individual participants. I argue that these criticisms are either misplaced, or apply only to a limited subset of possible formulations of the concept. Among those formulations to which they do not apply, I claim, is what Freedman calls clinical equipoise.

Any view of equipoise, however, faces perhaps the most radical and far-reaching objections from *moral foundations*. These objections hold that the equipoise requirement conflates the ethics of medical research and the ethics of clinical medicine. Once this conflation is recognized, this position holds, research can be given a new foundation on the imperative to avoid exploiting research participants. I argue that what is novel in this critique is not as successful as its proponents claim and that the ultimate success of this approach actually hinges on a version of the objection from utility. Nevertheless, this criticism highlights the limited scope of applicability of the equipoise requirement. I conclude, therefore, by describing the outlines of what I call an 'integrative approach' to clinical trials. This approach represents one way in which the normative requirements of equipoise and the non-exploitation approach might be unified under a single, broad framework.



## Objections from Indeterminacy: Whose Uncertainty? Which Equipoise?

One very basic charge leveled against the equipoise requirement is that it is something of a misnomer to speak of 'the' equipoise requirement. Rather, the growing literature on this topic is littered with alternative conceptions of equipoise and numerous interpretations of the corresponding equipoise requirement. Confronted with such variety, even those who are sympathetic to the ambitions of the equipoise requirement may be frustrated at the lack of clarity and uniformity that surrounds the subject (Ashcroft 1999; Miller and Weijer 2003). A less sanguine appraisal, however, holds that until proponents of this approach provide a determinate account of the concept of equipoise and its associated moral requirements it is not possible to evaluate the merits of this approach or to implement it consistently in practice (Sackett 2000).

To illustrate something of the diversity that motivates this charge, consider the following extended example. When Freedman opens his seminal paper 'Equipoise and the Ethics of Clinical Research', he writes:

> In the simplest model, testing a new treatment B on a defined population P for which the current accepted treatment is A, it is necessary that the clinical investigator be in a state of genuine uncertainty regarding the comparative merits of treatments A and B for population P. If a physician knows that these treatments are not equivalent, ethics requires that the superior treatment be recommended. (Freedman 1987: 141)

In this general introductory statement, Freedman follows Fried's formulation in which the uncertainty that is required to justify the trial is situated in the mind of the individual clinical investigator. Freedman does not himself endorse this view, however. He associates this position with what he calls 'theoretical equipoise', which he rejects. He refers to the view which he endorses as 'clinical equipoise', according to which the requisite uncertainty is located in the larger expert medical community. Equipoise obtains, on the latter view, when 'there is no consensus within the expert

clinical community about the comparative merits of the alternatives to be tested' (Freedman 1987: 144).

Confusion about this feature of clinical equipoise persists in the literature, however. For example, Ashcroft (1999: 320), describes clinical equipoise as:

> equipoise in the mind of the intending physician regarding treatment options. In many ways, this remains the best formulation. For clinical equipoise is a necessary condition on entering a patient into a trial, and if any clinician is not in clinical equipoise regarding a patient or a trial, then this (or any other of his patients) should not be entered by him or her into the trial. The ethical duty of the physician here is clear enough.

What Ashcroft refers to as 'clinical equipoise', however, is not what Freedman articulated. Freedman explicitly states that clinical equipoise can exist when there is 'a split in the clinical community, with some clinicians favoring A and others favoring B', and that clinical equipoise is 'consistent with a decided treatment preference on the part of the investigators. They simply recognize that their less favored treatment is preferred by colleagues whom they consider to be responsible and competent' (Freedman 1987: 144).

What Ashcroft identifies as 'clinical equipoise', therefore, is actually what Freedman identified as 'theoretical equipoise' and what Fried had referred to simply as 'equipoise'. Adding to the complexity, within literature from the United Kingdom this position is also commonly referred to under the name of 'the uncertainty principle' (Hill 1963; Peto *et al.* 1976; Peto and Baigent 1998; Sackett 2000). In contrast, what Freedman actually describes as 'clinical equipoise', Ashcroft calls '*collective* or *professional* equipoise', terms that are also more common among writers from the United Kingdom (e.g. Chard and Lilford 1998).

As this example illustrates, the proliferation of different nomenclatures and terminologies has exacerbated the difficulty of isolating and evaluating the underlying positions to which those terms are intended to refer. Putting such confusions aside, however, it is possible to construct as many conceptions of equipoise as there are combinations of alternative positions on four central issues.

The first issue, illustrated above, concerns *who ought to be in equipoise* or, in other words, *where the relevant uncertainty ought to be located*. In addition to the possibilities mentioned already, a view sometimes referred to as 'narrow patient equipoise' (Ashcroft 1999: 321) requires that the individual patient have no preference between treatment alternatives (Johnson *et al.* 1991; Veatch 2002), whereas 'wide patient equipoise or *community equipoise*' requires not only that patients and care givers be in equipoise, but that family members and the broader 'community' be in equipoise as well (Gifford 1995; Karlawish and Lantos 1997). Although these different accounts of where equipoise ought to be located are often treated as mutually exclusive, several writers have argued for the necessity of equipoise at more than one of these levels (Chard and Lilford 1998; Miller and Weijer 2003; Mann *et al.* 2005).



Such differences over where to locate the relevant uncertainty are only the first of four possible dimensions along which alternative conceptions of equipoise can be distinguished. In addition to deciding whose uncertainty is relevant for establishing equipoise we must also explain *what the epistemic threshold is for the state of uncertainty*. For example, Freedman was eager to reject the view that he attributed to Fried and which he referred to as 'theoretical equipoise', because he associated this position with a particularly fragile epistemic threshold. A fragile epistemic threshold is disturbed as soon as there is any reason to think that the odds that one treatment will be more successful than another are tipped past 50:50 (Freedman 1987: 143). On this model, equipoise requires an 'exact balance' between the prospects for benefit between each alternative, where such a balance can be tipped by something as flimsy as a hunch or a gut feeling.

