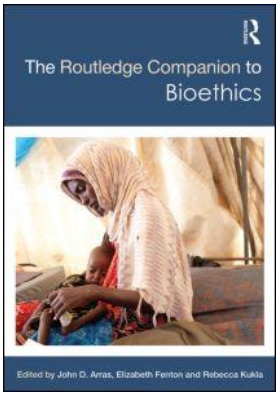

The Routledge Companion to Bioethics

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Publication details
https://test.routledgehandbooks.com/doi/10.4324/9780203804971.ch15
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Published online on: 12 Dec 2014

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THE DUTY OF CARE AND EQUIPOISE IN RANDOMIZED CONTROLLED TRIALS

Charles Weijer, Paul B. Miller, and Mackenzie Graham

The Ethical Challenge of Randomization

The randomized controlled trial (RCT) is widely regarded as a key approach to assessing the efficacy and safety of new medical treatments. RCTs are near the top of the evidence-based medicine hierarchy, and the results of well designed and carefully conducted RCTs influence physicians, drugs regulators, and health policy-makers (Sackett et al. 1996). In an RCT, patients with a medical illness are allocated by chance to one of two or more study arms or "conditions." Patients allocated to the experimental condition receive the new treatment under investigation, while patients allocated to the control condition receive a standard treatment to which the new treatment is being compared. All patients are followed for a defined period of time, and information on prespecified outcome measures is collected. Physician-researchers conclude that the new treatment is effective if patients in the experimental condition outperform those in the control condition in the primary outcome measure according to statistical tests of significance.

Randomization is an important methodological strength of the RCT: It helps ensure the comparability of patients in the experimental and control conditions; it enables both patient and physician-researcher to remain ignorant as to assignment of conditions; and it guarantees the validity of statistical tests of significance (Friedman et al. 1998). Despite the advantages, randomization is the source of one of the most difficult and persistent challenges in the ethics of research. Until recently, most patients were offered enrollment in an RCT by their own physician; in many cases, the physician-researcher conducting the RCT was the patient's physician. Physicians are widely regarded as having special ethical obligations to their patients. These include the obligation to ensure that the patient receives competent treatment. The problem is how can the physician, consistent with this ethical obligation, offer the patient enrollment in an RCT? As we have seen, in an RCT the patient will be randomly allocated to the experimental or control condition. On the face of it at least, tossing a coin to determine which treatment a patient will receive seems inconsistent with the physician's obligation. Can the physician ever ethically offer RCT enrollment to his or her patient? If so, under what circumstances?

In order to address these questions, we require a clearer picture of the physician's ethical obligations to his patient. The physician–patient relationship is a trust relationship. Trust relationships play a very important role in our lives. These relationships have been described as having a tri-partite, purposive structure: A trusts B *to do* C (Baier 1986). In this three-part relationship, the truster (in this case, the patient) trusts the trustee (the physician) to protect and promote a significant practical interest (the patient's health). The truster cedes control of the significant practical interest, and as a result, the trustee has discretionary power over the interest at stake (Miller and Weijer 2006b). Trust relationships are, as a result, not relationships between equals; rather, they are relationships of structural inequality in which the truster is dependent on the loyalty, judgment, and competence of the trustee. To mitigate the vulnerability of the truster, moral obligations accrue to the trustee, including a duty to act and advise the truster so as to protect and promote the significant practical interests at stake. Socially important trust relationships, including those between doctor and patient, lawyer and client, and chief executive officer and shareholder, are closely mirrored in a legal context by the law of fiduciary relationships (Miller and Weijer 2006a).

Thus, we argue that it is the trust relationship between physician and patient that grounds the physician's ethical duties to the patient. Prominent among these duties is the ethical duty of care: The physician must act and advise the patient so as to protect and promote the patient's health. And it is the duty of care that comes into conflict with randomization. Given the randomized nature of treatment allocation in an RCT, physicians cannot ensure that their patient will receive one treatment as opposed to another. How can physicians fulfill their duty of care to the patient if they cannot be sure which treatment their patient will receive? Finding a way to answer this question is a matter of considerable importance. If physicians cannot ethically offer their patients enrollment in RCTs, important medical research will be impeded and the development of new treatments will slow. The ethical challenge of randomization has troubled many bioethicists for decades. In this chapter, we will consider a few of the most prominent arguments that have been offered to address the problem, examine closely their underlying ethical foundations, and situate the debate as a part of a larger question regarding the origins of ethical norms. At stake is a foundational question in the ethics of research: To what degree, if any, may the medical interests of a patient be put at risk for the potential benefit of future patients and society?

