

This article was downloaded by:

On: 25 December 2009

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



## Journal of Medicine and Philosophy

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713658121>

### Two Dogmas of Research Ethics and the Integrative Approach to Human-Subjects Research

Alex John London <sup>a</sup>

<sup>a</sup> Carnegie Mellon University, Pittsburgh, Pennsylvania, USA

**To cite this Article** London, Alex John(2007) 'Two Dogmas of Research Ethics and the Integrative Approach to Human-Subjects Research', *Journal of Medicine and Philosophy*, 32: 2, 99 – 116

**To link to this Article:** DOI: 10.1080/03605310701255727

**URL:** <http://dx.doi.org/10.1080/03605310701255727>

## PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

# Two Dogmas of Research Ethics and the Integrative Approach to Human-Subjects Research

ALEX JOHN LONDON

*Carnegie Mellon University, Pittsburgh, Pennsylvania, USA*

*This article argues that lingering uncertainty about the normative foundations of research ethics is perpetuated by two unfounded dogmas of research ethics. The first dogma is that clinical research, as a social activity, is an inherently utilitarian endeavor. The second dogma is that an acceptable framework for research ethics must impose constraints on this endeavor whose moral force is grounded in role-related obligations of either physicians or researchers. This article argues that these dogmas are common to traditional articulations of the equipoise requirement and to recently articulated alternatives, such as the non-exploitation approach. Moreover, important shortcomings of these approaches can be traced to their acceptance of these dogmas. After highlighting these shortcomings, this article illustrates the benefits of rejecting these dogmas by sketching the broad outlines of an alternative called the “integrative approach” to clinical research.*

**Keywords:** *common good, common rule, equipoise, non-exploitation, reasonable risk, therapeutic obligation.*

## I. INTRODUCTION

To judge from a survey of recent literature, the foundations of research ethics are in disarray. Over roughly the past two decades the framework of clinical equipoise has emerged as the dominant method of managing the fundamental tension in clinical research between advancing the frontiers of science and the imperative not to sacrifice the interests of present individuals

---

Address correspondence to Alex John London, Ph.D., Department of Philosophy, Carnegie Mellon University, 135 Baker Hall, Pittsburgh, PA, 15213, USA. E-mail: [ajlondon@andrew.cmu.edu](mailto:ajlondon@andrew.cmu.edu)

to effectuate that goal. According to proponents of this approach, the parameters on the risks to which it is permissible to expose research participants are determined by the researcher's "therapeutic obligation" (Marquis, 1983) to those participants. Also referred to as "duties of personal care" (Fried, 1974) or "fiduciary duties" (Miller & Weijer, 2003), these duties are traced to, and grounded in, the professional role of researchers as physicians. Although the equipoise requirement has been attacked on one side as too restrictive and on the other too permissive, such critics usually accept the *prima facie* idea that researchers owe such duties to their subjects (Marquis, 1983; Gifford, 1986; Hellman, 2002). More recent critics, however, have argued that the very idea that researchers have such therapeutic or fiduciary obligations to research participants rests on a fundamental philosophical confusion.

According to proponents of the "non-exploitation" approach, the framework of clinical equipoise represents the solution to a non-problem. These critics claim that the ethical constraints that are appropriate for an activity are properly determined by the *conceptual goals* or *guiding purpose* of the activity and that the goals of clinical medicine and the goals of clinical research are "logically incompatible" (Brody & Miller, 2003, p. 332). Unlike clinical medicine, the purpose of clinical research is not to administer treatment to individual patients; it is to investigate scientific hypotheses in populations of subjects in order to gather generalizable data. From this standpoint, the idea that researchers have such fiduciary duties is diagnosed as a variant of what is known as the therapeutic misconception—the mistaken propensity of research participants (or, in this case, the research ethics community) to believe that clinical research is a therapeutic, rather than a scientific or investigative, endeavor. Once we jettison this misconception, we are told, we jettison the claim that researchers have "a fiduciary relationship with research subjects" (Brody & Miller, 2003, p. 336), leaving researchers free to conduct sound science on society's behalf as long as they don't exploit research participants in the process.

In the discussion that follows, I argue that the current uncertainty about the normative foundations of research ethics is perpetuated by two unfounded dogmas of research ethics. Briefly, the first dogma is that clinical research, as a social activity, is an inherently utilitarian endeavor. The second dogma is that an acceptable framework for research ethics must impose constraints on this enterprise whose moral force is grounded in role-related obligations of either physicians or researchers.

In the first section below I show how these dogmas are common to traditional articulations of the equipoise requirement and to the non-exploitation approach. In the second section I argue that important shortcomings of these approaches can be traced to their acceptance of these views. To illustrate the benefits of rejecting these dogmas, in the final section I sketch the broad outlines of an alternative that I call the "integrative approach" to clinical research.

