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RESEARCH ARTICLE

Pragmatic Clinical Research, Informed Consent, and Clinical Equipoise

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Abstract

There is a growing movement within contemporary medical ethics to blur the boundaries between clinical medicine and clinical research. Some writers now argue that the research-practice distinction is outdated and the importance of distinguishing between research and medicine is no longer as pressing as it once was or seemed to be. Instead, we are now urged to view the health-care system as a dynamic "learning health-care system" in which research components are embedded within standard clinical care. This essay defends the ethical significance of the research-practice distinction while acknowledging the reality and usefulness of integrated health care. A key claim that this essay advances is that the principle of clinical equipoise, which has largely been rejected by research ethicists, can be reinterpreted and repurposed to help distinguish medical practices that call for more demanding forms of informed consent from those that do not.

Keywords: pragmatic clinical research; beneficence; informed consent; equipoise; risk-benefit ratio

Introduction

Contemporary health care is a multifaceted institutional enterprise that has both a clinical and a research component. The clinical component consists of relationships between patients and their health-care providers that has, as its orienting purpose, the provision of medical benefit to them. In contrast, the research component consists of relationships between subjects and research teams that has, as its orienting purpose, the generation of knowledge for the benefit of future patients.[1] Both components are vital to good health-care practice. Where the clinical component serves the needs of the present patient, the research component enables the health-care system to serve future patients.

[1] Research on human subjects includes research on healthy volunteers and research on patient-subjects. This essay is concerned only with the latter.

Despite this complementarity, however, the challenges and risks of failing to distinguish between the two components are well known. Research ethics emerged as a field of study in the mid-to-late twentieth century in response to a series of abuses that involved misrepresentations of the research component.[2] Patients who thought that they were receiving clinical care were in fact being used as experimental subjects in research trials with risks of harm and no prospect for benefit. Subsequent research corroborated the widespread prevalence of this kind of misunderstanding, whether deliberately induced or not, among research subjects. The phrase "therapeutic misconception" was coined to describe the general phenomenon whereby research subjects erroneously believe that they are receiving clinical care.[3] In response to these developments, research ethicists began to press for a much stricter separation of the two components. They should be viewed as distinct ethical enterprises governed by different regulations, different oversight structures, and different standards of informed consent.[4]

Progress on this front has been mixed at best. Clinical research is routinely conducted by physicians at medical centers, unproven experimental "treatments" are commonly marketed as cutting-edge therapy, and Institutional Review Boards, which are the bodies charged with protecting the interests of research subjects, are frequently staffed by members who have an interest in eliminating barriers to the conduct of research at their institutions. What is more, and what is my main concern in this essay, is the movement in contemporary medical ethics to blur the boundaries between the two components. Some writers now argue that the research-practice distinction is outdated and the ethical importance of distinguishing between them is no longer as pressing as it once seemed to be. Instead, we are now urged to view the health-care system as a dynamic "learning health-care system" in which research components are embedded within standard clinical care.[5]

My aim in this essay is to defend the ethical significance of the research-practice distinction while acknowledging the reality and usefulness of integrated

[2] For an overview of the abuses, including the infamous Tuskegee syphilis experiments and the Willowbrook hepatitis experiments, see David Resnick, *The Ethics of Research with Human Subjects* (Cham: Springer, 2018), chap. 2.

[3] Paul Appelbaum et al., "False Hope and Best Data: Consent to Research and the Therapeutic Misconception," *Hastings Center Report* 17, no. 2 (1987): 20–24.

[4] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (U.S. Department of Health, Education, and Welfare, 1979), https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html.

[5] Ruth Faden et al., "An Ethics Framework for a Learning Health Care System: A Departure from Traditional Research Ethics and Clinical Ethics," *Hastings Center Report* (2013): S16–27; Nancy Kass et al., "The Research-Treatment Distinction: A Problematic Approach for Determining Which Activities Should Have Ethical Oversight," *Hastings Center Report* (2013): S4–15; Emily Largent, Steven Joffe, and Franklin Miller, "Can Research and Care Be Ethically Integrated?" *Hastings Center Report* 41, no. 4 (2011): 37–46; Jeremy Sugarman and Robert M. Califf, "Ethics and Regulatory Complexities for Pragmatic Clinical Trials," *Journal of the American Medical Association* 311, no. 23 (2014): 2381–82; and Stephanie Morain et al., "Towards Meeting the Obligation of Respect for Persons in Pragmatic Clinical Trials," *Hastings Center Report* 52, no. 3 (2022): 9–17.

health care. I extend the "two-models" approach to informed consent that I defend elsewhere[6] to the blurring of research and clinical care in modern medical practice. I argue that much pragmatic clinical research requires a more demanding form of informed consent than its proponents typically acknowledge, but that some pragmatic clinical research does not. We need, then, a way of determining when pragmatic clinical research requires the more demanding form of informed consent from when it does not. A key and somewhat surprising claim that I will put forward is that the principle of clinical equipoise, which has largely been rejected by research ethicists, can be reinterpreted and repurposed to help us distinguish between medical practices that call for more or less demanding forms of informed consent.[7] The principle of clinical equipoise, however, while central and significant, is not the only relevant consideration in making these determinations. Nor should the principle of equipoise be invoked to justify the absence of transparency.

Background

There is a broad consensus that ethically defensible medical care and research participation, subject to a few notable exceptions,[8] require informed consent on the part of patients or research-subjects.[9] It is also widely accepted that informed consent is not the whole story when it comes to the ethics of medicine and research. Health-care professionals are subject to a duty of (medical) beneficence, which constrains what they may do to their patients with or without their informed consent. The point of medical practice is to provide medical benefit to the patient. Physicians who use patients as opportunities to field-test risky and unproven medications wrong them and getting their informed consent is not enough to fix the problem.