In contrast, Freedman claimed that 'clinical equipoise' embodies a more robust epistemic threshold. According to this view, equipoise persists until evidence for the superiority of one intervention emerges that would be sufficient to forge a consensus in the relevant expert clinical community. This more robust epistemic threshold requires that the evidence supporting a claim to superiority be sufficiently compelling that it will influence the practice behavior, not just of one physician, but of the community of physicians. Clinical equipoise thus rests on an epistemic threshold that is set by the presence or absence of consensus in the relevant expert medical community. A third set of alternatives rely on decision theoretic tools to deal with this issue. For example, the Kadane–Sedransk–Seidenfeld design (KSS Model) creates computer models of the clinical judgments of expert clinicians and then applies methods from Bayesian decision theory to update those models as new data are generated from the trial. In such a decision theoretic approach, the epistemic threshold is operationalized as the point at which the data is sufficient to change the treatment allocations recommended by the decision models (Kadane 1996).

Conceptions of equipoise can be also be distinguished according to a third dimension: *the evaluative focus of the decision maker's concern*. A one-dimensional conception of equipoise focuses critical attention on a single attribute of the set of interventions in question, usually their relative efficacy. Efficacy here refers to an intervention's brute impact on a single, dominant clinical endpoint, such as tumor reduction or infection control. In contrast, a multidimensional conception of equipoise focuses critical attention on an all-things-considered evaluation of the various factors that determine the attractiveness of the interventions in question (Chard and Lilford 1998; Gifford 2000; London 2001). Freedman (1987: 143) refers to this as an intervention's 'net therapeutic index', in which its efficacy is evaluated along with factors such as its side-effect profile, ease of administration and use, and so on.

Finally, different interpretations of the equipoise requirement can be distinguished in terms of *the way they ground the moral obligation* to ensure that equipoise

obtains in clinical trials. Nearly all extent defenses of the equipoise requirement appeal to role-related obligations of physicians. For example, Fried was motivated by a concern for the 'duty of personal care' that clinicians owe to their patients (Fried 1974), and Marquis refers to a similar concern under the heading of the 'therapeutic obligation' which he explicates as follows: 'A physician should not recommend for a patient therapy such that, given present medical knowledge, the hypothesis that the particular therapy is inferior to some other therapy is more probable than the opposite hypothesis' (Marquis 1983: 42).

In both cases, the equipoise requirement is a constraint that is grounded in an obligation that physicians owe to their patients. Because Marquis's view of the therapeutic obligation builds in controversial features from some of the dimensions of equipoise mentioned here, others have chosen to ground the requirement simply in the clinician's fiduciary relationship to the patient (Miller and Weijer 2003). The latter approach views the duty of personal care in a way that is consistent with a more robust epistemic threshold, but it retains the traditional emphasis on role-related obligations that stem from the doctor–patient relationship.

In the integrative approach that I develop below, the equipoise requirement is grounded in a set of general values whose moral force does not depend on or emerge within the doctor–patient relationship. As I argue below, grounding the integrative approach in a broader set of social values gives it a significantly broader scope than traditional versions of the equipoise requirement. It also enables the integrative approach to avoid a tension that I argue undermines Freedman's attempt to embrace both the therapeutic obligation as the normative foundation of the equipoise requirement and a conception of equipoise that locates the relevant uncertainty, not in the mind of the individual clinician, but in the broader expert medical community (London 2006*a*, *b*).

This very brief discussion at least provides a sense of *the matrix of possible formulations of the equipoise requirement that emerge from different combinations of views on each of the above dimensions*. This matrix of possibilities is mapped out for a sample of representative views in Figure 1. It should be emphasized, though, that Figure 1 presents a fairly crude matrix. It is sufficient to show, for example, that what Freedman termed 'theoretical equipoise' and what is often referred to as 'the uncertainty principle' are the same view. However, some categories, such as decision theoretic approaches to the epistemic threshold, are too crude to reveal genuine differences that may exist between models that use different decision theoretic methods. These details can be put aside for the present discussion, however.

Although this brief analysis establishes that there are a variety of determinate formulations of equipoise, it provides little guidance for narrowing these options to a more attractive subset. To determine which of these alternatives is most philosophically and practically attractive, we must turn to objections from utility.



| | Whose uncertainty | | | | Epistemic threshold | | | Evaluative focus | | Normative grounds | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patient | Clinician | Medical community | Larger community | 50:50 fragile | Community consensus | Decision theoretic | One-dimensional | Multidimensional | Role related | Broader moral values |
| Freedman's clinical equipoise (1987) | | | X | | | X | | | X | X | |
| Theoretical equipoise (Fried as understood by Freedman) | | X | | | X | | | X | | X | |
| Uncertainty principle | | X | | | X | | | X | | X | |
| Fried as understood by Miller and Weijer (2003) | | X | | | | X | | | X | X | |
| Miller and Weijer (2003) | | X | X | | | X | | | X | X | |
| Chard and Lilford (1998) | X | X | X | X | | | X | | X | X | |
| Integrative approach | X | | X | | | | X | | X | | X |

**Fig. 1 Matrix of dimensions along which versions of the equipoise requirement may be constructed.**

## Objections from Utility

The most significant challenge to the utility of equipoise is the charge that it fails to reconcile (*a*) the duty to safeguard the interests of present participants with (*b*) the statistical and scientific requirements necessary to generate reliable, generalizable data. This perceived failure is what underwrites widespread claims that the equipoise requirement is too restrictive because it sacrifices scientific progress to a misplaced desire to protect certain perceived interests of participants. As I will indicate later on, this perceived failure also underwrites claims that some formulations, such as clinical equipoise, are too permissive because they permit participant interests to be sacrificed to the perceived interests of scientific progress.

Claims that the equipoise requirement cannot resolve the tension between these competing ends hinge centrally on two independent issues. The first concerns the nature and extent of the duty to safeguard the interests of present participants. Call

this the *responsiveness to participant interests condition*. The second concerns the proper epistemic threshold and evaluative focus of the equipoise requirement. Call this the *content of equipoise condition*. Claims that the equipoise requirement is overly restrictive usually presuppose a symmetric account of these conditions in which both the duty to safeguard the participant's interests and the content of equipoise embody a fragile epistemic threshold located in the mind of the individual clinician. Marquis's formulation of the therapeutic obligation is probably the clearest example: 'A physician should not recommend for a patient therapy such that, given present medical knowledge, the hypothesis that the particular therapy is inferior to some other therapy is more probable than the opposite hypothesis' (Marquis 1983: 42).