Fried and Freedman's Solutions

In his 1974 book *Medical Experimentation: Personal Integrity and Social Policy*, Charles Fried argued that the physician–patient relationship is a trust relationship, and concluded that the physician's duty of personal care to his patient requires "unqualified fidelity to that patient's health" (Fried 1974: 50). The physician must exercise his judgment in a manner that considers both the specific health interests and particular circumstances of the patient. Fried believed that personal care is a right that a physician "may not compromise in the general pursuit of the common good" (Fried 1974: 92). When a physician sacrifices the interests of the patient in receiving competent care in favor of the welfare of others, he violates the integrity of the relationship and thus his obligations to the patient. Fried argued that participation in an RCT is consistent with a patient's right to personal care only when a state of "equipoise" obtains, that is, when the physician is genuinely uncertain as to the preferred treatment for the patient (hereafter,

"Fried's equipoise"). Importantly, Fried's equipoise is specific to a particular patient, taking into account the patient's symptoms, diagnosis, and personal preferences. So long as Fried's equipoise exists, the physician does not know which treatment is best for the patient and, accordingly, the duty of personal care is indifferent to the patient being allocated to one condition or another in an RCT—both treatments are consistent with the considered judgment of the physician.

Fried's equipoise has been interpreted as an absolute standard in which physicians' uncertainty is balanced on a knife's edge; that is, their preference for one treatment compared with another is precisely 50:50 across a whole range of criteria (Schafer 1982; Marquis 1983). On this reading, Fried's equipoise sets a nearly impossible standard, one that is both too rigid and too fragile. Promising results from preparatory research required to motivate an RCT seem likely to disrupt Fried's equipoise. Even if Fried's equipoise exists at the start of an RCT, accumulating data on patients in the RCT would surely disrupt it long before the study is completed. Because of the difficulties, commentators have been skeptical of Fried's equipoise as a solution to the ethics of randomization (Joffe and Truog 2011).

In an effort to resolve this impasse, Benjamin Freedman proposed a more robust version of equipoise, which he called "clinical equipoise" (Freedman 1987). Clinical equipoise relocates the site of uncertainty regarding the preferred treatment from the individual physician to the expert medical community as a whole. Thus, when there exists "an honest, professional disagreement among expert clinicians about the preferred treatment . . . a state of clinical equipoise exists" (Freedman 1987: 144). For Freedman, the purpose of an RCT is to disrupt clinical equipoise and change clinical practice. When the accumulated evidence in favor of one treatment is such that no open-minded physician informed of the results would favor the other treatment, clinical equipoise is disturbed and the RCT must stop. Because preliminary research data or interim RCT results would be unlikely to resolve disagreement within the medical community, RCTs will generally need to continue to the planned point of completion in order to provide data sufficiently robust and reliable to change medical practice.

Clinical equipoise, with its emphasis on collective norms rather than individual opinion, can be understood as a reflection of a larger shift within the medical community towards evidence-based medicine (Sackett et al. 1996). For Freedman, standards of care are determined by consensus within the medical community. Clinical equipoise promotes consistent standards of care across groups of expert physicians, and diminishes the import of the (potentially idiosyncratic) judgment of individual physicians. As Freedman points out:

> competent (hence, ethical) medicine is social in nature. Progress in medicine relies on progressive consensus within the medical and research communities . . . Normative judgments of behavior rely on a comparison with what is done by the community of medical practitioners.
>
> (Freedman 1987: 144)

Accordingly, the physician's duty of care consists less of the individualized judgment advocated by Fried, and more of the provision of competent care consistent with broad communal practices among expert physicians. Indeed, such is the emphasis on communal norms that, consistent with clinical equipoise, an individual physician with a strong treatment preference may nonetheless ethically offer his patient trial enrolment, provided the less-favored treatment is preferred by responsible and competent colleagues.

Clinical equipoise is an important deontological constraint upon science. It requires that the experimental and control conditions in an RCT be consistent with competent care. It thereby prohibits exposing patients to the risks of an experimental or control condition that is known to involve substandard care. While placebo-controlled trials may offer certain advantages, including being cheaper and arguably easier to interpret, clinical equipoise restricts the use of placebos in RCTs (Freedman 1990). A placebo control may only be used when no proven and effective treatment exists, the trial selectively enrolls patients who have not responded to standard treatment, the medical condition is minor and non-treatment is consistent with competent practice, or all study participants receive standard medical care (as in an RCT in which the addition of a new drug to a standard regimen is compared with the standard regimen plus placebo) (Weijer and Miller 2004).