Informed consent is likewise not the whole story regarding the ethics of clinical research. Unlike medical practice, clinical research is not oriented toward the good of patient-subjects. Because the duty of medical beneficence is not straightforwardly applicable to the research context, some other limit, it has been thought, must supplement the requirement of full and informed consent. This limit is often expressed in terms of respect. Writers propose a hodgepodge of requirements, such as the requirement of a favorable risk-benefit

[6] Lynn A. Jansen, "Two Models of Informed Consent," *Social Philosophy & Policy* 38, no. 2 (2021): 50–71.

[7] Some have claimed that the principle of clinical equipoise is simply irrelevant to the justification of clinical research: "All that is needed is adequately informed, free, and unexploited consent." Robert Veatch, "The Irrelevance of Equipoise," *Journal of Medicine and Philosophy* 32, no. 2 (2007): 167. This overlooks the possibility that is explored in this essay. An appeal to equipoise may be needed to determine the nature and demandingness of the consent that is needed to justify the research.

[8] For example, in certain emergency situations, patients are not able to give their informed consent to treatment and no surrogate is available to authorize the treatment, but it can be permissible to provide them with it.

[9] For clarification, patients are those who receive medical care from health-care professionals, research-subjects are those who participate in research trials, and patient-subjects are those who receive medical attention from health-care professionals while participating in a research study.

ratio and the requirement that the privacy of research-subjects be protected and their well-being monitored during the trial. These are, it is asserted, necessary for research-subjects to be treated respectfully and, hence, in a way that is ethically justified.[10]

A different proposal—one that has fallen out of favor—appeals to the principle of clinical equipoise. This principle sets down an epistemological criterion, namely, for a clinical trial to be acceptable, the different arms (or potential treatments offered) in the trial must not be known to be better or worse than one another *and* there must not exist treatments available outside of the trial for which there is good evidence that they would be more effective in treating the condition at issue than the potential treatments offered in the trial would be.[11] When a trial satisfies this principle, no participant in it receives treatment that is known to be inferior (or there is evidence to suggest would be inferior) to available treatment options.[12]

The principle of clinical equipoise has been criticized on two main grounds. One objection is that it excludes valuable research; many trials that could inform improved treatment modalities for future patients would not be allowed. For example, potentially beneficial but unproven depression treatments would not be testable in clinical trials.[13] A second, more fundamental objection is that the principle of clinical equipoise rests on a theoretical error of viewing clinical research through a therapeutic lens. The critics allege that the principle seeks to reconcile experimental clinical research with the ethical demands of the physician-patient relationship, including the duty of medical beneficence. But the research enterprise is not best understood in these terms. Physician-investigators have duties to those who participate in their trials, yet these duties are not duties of beneficence. "The solution," the critics argue, "is to jettison clinical equipoise and develop a sound ethical framework for clinical research that is appropriate to the nature of the activity."[14]

[10] Ezekiel Emanuel, David Wendler, and Christine Grady, "What Makes Clinical Research Ethical?" *Journal of the American Medical Association* 283, no. 20 (2000): 2701.

[11] Charles Fried, *Medical Experimentation: Personal Integrity and Social Policy* (New York: American Elsevier, 1974); Benjamin Freedman, "Placebo-Controlled Trials and the Logic of Clinical Purpose," *IRB: Ethics & Human Research* 12, no. 6 (1990): 1–6. There are differences between Fried's and Freedman's formulations of the principle that we can ignore here. Also see, Paul B. Miller and Charles Weijer, "Rehabilitating Equipoise," *Kennedy Institute of Ethics Journal* 13, no. 2 (2003): 93–118.

[12] Franklin Miller and Howard Brody refer to the first part of the equipoise principle as "the honest null hypothesis" requirement and the second part as the "no inferior treatment" requirement. They claim that the first requirement "is not equivalent to, nor does it logically imply," the second requirement. That is correct, but the idea behind the second requirement of no inferior treatment does support the first requirement of the honest null hypothesis because if one arm of the trial were known to be better than the other, then denying it to other participants in the trial would amount to inferior treatment. Franklin Miller and Howard Brody, "Clinical Equipoise and the Incoherence of Research Ethics," *Journal of Medicine and Philosophy* 32, no. 2 (2007): 151–65.

[13] See, e.g., the Hypericum Depression Trial Study Group, "Effect of *Hypericum perforatum* (St. John's Wort) in Major Depressive Disorder: A Randomized Control Trial," *Journal of the American Medical Association* 287, no. 14 (2002): 1807–14.

[14] Miller and Brody, "Clinical Equipoise and the Incoherence of Research Ethics," 222.

The case against clinical equipoise that I have just reviewed clearly rests on the normative and practical significance of maintaining the research-practice distinction. A further point should be noted about the principle. Originally, clinical equipoise was introduced to "dissolve" the apparent conflict between the medical duty of beneficence and the requirements of experimental research. The concern centers on the potential for exploitation of patient-subjects in trials that do not satisfy clinical equipoise. As Charles Fried notes: "Intuitively it seems unfair to impose the burdens of experimentation on some who do not share fully in the benefits; a violation of their right not to be treated as a means alone, not to be treated as a resource available to other people."[15] The idea is that when the principle of clinical equipoise is satisfied, it is not the case that the burdens of experimentation come at the expense of the patient-subjects in the trial. Equipoise in this way silences the concern about exploitation.