## II. TWO DOGMAS OF RESEARCH ETHICS

The first dogma of research ethics is that clinical research is an inherently utilitarian enterprise. Although it has deep historical and conceptual roots in research ethics, this idea is given its clearest expression by Miller and Brody who argue that “clinical research is dedicated primarily to promoting the medical good of future patients by means of scientific knowledge derived from experimentation with current research participants—a frankly utilitarian purpose” (Miller & Brody, 2003). This passage from Miller and Brody can be seen as expressing the following inference:

- (a) The social justification for the institution of clinical research lies in its capacity to advance the common good of community members through the use sound scientific methods to investigate questions of appropriate social significance.
- (b) Therefore, clinical research is “an institution that serves a utilitarian purpose.” (Miller & Brody, 2007, p. 162).

To be clear, conclusion (b) is what I am calling the first dogma of research ethics and is primarily a claim about the structure or purpose of the *research enterprise*. It is not necessarily a claim about the proper *ethical framework* for evaluating or regulating that activity.

There is, however, a close relationship between the claim in (b) above and the idea that there is at least a fundamental utilitarian component to *research ethics*. In fact, Miller and Brody endorse two distinct arguments that derive such a conclusion (d) from (b). The first makes use of the following additional premise (c):

- (c) With respect to social activities such as clinical research, “the basic goal and nature of the activity determines the ethical standards that ought to apply” to it. (Miller & Brody, 2003, p. 22. See also Brody & Miller, 2003, p. 332)
- (d) Therefore, “a basic feature of clinical research ethics is utilitarian or consequentialist.” (Miller & Brody, 2007, p. 162)

The second argument for (d) does not rely on (c). Instead, it begins with a common definition of reasonable risk and then diagnoses this rule as a fundamentally utilitarian principle:

- (e) Definition of reasonable risk: risks that are not offset by benefits to individual trial participants are judged to be reasonable if and only if they are sufficiently offset by gains in the knowledge that the research is designed to generate.

- (f) If it is the production of such valuable information that constitutes the social value of clinical research then reasonable risks are those that are necessary in order to advance the common good (from (a) above).
- (g) Since advancing the common good in this way is a utilitarian enterprise (from (b) above) then it follows that (d) is true.

Each of these above arguments make explicit a set of views, often implicit, that are woven deeply into the history and theory of contemporary research ethics. Early philosophical pioneers in research ethics, such as Jonas (1969) and Donagan (1977), argued against more robustly utilitarian views that endorsed most of the above claims. Those utilitarian views also went further, however, by claiming that considerations of social utility are the dominant consideration in research ethics and are sufficient to justify the abrogation of other moral values such as respect for individual welfare and autonomy.

On what is a very common view, the central accomplishment of contemporary research ethics lies in having debunked the moral foundation for those stronger utilitarian claims about the proper structure for research ethics. But, as Miller and Brody illustrate, the idea that clinical research is itself an inherently utilitarian activity persists, as does the idea that there is a utilitarian core to research ethics. What has changed is the emergence of a social consensus that there are numerous important duties and obligations that have a central role in research ethics and that these duties and obligations function as side-constraints, tempering and limiting the reach of the remaining utilitarian substrata of clinical research and research ethics.

The second dogma of research ethics is that the side constraints that must be imposed on clinical research draw their normative force from role-related obligations. Although the proponents of clinical equipoise provide the clearest expression of this dogma, a similar idea remains operative in Miller and Brody's preferred framework. That is, Miller and Brody reject the idea that researchers have fiduciary obligations to research participants. They hold, instead, that researchers have the somewhat weaker duty of non-exploitation. This duty consists in ensuring:

1. that risks to subjects are reasonable (as defined in (e) above),
2. that the research has social value and
3. scientific validity,
4. that subjects give free and informed consent,
5. that there is fair subject selection,
6. independent review, and
7. respect for persons (Emanuel, Wendler, & Grady, 2000).

As the arguments outlined above make clear, however, the first three of these requirements are not side-constraints that limit the pursuit of the utilitarian

goals of clinical research. Rather, they serve partly to define those utilitarian goals and to express necessary conditions for their achievement. As such, these requirements would be endorsed by any legitimate utilitarian theory. Furthermore, with perhaps the exception of (1), each of these requirements is endorsed by all reasonable frameworks for research ethics.

What is distinctive in Miller and Brody's view, therefore, is that the only principle for determining how individual health or welfare can be traded off against gains in knowledge, and therefore the advancement of the common good, is outlined in (1) above. The other constraints require that such risks be imposed only on voluntary participants, for example, but they do not directly curb or limit the extent of the potential sacrifices that can be asked of trial participants in order to advance the common good. Since Miller and Brody endorse (c) above, it appears that what is distinctive in their account of the researcher's duty of non-exploitation, therefore, is derived from their view of the researcher's role *qua* researcher, and of research as a fundamentally utilitarian enterprise (b). Hence, their acceptance of the second dogma of research ethics.

What distinguishes frameworks that embrace the equipoise requirement from those that reject it is not that the latter embrace the first dogma of research ethics while the former reject it. Proponents of the equipoise requirement often portray the central tension in research ethics as a conflict between the therapeutic obligation or fiduciary duties of the individual researcher and the goals of scientific research. Rather than denying that the propositions in (a) and (b) above adequately express the proper goals of clinical research, the proponents of equipoise are at pains to show how the fiduciary duties of clinicians constrain or check those goals.