At the time that Fried and Freedman were writing, most patients were offered enrollment in an RCT by their own physician, and sometimes the physician-researcher conducting the RCT was that same physician. As a result, Fried and Freedman understood norms governing RCTs in terms of the physician–patient relationship. They both acknowledged that physicians owe a duty of care to their patients, and they both saw the duty of care as a key point of conflict with random allocation of patients to study conditions in an RCT. However, Fried and Freedman understood the demands of the duty of care somewhat differently. Fried understood the duty of personal care to require that physicians exercise individualized judgment on behalf of patients. This understanding of the duty of care in turn shaped Fried's equipoise: Only when the physician is uncertain as to the preferred treatment for his or her patient (considering the patient's history, diagnosis, and preferences) would an offer of RCT enrollment be ethically permissible. For Freedman, the norms of practice derive from the community of physicians and not the opinions of individual physicians; accordingly, the duty of care necessitates consistency with accepted communal practices. This understanding of the duty of care in turn shaped Freedman's concept of clinical equipoise: Only when there is disagreement in the relevant community of expert physicians as to the preferred treatment may the patient be approached for enrollment in an RCT.

Critics

Freedman's concept of clinical equipoise was—for a period of time at least—regarded by many as the definitive solution to the ethics of randomization. Clinical equipoise is widely used (and cited) by those who design and conduct RCTs to justify the choice of study conditions and the decision whether to continue a trial in light of interim data. Its role as an ethical constraint upon the practice of science has been particularly important. Clinical equipoise has been cited prominently in criticism of placebo-controlled trials and trials in developing countries (Rothman and Michels 1994; Angell 1997). Finally, it is a key concept in a systematic approach to the ethical analysis by research ethics committees of benefits and harms in clinical research called "component analysis" (Weijer and Miller 2004).

However, the years since 2002 have witnessed a vigorous debate in the bioethics literature about clinical equipoise and the duty of care as solutions to the ethical problem of randomization (Joffe and Truog 2011). Critics can be divided into at least three groups: Those who endorse the duty of care but deny clinical equipoise; those who endorse clinical equipoise but deny the duty of care as its moral foundation; and those

who deny both clinical equipoise and the duty of care. The first group of critics believes that clinical equipoise ignores the pivotal importance of clinical judgment in protecting the medical interests of patients in RCTs. Like Fried, they understand the duty of care as requiring that physicians exercise individual judgment on behalf of their patients, and the appeal of clinical equipoise to communal norms does not satisfy the duty of care so understood. For instance, Deborah Hellman points out that "what matters ethically is not whether the medical community is in equipoise about the merits of the standard versus the experimental therapy, but rather whether the individual physician enrolling patients in the study himself favors one treatment or another" (Hellman 2002: 375). As a result, she rejects clinical equipoise and argues that the ethical problem of randomization is "real and fairly intractable" (Hellman 2002: 379).

The second group of critics acknowledge the importance of clinical equipoise as an ethical constraint upon science, but questions whether it can be grounded in the role of the physician-researcher and his attendant duty of care to the patient. At least two reasons are given. First, as argued above, clinical equipoise seems inconsistent with Fried's view of the duty of care and its requirement of individual clinical judgment. As a result, Alex London concludes that clinical equipoise must be "revised or rejected because it is . . .. insufficiently responsive to the physician's fiduciary obligations to the individual patient" (London 2007: 106). Second, critics point out—correctly—that RCTs in health services and public health research may not involve physician-researchers, and thus clinical equipoise seems not to apply. Rebecca Kukla sees this as a troubling result: "To the extent that one grounds research ethics on the ethics of therapeutic clinical medicine, these other kinds of research will be left in an unconstrained ethical vacuum" (Kukla 2007: 172). Both London and Kukla go on to propose alternative moral foundations for clinical equipoise (or cognates), appealing to egalitarian political theory and the researcher's moral obligations to persons, respectively (London 2007; Kukla 2007).

The third group of critics rejects altogether the role of the duty of care and clinical equipoise in the ethics of randomization. Franklin Miller and colleagues have argued that invoking an ethical duty of care and the moral rule of clinical equipoise in RCTs conflates the ethics of research with the ethics of medical practice (Miller and Brody 2003a; Miller 2004). The differing roles of researchers and physicians are incompatible, according to Miller and colleagues, because the ends of the activities in which they are engaged are different. Medical practice aims *solely* to protect and promote the health of the patient, while medical research aims *solely* to produce generalizable knowledge. When a physician-researcher recruits a patient in an RCT, she is no longer acting as a physician, but rather as a researcher. As such, different ethical obligations apply. In particular, the physician-researcher does not have a duty of care to the patient in an RCT because the purpose of research is not to provide medical care. As a result, Miller and colleagues claim that clinical equipoise is "neither necessary nor sufficient for ethically justifiable RCTs" (Miller and Brody 2003a: 25). Since the ethical problem of randomization is generated by the special moral duties that physicians have to patients, they deny that there is an ethical problem in need of resolution.

To understand the force of Miller and colleagues' position, it is important to take account of recent changes in clinical research. Currently, although some patients may be approached for RCT enrollment by their physician, many—if not most—learn of RCTs through other sources, including the Internet. Typically, the patient has had no prior relationship with the physician-researcher conducting the RCT. Thus, the norms of the physician–patient relationship may *not* be immediately relevant. Given that the

ends of research are separable from those of medical practice, it would be hasty to assume that the ethical obligations of one domain *automatically* apply to the other. An argument is needed as to why the relationship between physician-researcher and patient in an RCT ought to be understood as one of trust.