The principle of clinical equipoise can be understood as an anti-exploitation norm,[16] but so understood it needs qualification. Patient-subjects in clinical trials can and sometimes do share the research aims of the trial. They can appreciate that participating in the trial has the potential to yield knowledge that will benefit others in the future and they can consent to participate for this reason, knowing full well that they may not benefit themselves at all from participation. Concerns about exploitation should not be taken to exclude reasonable altruism, and so the principle of equipoise should not be taken to be a strict requirement for ethical clinical research.[17] Notwithstanding this point, in most clinical trials, the patient-subjects expect to benefit themselves and it is this expectation of benefit that is the primary motivator for their participation. These expectations for therapeutic benefit are often unrealistically optimistic.[18] Those who conduct the trials have incentives not to disabuse patient-subjects of their therapeutic misconceptions or counter their optimistic biases, as doing so makes patient-subject recruitment to the trials more difficult and costly. Thus, in the context of the actual practice of clinical research, one might present the principle of clinical equipoise as a key component of an anti-exploitation norm. To avoid exploitation of patient-subjects, those who conduct clinical trials must either ensure that all participants in trials who do not satisfy clinical equipoise are motivated to participate on altruistic grounds—that is, sharing the research aims of the trial—or that the trials satisfy clinical equipoise.

Whatever one thinks of this proposal, it should be evident that the blurring of medicine and research present in "learning health-care systems" poses a formidable challenge to it. Once medicine and research are not viewed as distinct

[15] Fried, *Medical Experimentation*, 61.

[16] Lynn A. Jansen, "A Closer Look at the Bad Deal Trial: Beyond Clinical Equipoise," *Hastings Center Report* 35, no. 5 (2005): 29–36.

[17] See my "The Ethics of Altruism in Clinical Research," *Hastings Center Report* 39, no. 4 (2009): 26–36.

[18] Lynn A. Jansen, "The Problem with Optimism in Clinical Trials," *IRB: Ethics & Human Research* 28, no. 4 (2006): 13–19; Lynn A. Jansen et al., "Unrealistic Optimism in Early-Phase Oncology Trials," *IRB: Ethics & Human Research* 33, no. 1 (2011): 1–8; Jodi Halpern, David Paolo, and Andrew Huang, "Informed Consent for Early-Phase Clinical Trials: Therapeutic Misestimation, Unrealistic Optimism, and Appreciation," *Journal of Medical Ethics* 45, no. 6 (2019): 384–87.

enterprises, but as deeply intertwined components of a single enterprise, it no longer looks plausible to demand that we move beyond medical beneficence and "develop a sound ethical framework for clinical research that is appropriate to the nature of the activity."[19]

Pragmatic clinical research

I have claimed that the enterprises of clinical care and clinical research can be distinguished by their orienting purposes. Clinical care can produce results that contribute to the development of new therapies, as when a treatment prescribed for one condition, for example, sildenafil (Viagra), is found to be effective at treating some other condition. Conversely, clinical research can benefit research participants, as when an experimental therapy, for example, imatinib (Gleevac), proves to be effective for those enrolled in the trial. Despite these possibilities, the two enterprises are dissimilar insofar as they are guided by different purposes.

Of course, an enterprise can have more than one purpose. Those who conduct a phase 1 cancer trial, for example, may intend for the trial to benefit its participants as well as yield generalizable knowledge. What I am calling its orienting purpose is the purpose that takes precedence over any other purposes of the trial, such that when the orienting purpose conflicts with one of them, it guides what should be done. For example, it is sometimes said that research-investigators have a duty to minimize risks of harm to participants in their trials that are consistent with the scientific design of the trial. This duty of risk minimization may reflect a therapeutic aim or purpose, but it is one that is subordinate to the orienting scientific purpose of the trial. In parallel fashion, a physician might provide care to a patient partly for the purpose of gathering information that will be stored on and contribute to an electronic data base that relates to the patient's disease.[20] So long as the physician does not let this research purpose compromise her goal of providing optimal care to her patient, it would remain subordinate to her orienting beneficent purpose in providing clinical care.

Pragmatic clinical research practices and "learning health-care systems" may seem to have no single orienting purpose. They are "designed and intended to *simultaneously* deliver the care patients need while capturing the experience of clinical practice in systematic ways that produce generalizable knowledge to improve care for both patient and future patients."[21] Neither the beneficent clinical purpose nor the scientific purpose is dominant. If that were right, then with research practices of this kind we could not sort them into the clinical care and clinical research categories by referring to their orienting purposes.

[19] Miller and Brody, "Clinical Equipoise and the Incoherence of Research Ethics," 156.

[20] Nick Black, "Secondary Use of Personal Data for Health and Health Services Research," *Journal of Health Services and Research Policy* (2003): S36–40.

[21] Kass et al., "The Research-Treatment Distinction," S6.

What kinds of clinical research fall under the general category of pragmatic clinical research? It will be helpful to have some examples in mind. Each of the following practices illustrates how the clinical and scientific purposes in pragmatic clinical research are jointly pursued, with neither (allegedly) taking priority over the other.

Aggregation of clinical care data: Patients receive standard clinical care, but data and records from their care are carefully and precisely recorded and used as evidence for future observational studies and quality-improvement reviews, all with the aim of improving future patient care.

Comparative effectiveness trials with options on a par: Patient-subjects randomly receive one or another standard treatment for their condition. It is not yet known whether one treatment is significantly better than the other. The point of the trial is both to provide patient-subjects with optimal care and to gather data on the comparative effectiveness of the treatments provided in the trial.