Moreover, because the dominant framework that employs the equipoise requirement, known as "component analysis" (Miller & Weijer, 2004) explicitly accepts premise (e) it would not generate inconsistency for the proponent of such an approach to endorse, not only (a) and (b), but also (f), (g), and therefore (d) as well. What distinguishes these approaches from the non-exploitation view, rather, is their imposition of a further moral constraint on the tradeoffs in individual welfare that can be justified in the research context. This constraint takes the form of a requirement (roughly) that research participants must receive a level of care within a clinical trial that is consistent with the physician's duty of personal care. For this reason, the clearest articulation of the second dogma of research ethics appears in the literature on equipoise.

As it is traditionally understood, the duty of personal care binds the individual clinician to advance the health interests of the individual patient to the best of his or her ability. Interestingly, however, this duty itself has the structure of what I will call a patient-centered consequentialism. Deeply rooted in the Hippocratic tradition, this view is a form of consequentialism in that the decision maker—in this case the individual clinician—is obligated

to perform the act that maximizes the good. It is patient-centered, however, in that the good is identified with the individual best interests of the particular patient, rather than with the common good. The equipoise requirement can therefore be seen as an effort to reconcile these two forms of consequentialism: the duty to advance the best interests of the individual patient and the duty to advance the state of medical science can both be discharged if clinical research begins in, and is designed to eliminate, an honest state of uncertainty concerning the relative therapeutic merits of the trial interventions for treating the patient's condition.

### III. LIMITATIONS OF THE TWO DOGMAS

The non exploitation approach and frameworks that rely on equipoise each face serious shortcomings that can be traced back to what I am calling two dogmas of research ethics.

For our present purposes, different versions of the equipoise requirement can be distinguished by the answers that they give to the following three questions (London, 2007). First, where must the relevant uncertainty be located, i.e., whose uncertainty is the morally relevant uncertainty? Fried (1974) and others (Peto et al., 1976; Chard & Lilford, 1998) argue that the uncertainty must reside in the mind of the individual clinician or researcher. Freedman (1987, 1990), in contrast, claims that the uncertainty should reside in the larger expert medical community.

Second, what is the epistemic threshold that defines the state of uncertainty and when it is disturbed? Fried and others seem to adopt a fragile epistemic threshold according to which the relative net therapeutic advantage of each of the available treatment options must be an equal bet in prospect. Freedman, in contrast, argues for a robust epistemic threshold according to which uncertainty exists so long as there is a lack of consensus in the expert medical community about the relative therapeutic benefits of the set of interventions.

Third, what is the proper focus of the uncertainty? This requirement is often not explicitly clarified but it amounts to the following. Some hold that the uncertainty should focus on the individual patient and his or her particular interests. Others argue that equipoise deals with the views of the medical community about the relative therapeutic merits of the set of interventions in general, as a matter of policy, and not relative to the risks and benefits that they pose to individual subjects.

In slightly different ways, the second dogma of research ethics is responsible for twin challenges to frameworks that adopt the equipoise requirement. First is the charge that the equipoise condition will so rarely obtain, or that it will be so fragile when it does obtain, that it prohibits valuable clinical research from generating socially valuable data. This charge of

fragility is most telling against versions of equipoise that require the individual researcher to be uncertain about the net therapeutic advantage of the proposed treatment options for the particular patient, and which adopt a fragile epistemic threshold. To avoid this result, Freedman shifted the locus of uncertainty to the larger expert medical community and adopted a more robust epistemic threshold for what he calls "clinical equipoise." The second dogma of research ethics lies behind the charge that Freedman's view is insensitive to the interests of particular clinical trial participants because it permits clinical trials to begin, or to continue, even though the individual clinician may have formed a considered option about which of the interventions are best for him or her.

For the purposes of the present discussion I want to make two points. The first is that if the normative force for the equipoise requirement is grounded in the physician's therapeutic obligation, then that requirement must locate the relevant uncertainty in the mind of the individual researcher and focus on the interests of the particular patient. This, I argue, is what motivates significant criticisms of Freedman's clinical equipoise and has even led some proponents of that view to shift their position in this direction. The second point I want to make is that the view of equipoise that results from the physician's therapeutic obligation should be rejected for several reasons. The one that I defend here is a charge that such views are overly paternalistic.

The Belmont Report provides a standard expression of the physician's duty of personal care when it says that, "The Hippocratic Oath requires physicians to benefit their patients 'according to their best judgment.'" If the moral obligations of researchers are derived from the physician's duty of personal care, then at least two components of the equipoise requirement appear to be obligatory. First, the duty of personal care binds the individual physician in the clinical context. Each physician is charged with benefiting their individual patients according to their best judgment. As a result, this requires that the *individual clinician or researcher* must be uncertain about the relative net therapeutic merits of the available interventions in order to recommend that a patient enter into a clinical trial. Second, because this duty is owed to the individual patient it appears obligatory that the physician's uncertainty must focus on the health interests of the individual patient.