As Marquis and others argue (Gifford 1986; Hellman 2002), only in relatively rare circumstances will a physician believe that it is equally probable that two or more therapeutic options offer a particular patient the same degree of benefit. Without such a fragile state of equipoise, however, a clinical trial between therapeutic alternatives could not ethically be initiated. Alternatively, if it were the case that such a fragile state of equipoise obtained, critics argue, then it would not persist long enough to bring a clinical trial to its desired conclusion. As soon as the trial generates its first data points the physician is obligated to look for trends. If one option appears to fare better than another, the hypothesis that one option is inferior to the other would be more probable than its opposite. Once this fragile state of uncertainty is disturbed, the trial can no longer be justified on the grounds that equipoise obtains.

The equipoise requirement therefore appears to be overly restrictive because it would effectively prohibit the vast majority, if not the entirety, of clinical research. As a result, many reason that, since clinical research is such an important and socially valuable activity, what the above argument actually shows is that we must reject the equipoise requirement altogether. If we cannot reconcile the therapeutic obligation with the demands of sound science, then the necessity of scientific progress can legitimize the abrogation of the therapeutic obligation. In other words, if the interests of present participants must be weighed against the value of scientific knowledge and benefits to future patients, then it must be permissible to subordinate the former to the latter (Marquis 1983; Gifford 1986; Hellman 2002; Miller and Brody 2003).

In his defense of clinical equipoise, Freedman claimed to be able to avoid this particular objection from utility. The nature of Freedman's argument, however, remains poorly understood and is frequently misrepresented. In particular, critics often fail to realize that Freedman too offers a symmetric account of the responsiveness to participant interests condition and the content of equipoise condition. However, Freedman's account is symmetric because both conditions embody a robust epistemic threshold located in the state of consensus in the clinical community. In other words, while it is widely appreciated that Freedman rejects a view of equipoise that embodies a fragile epistemic threshold, critics often overlook the fact that he



also offers a distinctive account of the nature and extent of the duty to safeguard the interests of participants which rejects this fragile epistemic threshold. For Freedman, the obligation to safeguard participant interests is determined by the requirements of sound medical practice but, like Fried before him, he thinks that the requirements of sound medical practice are determined by the consensus of the expert medical community (Freedman 1987: 144; Miller and Weijer 2003). Let me explain.

It is best to begin with Freedman's view of the content of the equipoise requirement. Consider the following pair of situations. In one case, the members of the expert medical community are uncertain about the relative therapeutic merits of two interventions, A and B. Such a state of affairs might obtain, for example, if A is the current treatment for a medical condition, say A is an antibiotic treatment for a particular bacterial infection, and treatment B is a new antibiotic that has shown promise in treating this infection. In the laboratory and in Phase I and II clinical trials B has been shown to be safe and promising in humans. Assume further that A is often not well tolerated by patients because of its side-effects and that one of the hopes for treatment B is that it will have similar efficacy with less burdensome side-effects. At the current time, however, there is not enough experience with B to predict reliably whether it is sufficiently efficacious and well tolerated in patients as to be equally attractive or more attractive than A. We can refer to this sort of uncertainty in the clinical community as *clinical agnosticism* to reflect the idea that the members of the expert medical community have not yet made determinate judgments about the relative therapeutic merits of A and B.

The second scenario presents a case of what we might call uncertainty as *clinical conflict*. Imagine that things are largely as they were in the previous scenario with the following exception. In this new case, more is known about the therapeutic merits of B, and members of the expert medical community have formed definite opinions about the relative therapeutic merits of A and B. Now imagine, however, that the community of expert clinicians is divided in their preferences, with some preferring A over B and some preferring B to A. The division need not be 50:50, since what is at stake is not an issue of popularity (London 2000). Rather, the community may be in conflict as long as a 'reasonable minority' of informed and reflective expert clinicians would offer advice to patients that conflicts with the advice of the majority (Freedman 1987; Kadane 1996; Miller and Weijer 2003).

Unfortunately, Freedman lumps both clinical agnosticism and clinical conflict together as cases of uncertainty in the expert medical community. As I argue below, clearly distinguishing these scenarios helps to avoid confusion and adds an additional level of sophistication to the defense of the equipoise requirement. Nevertheless, Freedman seems to hold, correctly, that in each of these scenarios it is permissible to carry out a randomized clinical trial in which patients with the particular bacterial infection are assigned at random to either treatment A or treatment B (Freedman 1987: 144). That is, in each case clinical equipoise obtains because there is no consensus in the relevant expert medical community about

which treatment is best for patients with the relevant medical condition. This lack of consensus also provides the proper target for clinical research in that there is great social and clinical value in trials that are designed to disturb or to eliminate such a state of agnosticism or conflict. As a result, in addition to playing an important ethical role in clinical research, Freedman took the concept of equipoise to play an important epistemic or scientific role by identifying the proper focus of clinical research initiatives.

Freedman should be understood, therefore, as defending clinical equipoise on the ground that it not only allows clinical trials to be initiated, but permits their being carried out until such a time as they generate data that is sufficient to eliminate clinical agnosticism or to resolve the state of conflict in the clinical community. Finally, by targeting clinical research at questions about which the expert clinical community is conflicted, clinical equipoise ensures that clinical research targets important questions whose resolution will advance the care of future persons. As such, it ensures that clinical research has both scientific and moral merit.

It is at this point, however, that critics charge clinical equipoise with being overly permissive in allowing the interests of participants to be sacrificed to the perceived interests of scientific progress. Consider that within standard, fixed sized RCTs researchers stipulate in advance a P value or significance level (usually $\leq .05$) for ruling out the possibility of mistakenly accepting the hypothesis that the experimental intervention is superior to the control. As data are acquired over time, trends may emerge. Critics hold that in any trial that ultimately produces statistically significant results, there will be some point prior to reaching the desired level of statistical significance at which the hypothesis that one intervention is inferior to the other is sufficiently probable that allowing another patient to enroll in the trial, or allowing the trial to continue for current participants, violates the therapeutic obligation (Gifford 2000). Such scenarios are most compelling when they occur in a trial that is intended to eliminate clinical agnosticism. Surely, the critic claims, there is some point before the trial reaches the desired level of statistical significance at which it is sufficiently clear that one intervention is inferior to another that continuing with the trial violates the therapeutic obligation.