Trial combining experimental agent with standard therapy: Patient-subjects receive the standard therapy available outside of the trial, but in addition they receive an experimental agent, such as a new immunotherapeutic drug, that has some prospect for benefiting them, but also presents some risks and side effects.

Early-phase oncology trial with no good options: With many cancers there is no effective treatment available outside of research trials. Given this situation, medical centers and physicians often present participation in early-phase cancer trials as the best "treatment option" for their patients. Such trials purport to satisfy both of the following conditions: (i) participation in them is in the best medical interests of their participants and (ii) they will have some not insignificant prospect of improving understanding of how to treat the cancer in future patients.

The first of these examples involving data collection is the least controversial. So long as the data collected and recorded remains anonymized or confidential, the privacy interests of the patients are protected. More significantly, it seems the clinical care component and the research component in this example are not tightly integrated. They can easily be disentangled. The provision of patient care is one thing, the recording of data another. If the type of informed consent appropriate for clinical care is different from that which is appropriate for clinical research, then the collection of the data could require an additional consent process. But this is exactly what proponents of learning health-care systems oppose. Provision of clinical care and collection of data for future improvements in care, they contend, should be viewed as two sides of the same coin: "In a learning health care environment, practice is a continuous source of data for the production of generalizable knowledge, and the knowledge that is produced is used to continuously change and improve practice."[22] As such, there should be one informed consent process; proponents of pragmatic clinical research argue that it should be the less demanding and burdensome consent process associated with the provision of routine clinical care.

[22] Kass et al., "The Research-Treatment Distinction," S6.

The second example has been much discussed in recent medical literature on informed consent. On the one hand, trials of this type are straightforward instances of clinical research. Their point is to gather evidence on the comparative value of two or more standard treatment modalities. The fact that the treatments received by trial participants result from a random process makes it evident that the provision of treatment is not based on the individualized needs of patient-subjects. On the other hand, the participants in the trial are not receiving suboptimal treatment. With these trials, there is no good evidence, prior to the trial, that one or more of the randomized treatments is more effective or has worse side effects than the others. Thus, the random assignment of treatments to patients does not conflict with the clinical duty of medical beneficence.[23]

The third example illustrates trials that provide all participants with treatments or medications mandated by standard of care.[24] Some participants in such trials receive standard medical care and an experimental intervention, whereas others receive only standard medical care. Importantly, no trial participant is made worse off by participating in the trial compared with patients outside the trial with the same or similar medical condition, at least with regard to access to clinically appropriate medical treatment. Unlike trials that randomize one arm to a placebo group, these combination trials deny no participant the standard treatment available outside of the trial. It is true that the experimental agent administered in such a trial might prove to be harmful to those participants who receive it, but this would not be known prior to the initiation of the trial. The experimental agent might also prove to be beneficial to those who receive it, but the prospects for benefit and/or harm and how they might compare are not known prior to the trial.

The fourth example involving early-phase oncology trials is the most challenging of the examples I have listed to categorize as serving both treatment and research aims. Participants in these trials receive no treatment that has been shown to be effective and there is a high likelihood that they will not benefit from their participation in them. The vast majority of early-phase cancer trials (phases 1 and 2) go nowhere, failing to identify a treatment modality that proves to provide substantial medical benefit to anyone.[25] Still, when there are no effective treatments for the cancers at issue, patients may reasonably think that participation in the trial is their best treatment option. Moreover, some defenders of pragmatic clinical research take this kind of example to be the central case, as the other examples show merely that clinical research and clinical medicine

[23] Ruth Faden et al., "Ethics and Informed Consent for Comparative Effectiveness Research with Prospective Electronic Clinical Data," *Medical Care* 51, no. 8 (2013): S53–57.

[24] Standard of care in medicine is understood in different ways. Descriptively, it refers to the routine treatment practices within a specified domain of medical practice; normatively, it refers to what is considered to be the best or most appropriate available treatment, given current evidence, within a specified domain of medical practice. Franklin Miller and Henry Silverman, "The Ethical Relevance of the Standard of Care in the Design of Clinical Trials," *American Journal of Respiratory Care* 169, no. 5 (2004): 562–64. I have the normative sense in mind here.

[25] Faruque Azam and Alexei Vazquez, "Trends in Phase II Trials for Cancer Therapies," *Cancers* 13, no. 2 (2021): 178.

can occur together, while in this kind of example the treatment is the research. In this spirit, when discussing pediatric oncology trials, Kass and her coauthors claim that

> enrollment in the trial is considered to be a standard of care. The practice context is constructed to bring the most pertinent forms of scientific understanding to bear on clinical care, and clinical care generates new scientific learning. Generating and using generalizable knowledge can thus be a deliberate and integrated aspect or part of practice, not a set of maneuvers logically distinct from it.[26]

Consideration of early-phase cancer trials brings into clear view a distinction that should be borne in mind in assessing pragmatic clinical research generally. There is, on the one hand, what I have been calling the orienting purpose of the research trial and there is, on the other hand, the risk-benefit profile that the trial presents to its participants. The two things are not unrelated. If one is guided by concern for benefiting trial participants in designing the trial, it is more likely that trial participants will benefit than if one is not so guided. However, benefit to participants can occur with no such guiding intention, a side effect of the trial that is welcomed and hoped for, but not aimed at or intended. In the context of oncology research, this has led to some confusion. Some commentators have inferred from the fact that the trials are not designed to benefit their participants that no therapeutic benefit can reasonably be expected from them. Other commentators make the opposite mistake of inferring from the prospect of therapeutic benefit in a trial to the conclusion that the trial has therapeutic purpose.[27]

Proponents of pragmatic clinical research who cite early-phase cancer trials as central examples of how research and clinical medicine are inextricably linked are best interpreted as maintaining that while such trials have a research-centered orienting purpose, they also present cancer patients with options that have some nonnegligible prospect for significant benefit and therefore could motivate an informed and reasonable cancer patient to enroll in them for the purpose of receiving an effective response to their disease.[28] Such a prospect for benefit could also explain an investigator's therapeutic concern. She might hope and even believe that the trial will provide direct medical benefit to its participants. None of this would change the fact that the trial itself has the generation of scientific knowledge as its orienting purpose.