The third element of the above view, that the epistemic threshold should be a fragile one, may also appear to be obligatory for two reasons. First, as a form of patient-centered consequentialism, the duty of personal care is commonly taken to impose an obligation on the physician to recommend the best or optimal treatment for the individual patient. Second, this also seems to be required by the most common normative standard of rationality according to which agents are required to choose (or in this case, recommend) the best option out of the set of feasible options, where best is

understood as the option whose outcome has this highest expected utility. Unless the available options are an equal bet in prospect—unless they have the same expected utility—then the physician will not be in equipoise between them. It is difficult to overstate the importance of the role of this view of rationality in motivating the fragility argument against equipoise.

Both critics and proponents of clinical equipoise appear to recognize that the duty of personal care must have this structure to it. For instance, Chard and Lilford (1998) consider but then reject clinical equipoise on the grounds that it is not consistent with the duty of personal care, so understood. Similarly, Deborah Hellman (2002) argues that clinical equipoise should be rejected precisely because it articulates the conditions under which the community of expert clinicians is uncertain about the therapeutic merits of various interventions and does not address the clinician's question: Which of the available treatment options will best advance the health needs of this particular patient?

Finally, Charles Weijer is one of the most articulate and sensible proponents of the equipoise requirement and he has defended the view that Freedman's clinical equipoise locates the relevant uncertainty in the larger expert community and requires a robust epistemic threshold. Yet, in a recent article, Weijer and Paul B. Miller argue that Freedman's clinical equipoise and Fried's version of equipoise are not incompatible (Miller & Weijer, 2003). The reason is that Freedman's clinical equipoise lays out the conditions under which it is appropriate to initiate a clinical trial and Fried's version articulates the standard for determining whether an individual subject should be enrolled in that trial. Weijer and Miller's claim that in themselves these views are incomplete appears to represent a concession to those who argue that Freedman's clinical equipoise is insufficiently responsive to the fiduciary obligations that physicians have to their *individual patients*.

In each of these cases, Freedman's view is either revised or rejected because it is seen as insufficiently responsive to the physician's fiduciary obligations to the individual patient. One reason to be dissatisfied with any view that requires the individual clinician to be uncertain before a patient can be enrolled in a clinical trial, however, is that such views embody an unjustified vestige of medical paternalism in research ethics. To see this, consider the following example of what I call clinical conflict (London, 2006, 2007; Evans & London, 2006; London & Kadane, 2003):

Patent  $i$  suffers from condition D and visits clinician  $C_1$  who recommends intervention  $s_1$ .  $C_1$  recognizes that others in the field might recommend intervention  $s_2$  for this patient but  $C_1$  believes that this is the wrong way to go. She therefore advises  $i$  against taking  $s_2$ . Seeking to be sure of his treatment decision,  $i$  visits another clinician  $C_2$  who has the diametrically opposite view from  $C_1$ , recommending  $s_2$  as the optimal treatment and

advising *i* against taking  $s_1$ . So, *i* goes to his local library and finds that  $C_1$  and  $C_2$  represent competing schools of thought about how best to treat condition *D*. If there is no additional information that leads *i* to believe  $C_1$  over  $C_2$ , and if there is nothing about treatments  $s_1$  and  $s_2$  that lead *i* to independently prefer one to another, why would it not be permissible for *i* to allow himself to be assigned to  $s_1$  or  $s_2$  at random, within the context of a well-designed clinical trial, rather than forcing *i* to randomly choose between being treated by  $C_1$  or  $C_2$ ?

To be clear, this is not a case where either of the clinicians involved is uncertain of her views. Quite the opposite is true; each is adamant in her treatment recommendation for this particular patient. If each acts in accordance with what she views as her duty of personal care, she will not recommend that *i* participate in a clinical trial between  $s_1$  or  $s_2$  because she is not uncertain about the best course of treatment for *i*. If the equipoise requirement holds that a necessary condition for participation in clinical research is that equipoise must exist in the mind of the individual clinician then it will not be permissible to offer research participation to *i*. However, to prevent *i* from participating in a clinical trial between  $s_1$  or  $s_2$  in this circumstance represents unjustified paternalism: the restriction that it places on the choices of patients arbitrarily treats the opinion of a single expert as sovereign in determining the options that can be offered to potential trial participants, even though the care that subjects would receive as a result of randomization would be consistent with what would be recommended for them by at least a reasonable minority of expert clinicians.

This problem cannot be eliminated by adopting a robust epistemic threshold for the physician's duty of personal care according to which it is the consensus of the expert medical community that determines which medical interventions the physician is obligated to offer to her patients (Miller & Weijer, 2003). A physician may recognize that the existence of conflicting treatment recommendations indicates that the larger medical community is uncertain about which treatment is best for a patient, and, therefore, that both  $s_1$  or  $s_2$  are consistent with the standard of "competent medical care" in the eyes of the larger medical community. However, if as in the example described above each physician believes that one treatment is in the patient's best interest and that the other is not, then the fact remains that no individual clinician is uncertain about what is best for this particular patient. As long as the relevant uncertainty for the equipoise requirement must exist in the mind of the individual clinician then my objection stands.