Three responses, however, are open to the proponent of clinical equipoise. First, if the interim data from the trial are sufficiently persuasive that they resolve the agnosticism of the clinical community in favor of one intervention over another, then the trial should be stopped because equipoise has been disturbed. Second, if, in contrast, only some clinicians are persuaded by the interim data, then we have only moved from a state of clinical agnosticism to a state of clinical conflict. In this case, however, equipoise still obtains and it is *permissible* to carry out the trial until consensus emerges and the conflict is resolved.

Third, and more fundamentally, however, this criticism of the equipoise requirement retains a view of the therapeutic obligation that Freedman rejects. That is, the objection presupposes an asymmetric relationship between the conditions above



according to which the responsiveness to participant interests condition embodies a fragile epistemic threshold in the mind of the individual clinician and the content of the equipoise condition embodies a more robust epistemic threshold situated in the clinical community. Freedman's account of these conditions, however, is symmetric in that both conditions embody a robust epistemic threshold located in the state of consensus in the clinical community. This is a point worth emphasizing.

Freedman claims that the content of the obligation to safeguard the interests of trial participants is determined by the norms of sound medical practice. When there is conflict in the clinical community, however, he claims that '"good medicine" finds the choice between A and B indifferent' (Freedman 1987: 144). The use of the term 'indifferent' in this context is somewhat misleading because it treats cases of clinical conflict as though they were cases of clinical agnosticism. It is more accurate, therefore, to say that in cases of clinical conflict good medicine is conflicted. Moreover, when good medicine is conflicted, 'it is likely to be a matter of chance that the patient is being seen by a clinician with a preference for B over A, rather than by an equally competent clinician with the opposite preference' (Freedman 1987: 144). In this respect, enrolling in a clinical trial in which one is randomized to either A or B is not significantly different from chance determining that one sees a clinician with one treatment preference rather than an equally competent clinician with the opposite treatment recommendation. In both cases, the individual receives a therapeutic option that is favored by some clinicians, but not by others (see also Kadane 1996).

There is another respect, however, in which these situations do differ dramatically. Conducting the clinical trial has the advantage of generating the data that is necessary to resolve the conflict in the medical community by clarifying the relative net therapeutic advantages of A and B. As a result, the option of conducting the clinical trial dominates the option of not doing so because, in both cases, patients and participants receive a treatment that is recommended for them by at least a reasonable minority of the expert medical community over a contrary recommendation from others in the expert medical community, but when this happens within the context of a clinical trial there is the added advantage of generating the data that will resolve the conflict to the benefit of future patients.

This response on behalf of clinical equipoise helps to motivate additional refinements to the theory that avoid further unnecessary confusion. For example, Freedman and others often speak as though equipoise concerns the relative therapeutic advantage of a set of treatment options relative to a *population of patients*. This has led some critics to claim that equipoise requires individual clinicians to abandon their commitment to the interests of individual patients (Hellman 2002). The reason is that it is possible for a clinician to be uncertain about the relative therapeutic merits of two interventions for a large population of people, but not to be uncertain in this regard when presented with a particular individual with particular symptoms and needs. If equipoise is applied at the level

of treatment populations, so the objection goes, it would permit clinicians to enroll an individual in a clinical trial even though, in their considered medical opinion, one of the options in the trial is dominated by another for that particular person.

While this objection rests on some serious and important issues, it does not apply to the interpretation of equipoise that I have outlined here. As my treatment of equipoise in this section illustrates, equipoise should be understood as focusing on individual potential trial participants and whether, in each case, the expert medical community is agnostic or in conflict over the relative therapeutic merits for treating this particular individual. Clearly, good clinical medicine will always provide recommendations to individuals only in so far as they instantiate a more general clinical profile. And there is nothing wrong with speaking of 'well-defined patient populations' if what we mean is sets of individuals described at the finest level at which sound medicine can discriminate. As a purely interpretive matter, I think this is probably what Freedman has in mind when he uses similar terminology. It is important to be clear about this point, however, because we want to avoid a focus on populations that would give rise to well-known statistical problems of the relevant reference class in which a treatment could be beneficial for the aggregate population but harmful to all but one sub-population of the aggregate (Kadane 1996; London 2001, 2006*a*).

This, however, is a point about the conditions on which participating in a clinical trial can be justified as an admissible option for potential individual participants. It should not be confused with a very different claim, namely, that individual physicians must somehow disavow their own conscience and hide their treatment preferences from their patients. Quite the opposite, in fact. Even Freedman claims that if the individual physician has a particular treatment preference, this should be disclosed to the patient and the physician should be free to advise the patient as their conscience dictates (Freedman 1987: 144). However, this liberty of conscience does not eliminate the obligation to disclose to the patient that there exists sufficient disagreement in the expert medical community that different experts might provide treatment recommendations that conflict with this physician's advice (Chard and Lilford 1998).

There is a more radical argument, however, that can be made against objections to clinical equipoise that rely on a view of the therapeutic obligation that incorporates a fragile epistemic threshold in the mind of the individual clinician. In particular, such views embody an unjustified vestige of medical paternalism in research ethics. They are paternalistic because they limit the set of admissible options from which a patient may choose to those that happen to be recommended by a particular physician, regardless of what other equally competent experts would recommend to the same patient. Simplifying for this example an approach used in the KSS model (Kadane 1996), we can define a therapeutic option as 'admissible' if it would be recommended for a particular patient by at least a reasonable minority of clinicians in the expert medical community. In the case of clinical conflict, if both A and B are



admissible interventions, so would be the option of participating in a clinical trial in which one would be randomized to either A or B. To prevent individuals from using their own values to choose from among the options of A, B, and the trial of A & B is to place an arbitrary restriction on individual choice. This restriction is arbitrary because it treats the opinions of a single expert as sovereign in the face of dissenting views from equally competent experts.

It is worth noting, however, that the above example reveals a fundamental tension within Freedman's account of clinical equipoise. In particular, it provides strong grounds for questioning whether the moral basis of the equipoise requirement ought to be located in the role-related obligations of the individual clinician. This is because such role-related obligations are traditionally understood as binding individual clinicians; each clinician is obligated to minister to the best interests of his or her patients. As a result, such role-related obligations require a conception of equipoise that locates the relevant uncertainty in the mind of the individual clinician. Freedman's position, therefore, appears to be untenable; one must either locate the relevant uncertainty in the expert medical community and find a different normative basis for the equipoise requirement, or one must accept the physician's duty of personal care as the moral basis of equipoise and locate the relevant uncertainty in the mind of the individual clinician (London 2006*a*).