[26] Kass et al., "The Research-Treatment Distinction," S7.

[27] Compare Matthew Miller, "Phase I Cancer Trials: A Collusion of Misunderstanding," *Hastings Center Report* 30, no. 4 (2000): 34–43, with Amit Mahipal and Danny Nguyen, "Risks and Benefits of Phase 1 Clinical Trial Participation," *Cancer Control* 21, no. 3 (2014): 193–99.

[28] Clinical oncologists and those who undertake early-phase cancer trials often overstate the prospect for benefit for trial participants by focusing on "surrogate outcomes," such as tumor shrinkage, as opposed to real clinical benefit, such as increased life expectancy. See Franklin Miller and Steven Joffe, "Benefit in Phase 1 Oncology Trials: Therapeutic Misconception or Reasonable Treatment Option?" *Clinical Trials* 5, no. 6 (2008): 617–23.

Demands of informed consent

Informed consent is an ethical requirement for clinical care and clinical research. At a minimum, patients and patient-subjects should be informed of the nature of the activity they are engaged in. If they are receiving standard medical treatment, they should be told this; if they are participating in a research trial, they should be told this; and if they are participating in pragmatic clinical research, they should be told about the medical care they will receive and the experimental dimension of the activity they will be participating in. However, it does not follow from this that the type of informed consent that is required in each of these cases should be the same. We can distinguish among more and less demanding informed consent processes. For example, it has been widely accepted that the type of informed consent appropriate for clinical research is more demanding—requiring express written informed consent and institutional review board (IRB) approval—than that required for ordinary medical care.

A full discussion of the requirements of informed consent appropriate for different biomedical contexts is not possible here, but a few points can be mentioned.[29] Accounts of informed consent can differ along several different dimensions, chief among which are the standards they impose, the stringency of the standards imposed, and the regulatory mechanisms that must be in place. Consider the difference between a routine disclosure standard and a comprehension or understanding standard. In some contexts, a health-care professional may discharge their duty to those they serve by disclosing to them relevant information about risks and benefits with no further duty to ensure that the disclosed information is understood and comprehended. In other contexts, this further duty would be required. Likewise, in some contexts, there may be no need to worry about various psychological biases that patients bring with them to the consent process, but in others these biases, such as therapeutic misconceptions and unrealistic assessments of benefit, may occasion concern and efforts may be required to counteract them. Furthermore, different mechanisms of regulatory oversight may be required in some contexts, but not others. For example, the consent forms for research trials conducted in the United States that involve human subjects must be approved by IRBs. If these forms are not submitted for this approval or if they are submitted but rejected, then the participants' consent is not morally transformative and thus conducting the research is impermissible. The same regulations do not apply to standard medical care. The consensual nature of the physician-patient relationship is not overseen by outside panels. To the extent that consent to medical care is regulated, it is regulated by law, but in practice there is very little oversight of the informed consent process in standard medical care.

Proponents of pragmatic clinical research generally do not dispute the importance of distinguishing the research context from the clinical care context when articulating the requirements of informed consent. No one would dispute that a high-risk experimental trial, such as a controlled human-challenge trial

[29] This paragraph summarizes some points that are developed more completely in my "Two Models of Informed Consent."

for a vaccine candidate for an infectious disease,[30] should be subject to a more demanding form of informed consent than that required for a standard medical treatment. Proponents of pragmatic clinical research emphasize, though, that participation in research need not impose high risks of harm on its participants and that such participation can be integrated with the provision of clinical care. For this reason, the type of consent appropriate to it, they argue, can be "streamlined" in a way that more closely resembles informed consent for standard medical care.[31] Furthermore, proponents of pragmatic clinical research often press for relaxed or streamlined processes of regulatory oversight for the trials they champion.[32] When the boundaries between research and clinical care are blurred, it becomes less clear that a demanding form of informed consent is always required for research practices.

Risk-benefit-adjusted consent

My question is: How should we respond to pragmatic clinical research and, specifically, how should we think about the requirements for informed consent for this kind of research? No general answer to this question may be forthcoming. Different kinds of cases will need to be treated differently. Particular analyses rather than broad theoretical accounts may be what we should try to provide here. Nevertheless, proponents of pragmatic clinical research have called for a general rethinking of the requirements of informed consent in clinical research, a general rethinking that rejects the significance of the research-practice distinction. It is this bold proposal that I want to consider and resist. Unfortunately, most proponents of pragmatic clinical research have not contributed much to the proposed rethinking. They have emphasized the entanglement of research and clinical medicine in learning health-care systems and they have proposed various guidelines for informed consent in pragmatic clinical research, but little to no work is done to offer a deeper rationale for the guidelines that are proposed.