Concerns about fragility are a central factor in Miller and Brody's rejection of the equipoise requirement. Their view, however, suffers from different problems. To begin with, I suggested above that Miller and Brody provide a clear expression of a common view to the effect that (b) above somehow follows directly from (a). This inference, however, is not valid;

(b) only follows from (a) with the addition of further claims that are both controversial and morally problematic. This is because utilitarianism is the result of combining consequentialism with welfarism and sum-ranking (Sen, 1979). Consequentialism is the view that the goodness of an instrument—an act, rule, policy, etc.—is determined by the goodness of the state of affairs that it brings about. Even if (a) implies consequentialism, this alone is not sufficient to indicate how states of affairs should be evaluated.

Welfarism is the view that goodness consists in the welfare of individuals. Sum-ranking is the view that the goodness of an outcome is determined by the summed total of the welfare (utility) information contained in the state. For the utilitarian, therefore, one state of affairs is at least as good as another just in case the sum of the individual utilities is at least as large as the sum of the individual utilities in the other. For (b) to follow from (a), therefore, advancing the common good has to be understood as trying to maximize the summed utility of the individual community members. The latter view, however, is an overly simplistic view of the common good that has been widely criticized on moral grounds.

Whether or not we accept these additional claims, Miller and Brody's proposed framework requires deliberators to evaluate tradeoffs in individual welfare against gains in social utility. However, they do not define

1. how to represent or quantify the value of the information that a trial might generate
2. how to measure that value, so defined, in concrete cases, and
3. how to weigh or trade-off the value of that information against the interests of individual trial participants (London & Kadane, 2003).

What *is* clear in their framework is the permissibility of trading off the health interests of individuals for gains in social utility. Their acceptance of (b) above and the two supporting arguments in favor of (d) make this claim unavoidable on their view. But the variety of different ways of specifying the value of scientific information and of trading it off against the interests of individual trial participants are left as vast as the imaginations of different deliberators.

Miller and Brody have tried to dismiss these worries as misguided desires for a kind of precision that cannot be had: such issues ultimately boil down to matters of “judgment,” they claim, and cannot be quantified. But if losses to individual welfare really are justified by offsetting gains in social value, then we need some interpersonally useful decision rule for helping members of a pluralistic, liberal democratic community to arrive at reasoned judgments about when this criterion has been met (London, 2006). We therefore need a reasoned account of the issues outlined in the previous paragraph in order to know how to apply their proposed framework.

On the other hand, if such tradeoffs really cannot be specified, then the research ethics community should drop the pretense that it is providing individual decision makers with a standard that they can apply in order to guide their evaluations of clinical research and instead exhort deliberators to use their intuitions in order to decide whether the risks to subjects seem “worth it.” This, however, will leave research ethics without a means of providing reasoned guidance to deliberators in exactly those cases where it is needed most, cases where intuitions conflict.

#### IV. THE INTEGRATIVE APPROACH

What I call the integrative approach rejects both of the above dogmas of research ethics (London, 2006). Although it accepts (a) above, it rejects welfarism and sum-ranking, and therefore rejects the claim in (b) that clinical research is an inherently utilitarian enterprise.

As a result, it rejects the underlying idea that clinical research seeks to serve should the common good, understood implicitly as the aggregated welfare of community members, and the correlative and explicit claim that potential harms to present research participants are justified by sufficiently extensive benefits for future patients.

Instead, the integrative approach draws a very different distinction between the individual and the common good (London, 2003). On this view, the individual good of an agent is identified with what I refer to as that individual’s “personal interests.” These are the interests that agents have in light of their individual conception of the good and the particular life plans and projects that they adopt in pursuit of this. For example, while some individuals value intense personal challenge through activities such as mountain climbing or sky diving, others may incline more toward intellectual stimulation and may even view individuals in the former group as a little nuts.

In liberal democratic communities individuals may differ radically in their personal interests and these differences are a common source of conflict in social decision making and public policy. Fortunately, the individual members of such a community can recognize each as sharing a common set of what I will call “basic interests.” These are interests that each individual has in being able to cultivate and to exercise those fundamental human capacities that are constitutive of what the philosopher John Rawls refers to as our two moral powers: the capacity to formulate and to pursue a life plan based on a conception of the good and to regulate our conduct with others on the basis of principles of right (Rawls, 1982). Such basic or generic interests include developing and exercising one’s capacities for reflective thought and practical

decision making, developing and cultivating one's basic affective or emotional capacities and having the effective freedom to exercise those capacities in the pursuit of particular projects and meaningful social relationships.

The integrative approach uses this set of basic interests to define the "space of equality," the domain over which all community members have a just claim to equal treatment. It treats individuals as responsible for shaping and pursuing their personal interests, and therefore as responsible for looking after their individual good. It identifies the common good with the higher-order interest, common to all community members, in being able to exercise those basic intellectual, affective, and social abilities that make it possible for them to formulate and to pursue particular goals and projects and to engage in meaningful relationships with others (London, 2003).