To drive home the above point, consider the above situation from the standpoint of the patient. Each patient seeks advice that reflects the background beliefs and expert understanding of the physician, combined with an analysis of the available data regarding the therapeutic alternatives, to yield treatment advice that is tailored to the specific situation of the particular patient. The reflective patient may also realize, however, that different physicians may have different background beliefs, different interpretations of the available data about the therapeutic alternatives, and possibly different beliefs about the patient's specific clinical situation. Less idealistically, 'ordinary' patients may encounter these conflicting recommendations in person if they are able to seek several opinions about their case, or within the medical literature if they are able to research into the state of expert medical opinion. If the patient cannot determine with confidence which body of expert opinion is most likely to be correct, why would it be less reasonable to allow one's treatment to be allocated at random than to randomly decide to believe one expert rather than another? It should be noted, for example, that Marquis now appears to endorse this approach as a response to the conflict between the demands of clinical research and the therapeutic obligation (Marquis 1999).

To be clear, there may be reasons that might lead a potential trial participant to prefer one treatment over another even though expert opinion is conflicted. For example, a Christian Scientist might prefer treatment B to A if A involves an invasive surgical procedure while treatment B is medical in nature. In such a case, *the patient's* all-things-considered judgment about the available treatment options may not be conflicted once all of the patient's personal values are brought to bear

on the decision. When this is the case, participating in a clinical trial may not be a permissible option for that particular patient. However, participation would still be permissible for patients whose values are not sufficiently clear or not of sufficient personal priority to generate a determinate treatment preference in the face of conflicting medical advice. In these cases, both the patient and the clinician could endorse participation in a properly designed clinical trial as a means of resolving clinical conflict in the larger medical community. This example of clinical conflict provides additional reason to endorse a claim that others have made to the effect that equipoise ought to exist at a variety of levels (Chard and Lilford 1998). It also provides a clear focus for the goals of the informed consent process: to ensure that only those individuals participate in research who see the clinical trial as a reasonable option in light of the conflict or uncertainty that exists in expert medical opinion.

It is difficult to overstate the significance of this view of clinical trials as a legitimate response to conflicted opinion at the level of the expert clinical community and in the mind of the individual trial participant. In particular, this insight plays a foundational role in what I refer to below as an integrative approach to clinical trials. In order to motivate this transition, however, it is necessary to consider objections from moral foundations that have recently been raised against clinical equipoise.

## Objections from Moral Foundations

Perhaps the most radical critique of clinical equipoise holds that this entire approach is built upon the mistaken foundational presupposition that the ethics of clinical research must be derived from and constrained by the ethics of clinical medicine (Miller and Brody 2002, 2003). According to this view, the dilemma to which the equipoise requirement was meant to respond is actually a false dilemma. It appears compelling only under the false assumption that clinical research and clinical medicine are contiguous activities. These critics claim, however, that the goals of clinical medicine and the goals of clinical research are 'logically incompatible' (Brody and Miller 2003: 332). Unlike clinical medicine, the purpose of clinical research is not to administer treatment; it is to investigate scientific hypotheses and gather generalizable data. Once we jettison this misconception, we are told, we jettison half of the dilemma with it. We are thus left with the permissibility of pursuing clinical research as a socially valuable activity, but clinical researchers are no longer saddled with the therapeutic obligation. In fact, investigators explicitly do not have 'a fiduciary relationship with research subjects' (Brody and Miller 2003: 336). Instead, they have an obligation to conduct sound science on society's behalf and to prevent and avoid the exploitation of research participants in the process.



To be clear, the proponents of equipoise and the proponents of the non-exploitation approach agree that a variety of conditions must be met in order for a clinical trial to be morally permissible. For instance, Emanuel, Wendler, and Grady point to seven necessary conditions: scientific or social value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent, and respect for research participants (Emanuel *et al.* 2000). They endorse clinical equipoise as a means of ensuring that research is scientifically valid and as a necessary condition for medical research to be carried out when informed consent cannot be obtained. Implicit in the latter claim is that the existence of equipoise helps to ensure a favorable risk–benefit ratio. Proponents of the 'non-exploitation' approach agree with these seven conditions, but they reject any role for clinical equipoise in determining their content (Miller and Brody 2003: 26). In particular, they hold that the limits of morally permissible medical research do not have to remain within the restrictive boundaries of good clinical medicine—as in the equipoise requirement—but only within the more permissible boundary of the social obligation not to exploit research participants.

For the non-exploitation view, the content of the concept of exploitation is defined entirely in terms of the relationship between the risks to the interests of participants and the potential gains in scientific progress. When the risks to participants are justified by, proportionate to, or outweighed by the potential gains to science then research is not exploitative. When the risks are disproportionate to, not compensated by, or outweighed by the gains in science, then research is exploitative.

How successful is this critique of the moral foundations of equipoise? At best, this objection shows only that the equipoise requirement cannot govern the entire domain of clinical research if (*a*) as a constraint on permissible medical research equipoise is grounded in an obligation to provide a level of care for the needs of participants that falls within the boundaries of good clinical medicine and (*b*) some areas or aspects of clinical research do not directly involve treating, or testing a potential treatment for, participant needs. However, this limitation has been recognized and embraced by proponents of the equipoise requirement. Most notably, Weijer argues that the equipoise requirement applies only to those elements of a clinical trial that are being evaluated to clarify their potential value as therapeutic options. Elements of a clinical trial that are not candidates for therapeutic use, but which are instead necessary elements of a sound scientific and statistical design, must be evaluated in terms of the risks they post to participants. In particular, it must be determined whether the risks are necessary, whether they have been minimized, and whether they are justifiable in light of the potential benefits of the research to scientific progress (Weijer 1999, 2000, 2002; Emanuel *et al.* 2000: 2705–6).

Of course, proponents of the non-exploitation approach want to make a more radical claim, namely, that the entire enterprise of medical research falls under the

scope of (*b*) above since the point and purpose of research *as such* is not to minister to patient needs but to generate reliable scientific information. This is the point of their claim that the ends of clinical medicine and the ends of clinical research are 'logically incompatible'. Unfortunately, this argument for their more radical claim suffers from several serious flaws.