This section considers a line of thought that has some promise in supporting the claim that the research-practice distinction is unnecessary to an adequate understanding of the requirements of informed consent in pragmatic clinical research. The line of thought puts the spotlight on the risk-benefit profile that a trial presents to its participants. Roughly speaking, the idea is that the less

[30] Nir Eyal, Marc Lipsitch, and Peter G. Smith, "Human Challenge Studies to Accelerate Coronavirus Vaccine Licensure," *The Journal of Infectious Diseases* 221, no. 11 (2020): 1752–56.

[31] Nancy Kass and Ruth Faden, "Ethics and Learning Health Care: The Essential Roles of Engagement, Transparency, and Accountability," *Learning Health Systems* 2, no. 4 (2018): e10066, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6508806/.

[32] A survey of recent writings on pragmatic clinical research found that "authors view regulatory oversight as burdensome and a practical impediment to the conduct of pragmatic RCTs, and argue that oversight procedures ought to be streamlined when risks to participants are low." Cory Goldstein et al., "Ethical Issues in Pragmatic Randomized Controlled Trials: A Review of the Recent Literature," *BMC Medical Ethics* 19 (2018), https://bmcmedethics.biomedcentral.com/counter/pdf/10.1186/s12910-018-0253-x.pdf.

favorable the risk-benefit profile, the more demanding the requirements of informed consent should be. With trials that present either a positive risk-benefit profile or trials that present only a minimal to moderately unfavorable risk-benefit profile, the requirements of informed consent can be significantly relaxed.[33] Let us call this the Risk-Benefit-Adjusted Consent Proposal. At the limit, this proposal would support the claim that in trials that provide net positive benefits to their participants, no informed consent beyond that required for standard care from trial participants is required.[34]

The Risk-Benefit-Adjusted Consent Proposal must be informed by an account of the risk-benefit profile that trials present to their participants. To assess this proposal, we need to avoid a pitfall. In research ethics it has been common to run together the prospective benefits to trial participants and the prospective benefits to future patients in the risk-benefit profile. For example, a favorable or positive risk-benefit profile is described as one in which "the potential benefits to individuals and knowledge gained for society must outweigh the risks" to trial participants.[35] Thus, on this description, a trial could have a favorable risk-benefit profile in virtue of its promise for benefiting future patients, even if it was not a good deal for trial participants.[36] Running together prospective benefits to trial participants and potential benefits to society risks covering up the possible exploitation of trial participants, and so this should be avoided. The Risk-Benefit-Adjusted Consent Proposal should be understood as focused exclusively on the prospective benefits and risks to trial participants.

The strength of this proposal is that it explains something that is intuitively compelling. High-risk, low-benefit research should require a more demanding form of informed consent than does low-risk, high-benefit research. With the former, investigators, at least intuitively, have duties to ensure that trial participants comprehend and appreciate the risks and benefits at issue. With such trials, it is plausible to think that it would be wrong to enroll as participants patient-subjects who were under a therapeutic misconception, for example. The same is less plausible for research with very low risks or research with prospects for benefit that overbalance the risks. The type of informed consent appropriate for such trials might seem to mirror the less demanding informed consent required in clinical practice. If that is right, then pragmatic clinical research—in virtue of the fact that it provides substantial therapeutic benefits to its participants—might be thought to require a less demanding form of informed consent, just as its proponents allege.

On the Risk-Benefit-Adjusted Consent Proposal, then, what matters is not the orienting purpose of the biomedical enterprise, but rather the risks and prospective benefits that the practice presents to patient-subjects. An attractive

[33] Danielle Bromwich and Annette Rid, "Can Informed Consent to Research Be Adapted to Risk?" *Journal of Medical Ethics* 41, no. 7 (2015): 521–28.

[34] Gopal Sreenivasan, "Does Informed Consent to Research Require Comprehension?" *Lancet* 362, no. 9400 (2003): P2016–18. Sreenivasan argues that the relevant requirements need not go beyond disclosure of relevant information about the trials at issue.

[35] Emanuel, Wendler, and Grady, "What Makes Clinical Research Ethical?"

[36] Jansen, "Beyond Clinical Equipoise."

feature of this proposal is that it can help us to think more clearly about the respective responsibilities of investigator-clinicians and patient-subjects. Informed consent is a joint accomplishment. Investigators have duties to disclose relevant information about the research, to make appropriate efforts to help patient-subjects comprehend and appreciate the information, to guard against bias, and so on, while patient-subjects have responsibilities to pay attention, to deliberate, to ask relevant questions, to not consent thoughtlessly, and so on. It is plausible to think that the nature and demandingness of these duties and responsibilities is sensitive to the risk-benefit profile that the research presents to its participants; this is well-explained by the Risk-Benefit-Adjusted Consent Proposal.

Given its advantages, should we accept the Risk-Benefit-Adjusted Consent Proposal? My answer is both yes and no. The core idea behind the proposal has merit and should find its place in an account of informed consent for pragmatic clinical research. However, the proposal should not be taken to exclude the relevance of other factors that are not reducible to the risk-benefit profile. Some writers have suggested, for example, that the controversiality of research is relevant to how demanding the requirements of informed consent should be. If there is reasonable concern over the potential for the results of the research to be misused or if participation in the trial could conflict with the religious beliefs of potential participants, then the standards of informed consent may need to be higher.[37] Participants in these kinds of controversial research trials have non-medical concerns that can trigger the need for more demanding consent requirements.