The integrative approach also rejects the second dogma of research ethics. Instead of appealing to the role-related obligations of clinicians or researchers to define the parameters on the risks to which it is permissible to subject research participants, it looks instead to an egalitarian political ideal. In this view, clinical research is viewed as one element within a larger social division of labor that must be justifiable to the individual community members whose interests that division of labor is supposed to safeguard and advance. One of the central moral missions of the social division of labor is to create and to maintain basic social institutions that foster and advance the common good of each community member. This is done through the creation of *integrative solutions* to social problems. These are solutions that, though they may require alterations in the personal interests of one or more parties, are maximally responsive to the underlying basic interests of each of the relevant parties. In general, such solutions can be achieved by matching specific duties or functions with individuals who are willing to take on, as a personal interest, the project of ensuring that others have the opportunity to cultivate and exercise their basic capacities for agency and community.

On this view, when the basic interests of some are restricted, whether by sickness and disease, social deprivation or environmental hazard, or by the oppressive activities of others, they can make a legitimate claim on the assistance of others. Clinical research represents one way of dividing labor among community members for the purpose of producing the information and interventions that are necessary to provide such assistance to community members. The integrative approach, therefore, seeks to ensure that the enterprise of clinical research is carried out in a way that respects the fundamental moral equality of all community members understood within the above defined space of equality. This commitment is reflected in 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.

The first part of this definition quantifies over all of the interests of participants, both basic and personal, and represents the idea that in order to count as reasonable, risks must be reduced to those that are necessary for the conduct of sound science. The second part quantifies over the basic interests of participants. This distinction reflects the normative claim that it is permissible to ask individual community members to alter, risk, or even to sacrifice some of their *personal interests* as part of an effort to advance or secure the *basic interests* of others. This means that it is permissible to ask individuals whether they are willing to take up, as a personal project, participation in a research initiative that might involve the dedication of time and energy that might otherwise have been directed to other projects or goals. It is also permissible to ask them to endure experiences that are unpleasant, painful, or otherwise difficult. The constraint, however, is that such participation must not pose risks to the basic interests of participants that are inconsistent with the same degree of concern that is shown for the basic interests of other community members. This last claim will be explicated by the two operational criteria below.

This focus on basic interests represents a social judgment about the level of risk that it is permissible to *offer* to prospective participants. Participants are then free to decide for themselves whether the risks that remain in a trial that meets this standard are acceptable in light of their particular personal interests. It falls to additional requirements relating to equity and informed consent to ensure that participants are sufficiently free and informed to make these decisions.

Operational criteria for the application of this definition are generated by considering what conditions have to be met for clinical research to show equal regard for the basic interests of participants and non-participants. Two issues are particularly salient in this regard. The first relates to the situation in which research participants themselves suffer from sicknesses, injuries, or diseases that threaten or restrict their basic interests. This situation requires special consideration because restrictions on the basic interests of individuals prevent those individuals from sharing equally in the common good of being free to shape and to pursue a reasonable individual life plan.

The Integrative Approach, therefore, adopts the following as the first of two criteria for equal regard:

**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.

This operational criterion invokes the threshold of competent medical care, not as a source for 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 those whose basic interests are themselves threatened or restricted by sickness, injury, or disease.

The following practical test is then used to determine whether or not a particular clinical trial satisfies this operational criterion. Let  $I = \{1, \dots, i, \dots, n\}$  be the set of individuals with a particular medical condition for which there is a set of available treatment options  $S = \{s_1, \dots, s_m\}$ . Let  $U_i$  be the set of interventions from  $S$  to which individual  $i$  might be allocated within a particular clinical trial and let  $U_i^*$  be the set of interventions from  $S$  that are admissible treatment options for the individual  $i$ .

**Practical Test for First Criterion:** A treatment  $s_j$  is admissible for individual  $i$  just in case there is either uncertainty among, or conflict between, expert clinicians about whether  $s_j$  is dominated by any other members of  $S$  as a treatment for individual  $i$ . For each individual in  $I$ , the care and protection afforded to that individual's basic interests falls within the threshold of competent medical care just in case each intervention in  $U_i$  is a member of  $U_i^*$ .

This condition is similar in important respects to the criteria of admissibility recommended by Kadane and colleagues (Kadane, 1996). The most salient difference is that its scope is restricted to the basic interests of study participants. When this condition is met, each individual who participates in a clinical trial is assured of receiving a package of medical care that would be recommended for them by at least a reasonable minority of expert clinicians.

This practical test is also similar to Freedman's clinical equipoise, but here too there are some important differences. First, the moral force of this requirement grounded, not in the individual physician's therapeutic obligation, but in broader claims about the need for basic social structures to function so as to preserve and to advance the basic interests of all community members and about the role of clinical medicine as a social structure that fills this mission when the basic interests of community members are restricted by sickness, injury, or disease.