Skeptical of the existence of a trust relationship, Miller and colleagues believe that it is the "the basic goal and nature of the activity [which] determines the ethical standards that ought to apply" (Miller and Brody 2003a: 22). In their view, the differing purposes of research and medical practice entail separate ethical standards. The ethical obligations of the physician-researcher are defined by the norms internal to the practice of good science. These scientific norms require that physician-researchers ensure that the RCT asks an important question, the methodology is sound, the risks to the patient are outweighed by the benefits to future patients, patients provide informed consent, and are not exploited.[1] Physician-researchers do not, in their view, have a duty to protect and promote the medical interests of patients in an RCT. According to Miller and colleagues, "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 and Brody 2003a: 21).

Central to Miller and colleagues' rejection of the duty of care in clinical research is their resistance to the role of clinical equipoise as an ethical constraint upon science. As we have noted, clinical equipoise prohibits exposing patients to experimental or control conditions that are known to involve substandard care, and this limits the ethical use of placebo controls when proven, effective treatment exists for a medical condition. Miller and colleagues have argued that placebo-controlled trials have important scientific advantages, particularly in illnesses such as schizophrenia or depression, in which deterioration or improvement is difficult to measure accurately (Miller and Brody 2002). The importance of generating reliable scientific data from RCTs, they believe, outweighs the medical interests of patients. Thus, they claim that patients with schizophrenia and depression—conditions for which proven, effective treatment exists—can ethically be enrolled in an RCT with placebo as the control condition (Miller and Brody 2002, 2003a).

But can an appeal to the internal norms of science alone successfully ground the ethical obligations that Miller and colleagues would substitute for those that underlie clinical equipoise? For some requirements, the answer seems to be yes. The requirement of a well formulated scientific question and the use of an appropriate study method are scientific norms. In other cases, though, the answer is less clear. What norm internal to science grounds obligations to ensure that study benefits exceed harms, to obtain informed consent, or to ensure that participants are not exploited? These claims might be justified by appeal to broader ethical principles (e.g., Mill's Harm Principle) or utilitarianism, but doing so seems to violate the assumption that the "goal and nature of the activity determines the ethical standards" (Miller and Brody 2003a; Miller and Weijer 2007). Further, even if clinical research has a "frankly utilitarian purpose," deontological constraints, such as clinical equipoise, may have an important role to play. Consider the analogy with criminal punishment, which may be viewed as a utilitarian project limited by deontological constraints not grounded in utility, including "don't punish the innocent" (Hart 1968). Finally, their argument ignores the possibility that the moral obligations inherent in medical practice and research arise because of the nature of the relationships involved, and not simply the goals of the activities. We return to these issues in the final section of this chapter.

Revisions

We believe that a successful resolution to the ethical challenge of randomization must take account of these criticisms. First, the justification of clinical equipoise cannot rest solely on the trust relationship between physician-researcher and patient. Research ethics committees review RCTs prior to enrollment of any patients in the study (and hence prior to any physician-researcher and patient relationship) and some health research, including public health research, does not even involve physician-researchers. Second, there must be a defined role for clinical judgment in the enrollment and continuation of patients in RCTs. Third, if it is the case that a physician-researcher owes the patient in an RCT a duty of care, an argument must be given as to why the duty applies in research without appeal to the norms of medical practice. In this section we provide a revised account of equipoise and the duty of care responding to the first two points; in the next section we give an account of the trust relationship between the physician-researcher and patient.

There is something deeply appealing about both Fried's and Freedman's solutions to the conflict between randomization and the duty of care. Fried identifies an essential feature of medical practice, namely, the personalized judgment exercised by a physician on behalf of his patient; Freedman recognizes the role of the professional community as a whole in setting standards for medical care. However, we have argued that neither concept presents a sufficient moral condition for the conduct of RCTs (Miller and Weijer 2003). The lengthy history of abuses in research makes clear the shortcomings of relying solely on the character and judgment of physician-researchers, and highlights the importance of having research ethics committees in place to judge the ethical acceptability of RCTs. Indeed, it is difficult to see how Fried's equipoise provides research ethics committees with any guidance. While clinical equipoise seems well suited to guiding research ethics committees, it does not account for the protective judgment of individual physician-researchers. Given this, we argue that the two concepts may be productively viewed as having differing roles in the ethical justification of randomization.