First, the notion of 'logical incompatibility' is ambiguous. Certainly it is true that *at a purely conceptual level* the guiding purpose of clinical medicine and the guiding purpose of clinical research are distinct. But it does not follow that these conceptually distinct ends either are, or should be, mutually exclusive *in practice*. That is, it does not follow that these ends cannot both be integrated in practice by a single activity or that it is always desirable to keep them separate. For example, driving to work and showing concern for the interests of others are conceptually distinct activities. But that doesn't mean that they cannot be pursued simultaneously in practice or that it would always be advantageous to separate them! Similarly, when a patient receives conflicting advice about how to treat her medical condition, participating in a clinical trial that randomly assigns her to one of those competing options represents a means of pursuing the end of clinical research in a way that is consistent with her receiving a level of care that is consistent with what at least one group of competent clinicians would recommend. There is nothing inconsistent about claiming that these conceptually distinct goals are each being pursued in a single activity. It is necessary, however, to recognize that these distinct conceptual ends create tensions within the single practical activity, and these tensions must be addressed openly and explicitly in order to avoid confusion.

Such a straightforward position is very different from pretending either that this activity is only pursuing the goal of providing treatment or that it is only conducting clinical research. The former error is morally problematic because it prevents participants from recognizing the potential divergence between the needs of research and their own best interests. The latter error is also morally problematic, however, if it is taken to provide a justification for researchers to be insensitive to the basic interests of research participants. This point is especially important in those cases when research and treatment could not be neatly separated in practice, as when research focuses on precisely those needs that would be the subject of treatment in a clinical context. To say that these ends are 'logically distinct', therefore, is not to say anything about how those conceptually distinct ends ought to be treated when they cannot both be pursued separately in actual practice.

Second, by focusing on the fact that these activities are conceptually distinct, the non-exploitation approach risks begging the central moral issue. In particular, the non-exploitation view presupposes that the ethical constraints that are appropriate for an activity are properly determined by the *conceptual goals* or *guiding purpose* of the activity. The proper moral norms of clinical medicine, this view holds, are internal to or derived from the purpose of that activity and, similarly, the proper moral norms of research are internal to or derived from the purpose of that



activity. Since these purposes are different, the ethical requirements are different (Brody and Miller 1998; 2003: 332). This position can therefore be represented as contrasting two forms of consequentialism. Clinicians are required to act according to a *patient-centered consequentialism* according to which the goal is to maximize the welfare of the individual patient. Researchers on the other hand are required to act according to a *general consequentialism* that seeks to 'promote the medical good of future patients' (Miller and Brody 2003: 21).

Even if we grant (1) that the ends of clinical medicine and clinical research are conceptually distinct and (2) that the ethical constraints that are appropriate for an activity are determined by its conceptual goals, it does not follow (3) that in order to advance science it is permissible in practice for researchers to provide a level of care for participant interests that falls below the level of care that would be recommended by sound medical practice. The reason that (3) does not follow from (1) and (2) is that (1) and (2) entail only (3*) that clinical research requires that the interests of present participants be weighed against the interests of science and benefits to future patients. *This proposition, however, does not say anything about the specific weights that it is permissible to assign to these competing interests.* In other words, from (1) and (2) we can derive the need to weigh or compare competing interests of different individuals but there are many possible ways of doing this and (1) and (2) alone are not so specific as to mandate that these trades be made in a particular way.

In order to go beyond (3*) to (3) without simply begging the question, therefore, we need a substantive argument to justify setting the relevant weights in a way that allows the interests of present participants to be directly outweighed by gains to the interests of future patients. Proponents of the non-exploitation view often speak of research ethics as a utilitarian enterprise. In this spirit, one way to derive (3) from (3*) would be to hold that the interests of each individual should count for one, and no more than one, and that the interests of each future person should be summed together with the interests of each present person. Research initiatives that produce the highest utility score for the resulting aggregate would be morally justified. While such a utilitarian calculus would yield (3*) it would also permit researchers to exact significant sacrifices from research participants since for any new drug in development there will be a relatively small group of research participants whose interests would be greatly outweighed by the thousands or millions of future patients who would benefit from access to the medication. So, not only does (3) not follow directly from (1) and (2) but at least some of the most common means of deriving (3*) from (3) yield pernicious consequences that are antithetical to much of contemporary research ethics.

It is worth pointing out, therefore, that it would also be consistent with (3*) to adopt a different kind of *consequentialist calculus* according to which it is permissible to consider the interests of future patients in designing a clinical trial only if it is possible to ensure first that present participants receive a level of care that is

consistent with what would be recommended in their case by at least a minority of expert clinicians. If a great many people would stand to benefit from a particular research initiative, these numbers might provide a reason to give priority to that research relative to other endeavors. But ever greater numbers would not license exacting ever greater sacrifices from research participants. I will return to such a view in the final section below.

This analysis points out two sources of deficiency in the current debate. First, linking the normative force of the equipoise requirement to duties that are specific to the role of the physician makes it appear that proponents of the equipoise requirement must be committed to claim (2) above. However, as I will illustrate in a moment, the equipoise requirement can be grounded in values that are not derived from role-related duties. Second, the perception that both proponents and critics of equipoise endorse (2) above makes it easier to confuse conclusion (3*) with (3). It thereby exacerbates the difficulty in seeing that *the equipoise requirement can itself be understood as consequentialist calculus that provides the content to (3*) by detailing when tradeoffs in individual welfare for benefits to future patients become exploitative.*

Proponents of the non-exploitation approach do have an additional argument that they hope will make (3) above appear more attractive than a position that relies on equipoise to provide content to the tradeoffs required by (3*) above. However, this is simply a version of the argument from utility in which equipoise is associated with a duty to safeguard patient interests that embodies a fragile epistemic threshold in the mind of the individual clinician. Proponents of the non-exploitation approach have been able to leverage this argument more fruitfully than their predecessors, however, because they have focused on an area where proponents of the equipoise requirement have not always offered advice that is consistent with the specifics of their own theory, namely, the use of placebo controls in clinical trials (Emanuel and Miller 2001; Miller and Brody 2002).

Briefly put, proponents of the non-exploitation approach criticize proponents of equipoise for holding that it is only permissible to employ a placebo control in a clinical trial when no alternative treatment for the condition in question exists. Critics then point out that this would prohibit the use of placebo controls for studies in which subjects are not subject to more than the most mild risks, such as forgoing a current treatment for baldness or an analgesic for minor headaches. They charge in response that 'This argument conflates clinical research with clinical care. Clinicians frequently do not treat such ailments and patients often forgo treatment, indicating that there can be no ethical necessity to provide it' (Emanuel and Miller 2001: 916).