Second, the equipoise requirement is sometimes applied to entire trial populations whereas the above practical test is to be applied to each prospective trial participant individually. The reason for this is simply that conflict or uncertainty about the relative therapeutic merits of a set of interventions

may exist for some individuals and not for others, depending on their particular clinical characteristics. One reason that equipoise theorists have largely failed to see how the clinical *community* could be uncertain about how to treat an *individual patient* is that they fail to take seriously the phenomenon of value conflict that I described above (London, 2007; Evans & London, 2006). In that example, a particular patient received treatment recommendations from representatives of competing approaches to managing his medical condition. Those recommendations are in conflict because one physician (or set of physicians) recommends intervention  $s_1$  over  $s_2$  for individual  $i$  while the other recommends  $s_2$  over  $s_1$  for the same individual.

The above test also avoids the criticism of fragility that is often leveled at frameworks that endorse the equipoise requirement. As data from a fixed size clinical trial emerge, for example, individual clinicians who were once uncertain may form a preference for one treatment over the others. Views that require uncertainty in the mind of the individual clinician cannot permit trials to continue in such cases. However, the above standard requires the trial to be terminated only if it has generated sufficient evidence to eliminate clinical conflict. If some clinicians are no longer uncertain, but other reasonable clinicians are, or would continue to make a competing treatment recommendation, then conflict remains and the trial may continue (London, 2007).

The first operational criterion and its associated practical test facilitate the resolution of clinical conflict while, at the same time, ensuring that when individuals whose basic interests are threatened or restricted by sickness or disease participate in research they receive a level of care that is consistent with an equal regard for the basic interests of participants and non-participants alike. However, these conditions alone are not sufficient for establishing the reasonableness of the associated risks. For one thing, the conduct of sound clinical research sometimes requires research participants to undergo tests or diagnostic interventions to which they would not be exposed if they simply sought treatment in a clinical setting. Even when such procedures affect most immediately the personal interests of individuals, in that they involve discomfort or some degree of bodily or personal intrusion, they nevertheless pose some incremental risk to the basic interests of research participants. The same is true for healthy subjects who expose themselves to research procedures that often most directly impact their personal interests but which nevertheless pose some additional degree of risk to their basic interests.

It remains to establish, therefore, what kind of incremental risks to the basic interests of subjects it is permissible to ask potential subjects to take on solely for the purposes of facilitating scientific inquiry. This constitutes a fundamental open problem in research ethics. In the space remaining I will only be able to gesture at how the requirement to show equal regard that is central to the integrative approach might be extended into this context (London, 2006).

Consider the following operational criterion for equal regard:

**Second Operational Criterion:** In all cases, the cumulative incremental risks to the basic interests of individuals that derive from research 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.

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.

To refine the operational content of this requirement, it is necessary to construct practical tests for this second operational criterion. This, in turn, requires the identification of an appropriate comparison class of activities and consideration about how finely to individuate the risks that are being compared across these activities. I conclude with some brief suggestions about how this might be achieved.

Four features of the research enterprise are particularly salient for establishing the structural similarity of another social activity. First, unlike some activities, such as rock climbing or racecar driving, the risks associated with clinical research do not add to the social value of the activity. Rather, these risks are necessary evils whose complete elimination would not detract from the value of clinical research. As such, appropriate comparator activities should embody this same attitude toward the associated risks.

Second, appropriate comparator activities should be the subject of active public oversight so that the risk-profile associated with the activity can be seen, at least *prima facie*, as representing a level of risk that is deemed socially acceptable after due reflection. In particular, it is imperative to avoid using as comparators activities where oversight mechanisms or safety regulations are poorly enforced or are widely recognized to be inadequate.

Third, participants bear the risks associated with purely research-related activities in order to facilitate an activity that will primarily benefit others. Where possible, therefore, appropriate comparator activities should have a similar structure in which incremental risks to the basic interests of individuals are born primarily for the benefit of others.

Finally, individuals are often willing to accept greater risks to their interests when they perceive themselves as having control over salient features of an activity. In clinical research, however, participants put their interests in the hands of identifiable parties who possess a particular expertise

where this creates limited but important responsibilities on the part of those parties to protect and to safeguard the interests of those participants. As a result, the risks to the basic interests of research participants that emanate from purely research-related procedures should be compared to risks to the basic interests of community members that are associated with social activities that also involve a principle-agent relationship.

Perhaps the most promising place to look for appropriate comparator activities is to volunteer public service professions, such as volunteer firemen and paramedics. The volunteer nature of these activities, their orientation to serving the public interest, and the fact that they are subject to varying degrees of public oversight constitute important structural similarities to the research enterprise. However, because there is no principal-agent relationship in these activities it may not be appropriate to permit in clinical research activities that have a risk profile that is similar to the most dangerous activities that individuals in these roles sometimes undertake.

Obviously, considerable work remains to be done to flesh out the details of the framework that I have sketched here. This approach has the advantage of providing a compelling normative foundation for a practical test that is similar to clinical equipoise, but which applies to individual trial participants and highlights the role of clinical research as a means of resolving clinical conflict. This alone makes this framework worth pursuing further. It also sketches an approach to what remains an open problem in research ethics that tries to frame the salient issues in a way that would make them more operationally tractable. Hopefully, the above arguments convey the importance of taking up these challenges in earnest.