While Freedman understood the physician–patient relationship as the sole foundation for clinical equipoise, we believe another trust relationship, namely that between the state and research participant, plays an important role in grounding the concept (Miller and Weijer 2006b). RCTs are key to the rigorous assessment of the safety and effectiveness of novel medical treatments, and the resulting evidence base for medicine is a public good. Without the voluntary participation of patients in RCTs, this evidence could not be generated and the public would be deprived of an important good. Patients enroll in RCTs trusting that the state will protect their interests in exchange for their contribution to the scientific enterprise. The interests of patients in RCTs are several, and include interests in receiving competent medical care and not being exposed to undue risk for the benefit of others. As a result of the public good of RCTs and the trust shown by patients who agree to participate in them, the state is obligated to protect the interests of patients in RCTs. The state fulfills its trust-based obligations in promulgating guidelines for the ethical conduct of research and ensuring that they are enforced. On this view, the research ethics committee may be viewed as an arm of the state that ensures the protection of the liberty and welfare interests of research participants (Miller and Weijer 2006b).

Clinical equipoise is a specification of the state's trust-based obligation to protect the patient's interest in receiving competent medical care (Miller and Weijer 2006b). It

guides research ethics committees in their review of RCTs by directing their attention to the relative merits of study treatments (or therapeutic procedures) in light of available evidence and current medical practices. The research ethics committee must ensure that sufficient evidence exists to support the experimental condition; they must also ensure that the control condition does not involve treatment known to be substandard. Study conditions are permissible if the research ethics committee concludes that honest, professional disagreement in the community of expert practitioners exists (or would exist, were the evidence widely known) as to the preferred treatment. Research ethics committee approval signifies that study conditions conform to broad professional standards for the treatment of a defined population of patients. As such, clinical equipoise is a key concept in a systematic and comprehensive approach to the ethical analysis of study benefits and harms we call "component analysis" (Weijer and Miller 2004).

It is important, however, to recognize the limits of research ethics committee approval. Conformity with clinical equipoise does not entail the moral acceptability of either enrolling or retaining *particular* patients in an RCT. For instance, patients may satisfy all of an RCT's eligibility criteria, but their medical history may suggest that study participation will be unduly harmful or burdensome. Physician-researchers meet their duty of care in enrolling and retaining patients in an RCT by making an expert judgment that takes into account the evidence on treatment alternatives *and* the particular circumstances of the patient. Knowing that a research ethics committee has determined that clinical equipoise is fulfilled, the physician-researcher may enroll or retain a patient in an RCT unless the physician-researcher believes it would be medically irresponsible to do so, and this belief is supported by evidence that would be convincing to colleagues. We refer to this ethical requirement as the "clinical judgment principle," a more robust variant of Fried's equipoise. Protecting the medical interests of patients in RCTs requires that both clinical equipoise *and* the clinical judgment principle are satisfied in the design, review, and conduct of an RCT (Miller and Weijer 2006b).

A Moral Foundation for the Physician-Researcher and Patient Relationship

The explanation in the previous section both grounds clinical equipoise in the trust relationship between the state and research participant and articulates a clear role for the expert judgment of the physician-researcher in enrolling or continuing patients in RCTs. Here we address the third concern: Why should we think that physician-researchers owe a duty of care to patients in RCTs similar to that which physicians owe their patients? Both of these are fiduciary relationships characterized by trust (Miller and Weijer 2006a, 2006b). As discussed in the first section of this chapter, a trust relationship is defined by several important features. First, it involves a relationship characterized by structural inequality. Second, it typically involves the transfer of discretionary power over certain interests from the truster to the trustee. Third, because the trustee has been entrusted with these powers, he incurs an obligation to use them in a way that protects and promotes the interests of the truster. Because the duty of care is rooted in the nature of the trust relationship, this duty applies whether the physician's goal is to improve the health of a patient in a care context, or to produce generalizable knowledge in a research context. The ends of the activities are immaterial to the moral obligations of the parties involved; it is the structure of the relationship between the parties that is morally salient.

The physician-researcher and patient relationship in an RCT bears all of the hallmarks of a trust relationship. First, given that therapeutic modalities are administered in RCTs, the patient necessarily relies on the expertise of the physician-researcher in improving his or her health. Only the physician-researcher is socially authorized to provide the patient with the treatments prescribed by the study protocol. Further, the physician-researcher possesses specialized knowledge that the patient does not have. Thus the relationship between physician-researcher and patient is structurally unequal.

Second, the patient grants the physician-researcher discretionary powers over the former's health interests, and by ceding these powers the patient is exposed to the risk of having these interests compromised. Among other things, physician-researchers are authorized to:

- collect and use confidential information about patients;
- determine eligibility for RCT participation;
- administer and withdraw therapeutic interventions (standard and experimental drugs and procedures);
- administer and withdraw non-therapeutic procedures;
- order alternative therapy (or the resumption of standard therapy) in the event the study must be terminated or the patient removed from the RCT.