The same point is sometimes emphasized in the context of clinical medicine. Advocates of shared decision-making between physician and patient point out that different treatment options may be appropriate for different patients not in virtue of the risk-benefit profile of the different options, but because of the different preferences and values of the patient. The point can be pushed too far, though. Robert Veatch made a career out of arguing that all medicine requires shared decision-making because all medical decisions have the potential to impinge on the values and concerns of patients.[38] But this view ignores the costs of shared decision-making. Physicians have only so much time to spend with patients and they should engage in shared decision-making with them only when there is sufficient reason to believe that there is a significant likelihood that doing so would affect the decisions that the patients would make.[39] Much of clinical medicine is routine—for example, the setting of a broken arm or the prescribing of antibiotics for a bacterial infection—and does not call for shared decision-making. In some contexts, though, such as breast cancer treatment, quite a lot is at stake, there are multiple treatment possibilities, and different patients can be expected to prefer different treatments. These contexts invite shared decision-making and trigger more demanding duties on the part of

[37] Bromwich and Rid, "Can Informed Consent to Research Be Adapted to Risk?"

[38] Robert Veatch, *Patient Heal Thyself* (New York: Oxford University Press, 2008).

[39] Lynn A. Jansen, "Medical Beneficence, Nonmaleficence, and Patients' Well-Being," *Journal of Clinical Ethics* 33, no. 1 (2022): 23–38.

physicians to make sure that their patients understand and appreciate the decisions that need to be made.

The Risk-Benefit-Adjusted Consent Proposal does not need to be interpreted as denying the importance of these other factors. It can allow that the risk-benefit profile of a trial or treatment decision is not the only consideration that should raise the standards of informed consent. Applied to pragmatic clinical research, it can allow that controversiality and significance also should be given their due. But if this is the line that is taken, then we need to ask whether the research-practice distinction itself is a relevant factor in setting the requirements of informed consent. Recall that the proposal, as it was introduced above, advises us to turn away from the research-practice distinction and focus instead on the risk-benefit profile of the practices under consideration. That advice seems welcome to the proponent of pragmatic clinical research insofar as it silences the need to distinguish clinical research from clinical practice in learning health-care systems. Once the proposal is cast as a proposal about one key factor among other relevant factors, though, it no longer is clear that it silences that need.

The two-models approach

The *Belmont Report*, published in 1979, calls attention to the most fundamental differences between clinical research and clinical practice:

> The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge.[40]

The authors of the *Belmont Report* did not make specific recommendations, but their discussion of the special ethical challenges that pertain to research on human subjects suggested to many that the practice for informed consent for clinical research should be more demanding than that standardly relied on in clinical medicine. This two-models approach, I will argue, is basically sound, but it needs refinement in light of the reality and desirability of pragmatic clinical research.

The model of informed consent appropriate for clinical research differs from the model appropriate for clinical care in three fundamental respects. First, extensive written consent forms are required for research trials, but not for clinical care. Second, the duties of researchers, as contrasted with clinicians, to secure comprehension and appreciation of the nature, risks, and potential benefits of research participation are more demanding than the duties of clinicians to secure understanding and appreciation of the nature, risks, and

[40] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report.*

potential benefits of medical care. Failures of understanding and biases of various sorts are more problematic when consent is to research as compared to clinical care. Third, a more demanding form of regulatory oversight is required for informed consent to be valid in the research context as opposed to the clinical care context.

Critics of the *Belmont Report*'s two-models approach often charge it with ignoring clinical realities in its effort to distinguish sharply clinical research from clinical practice. Clinicians in the course of providing care to their patients sometimes prescribe off-label medications, for example. Is this not itself a type of experimental research? The authors of the *Belmont Report*, however, were fully aware of this reality: "When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is 'experimental,' in the sense of new, untested or different, does not automatically place it in the category of research."[41] This report proposes, in effect, a three-part classificatory scheme: standard clinical care, experimental clinical care, and clinical research. The first two have the same orienting purpose, while the last two share a commitment to experimentation. This does not mean that experimental clinical care does not present its own ethical challenges. New and unproven procedures "should be made the object of formal research at an early stage in order to determine whether they are safe and effective."[42] However, the fundamental distinguishing mark between clinical medicine and clinical research, according to this report, is not experimentation, but underlying orienting purpose.

Critics of the *Belmont Report* also charge it with failing to appreciate how medicine and research can be and often are pursued together. This, of course, is the main objection advanced by the proponents of pragmatic clinical research. Once again, however, the authors of the *Belmont Report* were not blind to this reality:

> Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.[43]

The general rule proposed in this passage is not the right rule, I think. The principle of clinical equipoise points to a better rule, but the suggestion that the intermixing of research and practice need not cause trouble for the two-models approach is correct, important, and has not been sufficiently considered by proponents of pragmatic clinical research. Roughly, the suggestion is that when

[41] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report*.

[42] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report*.

[43] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report*.

clinical medicine and clinical research are intermixed in practice, then we should look to a rule or standard to sort the practice into one or the other model. We should abandon the two-models approach for pragmatic clinical research only if we find that no defensible rule or standard can be found.