It is not that this argument conflates clinical research and clinical care, since, as the critics themselves point out, there are many instances where effective medical care exists *but non-treatment remains an admissible treatment option.* The problem lies, rather, in a misunderstanding of the responsiveness to participant interests



condition discussed above. That is, as the above comment nicely illustrates, the problem here lies with a view of the duty of personal care or the therapeutic obligation that embodies a fragile epistemic threshold and that requires treatment for absolutely any problem. As a result, proponents of equipoise should simply accept this point and argue that placebo controls are permissible if no effective therapeutic option exists or if such options do exist but non-treatment remains an admissible therapeutic option. Recent treatments of equipoise make just this move (Weijer and Glass 2002; Weijer and Miller 2004). In the following section I provide a more careful analysis of the latter condition. For the moment I simply want to claim that conceptions of equipoise that adopt a multidimensional evaluative focus and a robust epistemic threshold are not committed to the simplistic attitude toward placebo controls that critics often saddle them with.

Finally, one must also ask how successful the non-exploitation approach is in offering an alternative to the equipoise requirement. In particular, if one rejects the equipoise requirement as a method for determining when research participants are being exploited, then what is the substantive criterion according to which exploitative and non-exploitative research can be discriminated? If medical research is concerned with promoting the good of future patients, then is it permissible, for example, to withhold effective medical care for a severe (what about debilitating or life threatening) medical condition if the trial in question will generate an intervention that could potentially help thousands (what about tens of thousands or millions) of future patients?

Unfortunately, this aspect of the non-exploitation approach has not been fully worked out. Although the partisans of this view are clear that it is permissible to trade the welfare of participants for gains in science, we are only told that the limit of permissible tradeoffs is imprecise or fuzzy and a matter of judgment. In other words, the talk of 'weighing' or 'trading off' is purely metaphorical since the underlying judgments cannot be explicitly quantified. This is particularly disappointing for an approach that views medical research as an inherently utilitarian enterprise. It is also a significant limitation for a theory that will be needed most in precisely those cases where well-intentioned people are likely to disagree (London and Kadane 2003; London 2006*a*).

To be clear, it would be a mistake to think, as proponents of the non-exploitation approach sometimes seem to imply, that these are tradeoffs that cannot be quantified. The problem, I submit, is exactly the opposite—there are uncountably many different tradeoff schedules that could be specified. It is not that no such calculus exists, therefore, so much as that there are too many possible calculi from which to choose and what we need are non-arbitrary reasons for narrowing the class down to an admissible set or, if possible, a preferred schedule. It is also worth stressing that while this problem is more pressing for the non-exploitation view—since it relies on such judgments as the sole means of determining when the risks posed to subjects are morally appropriate—it must also be faced by proponents

of the equipoise requirement in those areas of research to which equipoise does not apply.

At best, therefore, proponents of the non-exploitation view can be seen as underscoring the claim that clinical equipoise cannot alone govern the entire domain of human-subjects research. While they are clear in their assertions that a more comprehensive framework will be consequentialist in nature, their view remains sufficiently undefined as to be consistent with uncountably many different accounts of how to make the requisite tradeoffs. Clearly, however, not just any consequentialism can function as a defensible foundation for research ethics. For example, assigning the same weight to the interests of each future patient and each present research participant would effectively license exposing present participants to an unbounded degree of risk since the number of future beneficiaries of any successful research initiative is potentially unlimited. Fortunately, however, the space of viable options is populated by more reasonable approaches than this relatively anemic framework of moral accounting.

## The Integrative Approach to Clinical Trials

In the previous section I suggested that the degree of fragmentation at the foundations of research ethics is greatly exaggerated. In this final section I amplify this claim by sketching the outlines of a view of research ethics that has been more fully developed and articulated elsewhere (London 2006*a*, *b*). This outline should be sufficient to illustrate how the equipoise requirement itself can be seen as a means of specifying the content of the requirement not to exploit research participants and, therefore, as illustrating how what are currently perceived to be mutually exclusive ethical ideals can be united under a single heading.

Like the non-exploitation approach, the integrative approach holds that the social justification for the institutions of clinical research lies in their capacity to advance the common good of community members by investigating socially significant questions using sound scientific methods. It also holds that it is sometimes permissible to subordinate the individual good of particular persons to the common good. The integrative approach, however, rejects the idea that the individual good and the common good refer to the complete set of interests of two different entities, one of which is an individual and the other an aggregate of individuals united into a corporate body. Rather, these terms distinguish *two sets of interests, each of which can be attributed to every individual person* (London 2003).

In liberal democratic communities, individuals often differ radically in their *personal interests*. These are defined as interests that individuals have in virtue of the particular projects and life plans embraced by that individual. The integrative approach identifies the personal or *individual good* of agents with the pursuit of the goals and ends that constitute their personal interests. This diversity in personal interests can frustrate social decision making because it is often the source of disagreements about how to value risks, activities, goals, and ends.



Amidst this diversity in personal goods, however, individuals in liberal democratic communities share a higher order interest in being able to cultivate and to exercise the basic human capacities they need in order to pursue their personal interests. This shared higher order interest provides a social perspective from which the members of such communities can identify a set of *basic interests*. These are interests that each individual has in being able to cultivate and to exercise their capacities for reflective thought and practical decision making, to develop and exercise their affective or emotional capacities, and in having the external necessities to exercise those capacities in pursuit of particular projects and meaningful social relationships. The integrative approach identifies the *common good* with this set of basic interests and the basic social interest of every community member in ensuring that their basic interests are secured and advanced by the social structures of their community. It then uses this set of basic interests to define the space of social equality, the domain with respect to which each community member has a just claim to equal treatment.

Because the basic interests of individuals can be profoundly restricted or defeated by sickness and disease, each can recognize a reason to support medical research as a social institution in so far as it strives to advance the state of medical science and, with this, the standard of care that is available to future patients. The institutions of clinical research represent one element within a larger social division of labor that must be justifiable to the members of the community whose basic interests those institutions are supposed to serve (London 2005). As such, the integrative approach holds that clinical research must pursue this goal of advancing the interests of future patients in a way that is consistent with an equal regard for the basic interests of the present persons whose participation makes those results possible.