Exercise of these powers entails considerable discretion. Physician-researchers must exercise judgment regarding patient eligibility, as well as in the development and execution of study protocols. It is up to the discretion of the physician-researcher to determine whether protocol adherence is appropriate for a particular patient. Whether the patient receives competent care and is protected from undue harm will thus depend on the decisions made by the physician-researcher.

Third, because the physician-researcher has been entrusted with these powers, he incurs a duty to protect and promote the health interests of the patient. That is, in the context of an RCT, the physician-researcher owes the patient a duty of care.

The trust-based nature of the physician-researcher and patient relationship is underscored by the fact that it fits the legal definition of a fiduciary relationship as well. We have argued that a fiduciary relationship is established where, "One party entrusts another with discretionary power over the legal, economic or other practical interests of a beneficiary, and the other party undertakes, expressly or impliedly, to exercise that power" (Miller and Weijer 2006a: 427–8).

In contrast to most private law relationships, in which parties are presumed to have an equal and independent capacity to pursue their respective interests, the transfer of discretionary power that characterizes the fiduciary relationship results in structural inequality and dependence. Haavi Morreim has argued that the relationship between physician-researchers and patients cannot be fiduciary because RCT protocols constrain the exercise of discretion by physician-researchers (Morreim 2005). However, she misapprehends the nature of fiduciary discretion. Fiduciaries are not expected to enjoy—and rarely do enjoy—unfettered discretion to advance the interests of their beneficiaries. Rather, they have a contextual kind of discretion, that is, discretion within the ambit of constraints peculiar to the activity in which they and their beneficiaries are involved. These constraints may be owing to the nature of the activities, the environment within which they are undertaken, or overarching legal or regulatory requirements. As we explain above (and elsewhere in a detailed response to Morreim), physician-researchers

have discretion in determining whether to enroll or to continue the enrolment of patient-subjects in RCTs, notwithstanding that their fiduciary discretion differs in certain particulars from the kind of discretion enjoyed by physicians in clinical settings (Miller and Weijer 2006a).

What obligations arise from the relationship between the physician-researcher and patient, understood in terms of the discretionary power that the former enjoys over the latter? As noted above, the vulnerability inherent in the trust relationship determines the obligations of the physician-researcher. Perhaps the most obvious vulnerability of the patient is to exploitation by the physician-researcher when discretionary power is misused to promote the interests or goals of the latter at the expense of the former. Exercise of power in this way is exploitative because it involves treating the patient as a mere means to an end; that is, the patient's interests are actively subordinated in service of the interests of others. Vulnerability to exploitation grounds a duty of loyalty, which requires the physician-researcher to avoid or properly manage conflicts of interest and duty.

Additionally, the patient is vulnerable to neglect by the physician-researcher. Because exercise of discretionary power requires judgment, the patient is vulnerable to failure by the physician-researcher to make responsible judgments. Accordingly, the physician-researcher owes the patient a "duty of discretion," which requires the former to exercise discretion or judgment when making decisions on behalf of the latter.

Finally, the patient is vulnerable to carelessness. Accordingly, the physician-researcher owes the patient a "duty of care." One way in which the physician-researcher can fulfill this obligation is by appealing to the "clinical judgment principle," which permits the enrollment of patients in an RCT by physician-researchers (provided the study has been reviewed by a research ethics committee and found to be consistent with clinical equipoise) unless "they believe that it would be medically irresponsible to do so and this belief is supported by evidence that ought to be convincing to colleagues" (Miller and Weijer 2006b: 546). This principle emphasizes the role of expert judgment in fulfilling the duty of care. If the physician-researcher has good reason to believe that one of the treatments being tested in an RCT would expose a patient to undue harm, enrollment would be medically irresponsible and ethically impermissible.

We have seen that although the goals of clinical research and medical practice are different, the relationship between the physician-researcher and patient is similar to that between physician and patient; both are trust relationships. It is because both are trust relationships—and *not* because they are similar in other respects—that the duties of loyalty, discretion, and care apply equally to both physicians and physician-researchers. Denying the relevance of the duty of care is not an acceptable answer to the ethical challenge of randomization. Physician-researchers must abide by some form of equipoise (as exemplified by clinical equipoise and the clinical judgment principle) when enrolling and continuing patients in RCTs.

Normative Externalism and Internalism

In the final section of this chapter, we situate the debate about the ethics of randomization as a part of a larger question regarding the origins of ethical norms. As we have seen, at stake is whether and, if so, to what degree the medical interests of a patient in an RCT may be put at risk for the potential benefit of future patients and society. We argue that both the state and the physician-researcher have a trust-based duty of care to the patient

that grounds clinical equipoise and the clinical judgment principle. These moral rules are important deontological constraints on science; they prohibit knowingly providing patients with substandard care and require physician-researchers to exercise expert judgment on their behalf. Franklin Miller and colleagues reject this approach. They deny the existence of a duty of care and reject related deontological constraints upon science. In their place, they offer an essentially utilitarian apparatus in which the medical interests of patients may be put at risk provided that the potential benefits to future patients and society are sufficiently significant. They endorse as ethical placebo-controlled trials involving patients with conditions such as schizophrenia and depression, for which proven effective treatment exists. Finally, they deny that physician-researchers have a duty to exercise judgment to protect the medical interests of patients.