## ACKNOWLEDGMENT

My work on this article was supported by a New Directions Fellowship from the Andrew W. Mellon Foundation.

## REFERENCES

- Brody, H. & Miller, F. G. (1998). 'The internal morality of medicine: Explication and application to managed care,' *Journal of Medicine and Philosophy*, 23, 384–410.
- Brody, H. & Miller, F. G. (2003). 'The clinician-investigator: Unavoidable but manageable tension,' *Kennedy Institute of Ethics Journal*, 13 (4), 329–346.
- Chard, J. A. & Lilford, R. J. (1998). 'The use of equipoise in clinical trials,' *Social Science and Medicine*, 47(7), 981–998.
- Donagan, A. (1977). 'Informed consent in therapy and experimentation,' *Journal of Medicine and Philosophy*, 2, 318–329.
- Emanuel, E. J., Wendler, D., & Grady, C. (2000). 'What makes clinical research ethical?' *Journal of the American Medical Association*, 283(20), 2701–2711.

- Evans, E. L. & London, A. J. (2006). 'Equipose and the criteria for reasonable action,' *Journal of Law, Medicine, and Ethics*. In press.
- Freedman, B. (1987). 'Equipose and the ethics of clinical research,' *The New England Journal of Medicine*, 317, 141–145.
- Freedman, B. (1990). 'Placebo controlled trials and the logic of clinical purpose,' *IRB: A Review of Human Subjects Research*, 12(6), 1–6.
- Fried, C. (1974). *Medical Experimentation: Personal Integrity and Social Policy*. Amsterdam: North-Holland Publishing.
- Gifford, F. (1986). 'The conflict between randomized clinical trials and the therapeutic obligation,' *Journal of Medicine and Philosophy*, 11(4), 347–366.
- Hellman, D. (2002). 'Evidence, belief, and action: The failure of equipose to resolve the ethical tension in the randomized clinical trial,' *Journal of Law, Medicine, and Ethics*, 30, 375–380.
- Jonas, H. (1969). 'Philosophical reflections on experimenting with human subjects,' *Daedalus*, 98(2), 219–247.
- Kadane, J. B. (Ed.). (1996). *Bayesian Methods and Ethics in a Clinical Trial Design*. New York: John Wiley & Sons, Inc.
- London, A. J. (2003). 'Threats to the common good: Biochemical weapons and human subjects research,' *The Hastings Center Report*, 33(5), 17–25.
- London, A. J. (2006). 'Reasonable risk in clinical research: A critique and a proposal for the integrative approach,' *Statistics in Medicine*, 25(17), 2869–2885.
- London, A. J. (2007). 'Clinical equipose: Foundational requirement or fundamental error?' In B. Steinbock (Ed.), *The Oxford Handbook of Bioethics*. New York: Oxford University Press, 571–596.
- London, A. J., & Kadane J.B. (2003). 'Sham surgery and genuine standards of care: Can the two be reconciled?' *The American Journal of Bioethics*, 3(4), 61–64.
- London, A. J. & Kadane, J.B. (2006). 'Sham surgery and reasonable risks,' in D. Benatar (Ed.), *Cutting to the Core: Exploring the Ethics of Contested Surgeries* (pp. 211–228). New York: Rowman & Littlefield.
- Marquis, D. (1983). 'Leaving therapy to chance,' *Hastings Center Report*, 13(4), 40–47.
- Miller, F. G. (2003). 'Sham surgery: An ethical analysis,' *American Journal of Bioethics*, 3(4), 41–48.
- Miller, F. G. & Brody, H. (2003). 'A critique of clinical equipose: Therapeutic misconception in the ethics of clinical trials,' *The Hastings Center Report*, 33(3), 19–28.
- Miller, F. G. & Brody, H. (2007). 'Clinical Equipose and the Incoherence of Research Ethics,' *Journal of Medicine and Philosophy*, 32, 151–165.
- Miller, P. B. & Weijer C. (2003). 'Rehabilitating equipose,' *Kennedy Institute of Ethics Journal*, 13(2), 93–118.
- Peto, R., Pike, M. C., Armitage, P., Breslow, N. E., Cox, D. R., Howard, S. V., Mantel, N., McPherson, K., Peto, J., Smith P. G. (1976). 'Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design,' *British Journal of Cancer*, 34, 585–612.
- Rawls, J. (1982). 'Social unity and the primary goods,' in A. Sen & B. Williams (Eds.), *Utilitarianism and Beyond* (pp. 159–185). New York: Cambridge University Press.
- Sen, A. (1979). 'Utilitarianism and welfarism,' *The Journal of Philosophy*, 76(9), 463–489.
- Weijer, C. & Miller, P. B. (2004). 'When are research risks reasonable in relation to anticipated benefits?' *Nature Medicine*, 10(6), 570–573.