In light of this requirement, the integrative approach adopts the following definition of reasonable risk:

> *Definition of reasonable risk*: Risks to individual research participants are reasonable just in case they (1) require the least amount of intrusion into the interests of participants that is necessary in order to facilitate sound scientific inquiry and (2) are consistent with an equal regard for the basic interests of study participants and the members of the larger community whose interests that research is intended to serve. (London 2006*a*)

This requirement of equal regard is intended to reflect the claim that although there is a moral imperative to carry out research that will advance the basic interests of community members in the future, this imperative is not sufficient to legitimize sacrificing or forfeiting the basic interests of other community members in the process. To say that it may be morally permissible, when necessary, to subordinate the individual good of particular persons to the common good is not to set up a calculus in which all of an individual's interests are weighed in a balance against the

interests of the other individuals in the community or against the interests of future individuals. It is, instead, to say that it is permissible to ask individuals to modify or even to sacrifice some of the particular goals and ends that are a part of their individual good in order to provide others with the conditions necessary to cultivate and engage those basic capacities for agency and sociability that constitute their share of the common good. The integrative approach, therefore, seeks to create the social conditions in which community members can take on, as a personal project, the goal of assisting future patients, while being assured that their basic interests are treated with the same moral concern as that which provides the moral motivation for the research enterprise itself.

Operational criteria for this conception of reasonable risk are generated by considering how the basic interests of community members are safeguarded and advanced in other areas of the social division of labor. When the basic interests of individuals are threatened or restricted by sickness, injury, or disease, this job falls in large part to the health care system. The integrative approach therefore adopts the following as the first of two operational criteria:

*First operational criterion*: Equal regard for the basic interests of research participants and non-participants requires that when the basic interests of an individual participant are threatened or compromised by sickness, injury, or disease, the basic interests of that individual must be protected and advanced in a way that does not fall below the threshold of competent medical care. (London 2006*a*)

This operational criterion invokes the threshold of competent medical care, not as a source of the normativity of this framework, but as a standard for determining what is required in order to show equal regard for the basic interests of individuals whose basic interests are threatened or restricted by sickness, injury, or disease. Similarly, its scope is limited to the basic interests of individuals because this criterion delineates the level of risk that it is permissible to *offer* to prospective research participants. Participants are then free to decide for themselves whether the risks that remain are acceptable in light of their various goals and commitments.

This focus on basic interests also reflects the normative claim that it is permissible to ask individual research participants to alter, risk, or even to sacrifice some of their personal interests in an effort to advance the basic interests of others. This means that it is permissible to ask individuals to undergo intrusive, painful, and otherwise uncomfortable experiences in order to advance scientifically meritorious research. The constraint is simply that the risks that such research poses to the basic interests of participants must be consistent with the requirement of equal regard expressed in the above operational criterion.

The following practical test can then be used to determine whether or not a particular clinical trial satisfies this operational criterion.

> *Practical test for first criterion*: A specific intervention *s* is admissible for an individual *i* just in case there is either uncertainty among, or conflict between, expert clinicians 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 clinical trial, the care and protection afforded to that individual's basic interests falls within the threshold of competent medical care just in case each intervention to which that individual might be allocated within the clinical trial is admissible for that individual. (Adapted from London 2006*a*)



This practical test is similar to Freedman's clinical equipoise, but there are important differences. First, the scope of this requirement is limited to the basic interests of participants and its moral force is grounded, not in the role-related obligations of physicians, but in broader claims about the need for basic social structures to provide equal regard for the basic interests of all community members. Second, this practical test explicitly distinguishes uncertainty in the mind of expert clinicians from the state of clinical conflict between such clinicians. Third, where the equipoise requirement is often applied to entire trial populations, the above practical test is applied to each individual trial participant.

The integrative approach therefore permits the use of a placebo control as an admissible arm of a clinical trial:

1. if no effective therapeutic option exists, or
2. if an effective therapeutic option exists but the condition in question is such that non-treatment remains an admissible therapeutic option because either
   (*a*) the condition being treated does not threaten the individual's ability to function in a way that would adversely affect their basic interests, or
   (*b*) the condition is more severe but an all-things-considered evaluation of the benefits and burdens of the existing interventions reveals that they do not necessarily offer a clear net therapeutic advantage over non-treatment.

When these conditions cannot be met, a placebo control will not be an admissible option. Alternative means of generating scientific information will have to be pursued that provide an admissible treatment option to research participants. If this makes science in the service of the common good more costly in terms of time and other resources, then such inefficiencies must be tolerated as an unfortunate byproduct of a fundamental commitment to safeguarding and protecting for each individual the very basic interests that justify initiating the research enterprise itself.

When research involves individuals whose basic interests are not compromised or threatened by sickness and disease, the equipoise requirement does not apply. However, the more general requirements of the integrative approach remain in force. The integrative approach uses the following, second, operational criterion to make operational in this context the goal of advancing science in a way that is consistent with an equal regard for the basic interests of all community members.

*Second operational criterion*: In all cases, the cumulative incremental risks to the basic interests of individuals that derive from purely research-related activities that are not offset

by the prospect of direct benefit to the individual must not be greater than the risks to the basic interests of individuals that are permitted in the context of other socially sanctioned activities that are similar in structure to the research enterprise. (London 2006*a*)

Respect for the moral equality of individuals cannot require that individuals be prohibited from voluntarily assuming some risk to their basic interests, since such a standard simply cannot be achieved. This proposal therefore seeks to identify social activities that are structurally similar to the research enterprise and to ensure that the incremental risks to the basic interests of participants associated with purely research-related activities do not exceed the incremental risks to the basic interests of individuals associated with those structurally similar social activities.

I have proposed elsewhere criteria that might be used to construct practical tests for this second operational criterion (London 2006*a*). For my present purposes I merely want to indicate how a single overarching approach to research ethics might provide a foundation for research ethics within which the equipoise requirement itself might be seen as a means of specifying the content to the ideal of not exploiting research participants. Clearly, key concepts within this approach have to be explicated more carefully and then wedded to a particular decision theory in order to provide more precise guidance to practical decision making. Nevertheless, even these broad outlines are sufficiently suggestive as to provide a motivation to take up such a project in earnest. At the very least, they should provide a clear indication that the foundations of research ethics may appear to be more fragmented than they actually are and that, with effort, we may yet find a philosophical theory that brings unity to this apparent diversity.

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