A key feature of the debate is disagreement as to the source of norms in clinical research, one that we might productively characterize as a debate between ethical externalism and internalism. For the externalist, norms governing an activity are imposed from without, either by broad ethical or legal norms that apply to society as a whole, or the more fundamental ethical principles upon which these norms are based. For the internalist, the norms governing an activity are generated by the nature of the activity itself. So long as the nature of the activity or practice can be adequately specified, choosing among competing ethical norms will not raise intractable problems.

Charles Fried, Benjamin Freedman, Rebecca Kukla, Alex London, Paul Miller, and Charles Weijer adopt an externalist view of ethical norms. For Fried, Freedman, Miller, and Weijer, physician-researchers owe an ethical duty of care to patients in RCTs because of the asymmetry, dependence, and vulnerability of the trust relationship. Miller and Weijer argue further that the state also owes a trust-based duty of care to patients in RCTs. Importantly, all trust relationships possess these characteristics, and thus, the ethical obligations of the actors in RCTs are imposed from outside of the activity. While the norms of science, including the importance of a valuable study question and appropriate methodology, are a part of the ethics of RCTs, the ends of science are constrained by ethical duties that trustees owe trusters broadly within society. For instance, even if the use of a placebo control would be scientifically desirable in some cases, clinical equipoise (and the duty of care) prohibit its use when proven, effective treatment exists and is available in a sustainable manner.

Franklin Miller and colleagues' critique of the duty of care and equipoise may be viewed as a rejection of externalism. Defenders of the duty of care err, according to them, in "drawing the line" in the wrong place because they fail to give sufficient weight to the ends of science (Miller and Brody 2003a). In their internalist approach, Franklin Miller and colleagues argue that physician-researchers must see themselves as "scientists only and not as doctors," and should thus derive their ethical obligations from the goals of science (Joffe and Miller 2008). This explains why they argue that norms cannot be imported from one activity into another (i.e., from clinical practice to research); the differing ends of each activity generate different ethical norms. In their view, the duty of care does not apply within the research context because it is the ends of medical practice, and *only* these ends, that generate such obligations (Miller and Brody 2003b).

Franklin Miller and Steven Joffe, in the most detailed exposition of this internalist view, point out that "biomedical research constitutes a spectrum of activities," with in vitro experimentation at one end, and clinical research on patients at the other (Joffe and Miller 2008: 32). They claim that it is a necessary condition of biomedical research that its goal be the production of generalizable knowledge, and that it respect "the internal

norms of science," which requires the use of the scientific method as well as respect for scientific integrity (Joffe and Miller 2008: 33). Biomedical research is also subject to ethical constraints, which accumulate incrementally.

Research involving inanimate or nonsentient materials, such as molecules, DNA, and cell lines, must "minimize external risks," and "proceed under the good-faith assumption that the societal benefits of the research are likely to outweigh any potential harms" (Joffe and Miller 2008: 35). When research involves laboratory animals, including mice, cats, dogs, pigs, and primates, these same ethical constraints apply, with the additional requirement that the risks and burdens to the animals be minimized. Research on healthy human volunteers imposes additional constraints, including avoiding unacceptable risks, respecting participants, ensuring fairness in subject selection, and satisfying ancillary care obligations. When research involves patients, further ethical constraints must be observed, including "maximizing direct benefits, consistent with achieving the scientific aims of the study," honesty regarding the nature of the research, and the adoption of a "caring attitude" which acknowledges the patient's illness or limitation (Joffe and Miller 2008: 35). Due respect for the variable moral status of the experimental materials coupled with regard for the internal norms of science is thought sufficient to ensure that patients are protected.

The internalist view is not without difficulties. If the internalist seeks to ground specific moral constraints in the ends of an activity, she must first determine what precisely constitute the "ends of research." Numerous stakeholders may be involved in a particular research study (patients, families, research ethics committees, academic institutions, public funding bodies, and private sector funders), and research can take many different forms (e.g., market surveys, ethnographies, gene sequencing, and RCTs). Many social scientists would deny that their research is designed to produce generalizable knowledge. Even if we take the core end of science to be production of generalizable knowledge, this goal needs to be refined further for it to be useful: Who or what is the knowledge for? Is it knowledge purely for its own sake? How generalizable must it be?

Moreover, research is a complex activity, and it is not entirely clear just what is meant by the term "research context." Rather than playing a single role at any given time, researchers often perform many different roles. For example, if a physician-researcher undertakes a routine examination of a patient, performs an extra blood draw to monitor the experimental drug the patient is taking for hypertension, and then prescribes a medication for an ear infection, all in the span of 15 minutes, what role is the physician-researcher actually playing? In a theoretical sense, one might say that he starts out in the role of the physician, and then takes on the role of the researcher, before returning to his previous role. In practice, however, this exchange of roles is not obvious to either the patient or the physician-researcher.

The internalist might respond that an externalist view offers no clearer a picture of what the "ends of research" are or ought to be. But this is less of a problem for the externalist, as she doesn't seek to ground ethical constraints upon science in the ends of research. Moreover, the internalist might agree that research is a complex activity, yet insist that it is incumbent upon researchers that they do their utmost for their own sake to maintain a clear separation between roles (Miller and Rosenstein 2003).

The difficulty of justifying moral constraints becomes more pronounced when the internalist considers research on human participants. Miller and Joffe claim that researchers are required to fulfill familiar moral obligations (non-maleficence, respect for persons, justice) in the conduct of their research on healthy human participants,

with additional requirements for patients who are in need of care. In order to remain consistent with the view that researchers are acting as scientists, the internalist must reject constraints on study design (such as equipoise requirements) which are not entailed by good scientific practice. Miller and Joffe argue that such constraints result from physicians "graft[ing] the pursuit of research objectives onto [their] primary therapeutic commitments," and that these are external to the practice of good science (Joffe and Miller 2008).

What sort of argument can the internalist employ to justify appropriate moral constraints on research, without resorting to moral principles that go beyond the practice of "good science"? Miller and Joffe claim that, in all instances, researchers must minimize the external risks associated with their research, and proceed under the good-faith assumption that the social benefits of their work will outweigh any potential individual or societal harms. When research requires testing on laboratory animals, researchers must ensure that the number of animals used is minimal, and that the pains or burdens to which these animals are subjected are minimized. One could envision this constraint emerging from a scientific requirement to maximize the use of limited scientific materials; subjecting animals to unnecessary testing would simply be wasting a valuable resource. Perhaps this same justification could be applied to minimizing harm to human subjects, although this would seem somewhat morally obtuse.

Miller and Joffe also state that there must be some limit on the acceptable level of risk to which research participants can be exposed (though it is not clear what that limit is), and assert that researchers must maximize direct benefit to participants, provided doing so is consistent with answering the relevant scientific questions (Joffe and Miller 2008). They also suggest that researchers adopt a "caring attitude" towards participants in recognition that they are "human beings rather than data points" (Joffe and Miller 2008: 38). But these harm–benefit requirements rest on a utilitarian foundation. Any plausible view of utilitarianism requires a principle of utility and a theory of welfare and, thus, their view of acceptable harms and benefits appeals to norms external to the practice of good science (Miller and Weijer 2007). The same can be said for adopting a "caring attitude." Why is adopting a "caring attitude" an inherent norm of scientific activity, and not a moral constraint that is grounded in more general moral principles? Imagine a physician-researcher who has the same attitude to patients as Dr Harry Harlow, the author of the now notorious monkey maternal separation experiments, had to his experimental subjects. (Harlow once remarked: "The only thing I care about is whether the monkeys will turn out a property I can publish. I don't have any love for them. Never have. I don't really like animals. I despise cats. I hate dogs. How could you like monkeys?") (Blum 1994: 92). Such an attitude would surely be unethical, but it seems tenuous to call it unscientific. Finally, if the ethical norms that govern activities do not in fact overlap, then it is difficult to see how Miller and colleagues could argue that physician-researchers have an obligation to obtain informed consent when this is clearly an obligation for physicians.

We conclude that internalists encounter several obstacles in their attempt to justify an acceptable level of protection for research participants, and are forced to import supplemental moral constraints that are externally derived. Miller and colleagues repeatedly invoke utilitarian moral philosophy and general ethical principles in explaining their position (Miller and Weijer 2007). Unsurprisingly, many proponents of the internalist position have come to recognize the deficiencies of their account, and have moved towards more open and sophisticated externalist orientations (Dickert and Wendler

2009; Rid and Wendler 2011). An externalist orientation provides principled constraints on what we can do to patients in the service of producing generalizable knowledge. It asserts that patient-subjects' right to competent care limits the design and conduct of RCTs, such that patients may not be randomly assigned to therapeutic modalities when existing evidence suggests this would entail substandard treatment. The account given here locates these constraints in the trust relationships that bind the state and physician-researchers with patients in RCTs.

Related Topics

Chapter 12, "Bias, Misconduct, and Integrity in Scientific Research," David B. Resnik
Chapter 14, "Biomedical Research Ethics: Landmark Cases, Scandals, and Conceptual Shifts," Jonathan D. Moreno and Dominic Sisti

Note

1 Exploitation is a contested concept in the bioethics literature. For further discussion, see: Wertheimer (1996); Resnik (2003).

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