To get a feel for how the two-models approach would work for pragmatic clinical trials, it will be useful to consider the relevance of the therapeutic misconception for the validity of informed consent. Recall that the therapeutic misconception involves a failure to comprehend or appreciate the difference between research and therapy. This misconception cannot occur in the context of standard clinical medicine. If a patient is receiving clinical care and is not participating in a research trial, then she cannot mistakenly confuse the two.[44] With regard to standard clinical care, it is not necessary to screen for the therapeutic misconception, because it does not apply, but with regard to research trials, it may be necessary to do so. The two-models approach accounts for this difference. Think now, though, about a case in which standard medical care is being provided to patients, but the practice of providing the care is embedded within a larger research study. Two standard treatments are available for treating a certain condition. Neither is known to be better than the other and neither has side effects or presents risks that differ significantly from the other. As matters stand, Hospital A prescribes one of the treatments to its patients and Hospital B prescribes the other to its patients. Physicians at both hospitals disclose to patients that they prescribe the treatment that they prescribe and that another treatment that is not known to be better or worse is available at the other hospital. So far, there is nothing here but differentiated standard medical care. Now add one more detail: the hospitals are participating in a comparative effectiveness research study. Data concerning patient outcomes from both hospitals will be collected and analyzed to determine whether one treatment is better than the other.

Does that last step—the collection and analysis of data from the two hospitals—turn the clinical care at the two hospitals into research? The rule from the *Belmont Report* suggests an affirmative answer. There is "an element of research" in the care provided, but intuitively that last step should not make a difference in the demandingness of the informed consent that is required.[45] If the informed consent was good enough prior to the data collection, then intuitively it is good enough after the data collection. Why might that be? The clinical care that patients receive is not affected by the element of research that is present when data collection and analysis is added. A beneficent physician would have no reason to advise her patients to seek medical treatment elsewhere, where no

[44] This is not quite right. Think about what we might call the "reverse therapeutic misconception," which occurs when a patient receiving standard clinical care believes wrongly that they are participating in a research trial. This error is possible, but not at all likely; its significance for informed consent to medical treatment would not be a pressing matter.

[45] Should patients be informed of the fact that data is collected from their care that will be used for research purposes? Presumably yes, but this could be included within the routine consent that is secured for medical care.

such data collection would occur. Her duty of providing the best care to her patient is unaffected by the element of research at issue.

The explanation for why the need for a stricter informed consent process is not triggered by the inclusion of the research component in the standard care, however, is neatly explained by the principle of clinical equipoise. A beneficent physician should be indifferent between the case where her patient receives standard care without data collection and the case in which the patient receives the same care with data collection. The verdict given by the principle of clinical equipoise, in this case, dovetails with that urged by proponents of pragmatic clinical research. No more stringent demands of informed consent beyond those required by standard clinical care are needed, although patients should be informed of the experimental component, and it would be a mistake to insist that because "an element of research" is involved in the activity that a more demanding form of informed consent is required.

Data collection that does not affect patient care is an easy case for the principle of clinical equipoise. Consider next a comparative-effectiveness trial. Patient-subjects randomly receive one or another standard treatment for their condition. Neither treatment is significantly better than the other, given the current state of clinical knowledge. The point of the trial is both to provide patient-subjects with optimal care and to gather data on the comparative effectiveness of the treatments provided in the trial. Is equipoise violated here? Would a beneficent physician hesitate here in advising her patient to participate in such a trial?

These are the right questions to ask. Some comparative-effectiveness trials are not in the best medical interests of their participants. The reason why is that participation in research standardly brings with it "a loss of personalization" in the care provided. In the course of the trial, it might become apparent that a treatment prescribed to a particular participant brought with it an unwanted side effect not experienced by others in the same trial. If physicians were not permitted to switch treatments for this patient, because doing so would compromise the design of the trial, then participation in this trial would not be in the best medical interests of this participant. In contrast, consider a comparative-effectiveness trial that freely permits treating physicians to override the treatment initially assigned to their patients in the trial. In consultation with their patients, physicians in such a trial could switch treatments, adjust dosages, and provide supplementary therapies, all based on their understanding of what was in their patient's best medical interests.[46] Because this trial would provide its participants with the type of clinical care that they would receive outside of the trial and because physicians participating in the trial could fully live up to their duties of medical beneficence, the principle of clinical equipoise would be satisfied here. Accordingly, consent to participate in a comparative-effectiveness trial of this kind, on the view I am proposing, need not require any form of consent that is more demanding than that which is appropriate for standard clinical care.

[46] Ruth Faden, Tom Beauchamp, and Nancy Kass, "Informed Consent, Comparative Effectiveness, and Learning Health Care," *New England Journal of Medicine* 370, no. 8 (2014): 767.

One might worry that a comparative-effectiveness trial of the sort I have just described, in which personalized care is provided and equipoise is satisfied, still presents an ethical challenge not present in clinical care. The initial treatment that patients receive in the trial is determined randomly and that fact alters the nature of the activity. Two points can be made in reply. First, physicians in clinical practice may and sometimes do randomly select one treatment over another in treating their patients. If no good evidence exists that one treatment is better than another, the physician must make a choice on some basis; random choice or simply picking one seems unobjectionable. Thus, if random initial choice of treatment is consistent with clinical care and medical beneficence in standard practice, then it should not be considered problematic when it occurs in a comparative-effectiveness trial. Second, in saying that informed consent need not be more demanding for participation in the trial than for clinical care, I am not saying that participants in the trial should not be informed of the fact that they are participating in such a trial. Some researchers have argued that if a trial satisfies equipoise, then there is no need to tell participants that they are participating in a trial.[47] That is not the view I am proposing here. The principle of equipoise, I have emphasized, should not be invoked to justify the absence of transparency.[48] The role of the principle, rather, is at least partly to determine the nature or demandingness of the informed consent that is required.

Consider, next, trials that combine an experimental agent with standard therapy. The thought here is that such trials do not deny any participant standard clinical care. The experimental agent presents some prospect for benefit and some level of risk. Do the prospective benefits justify the risks? Recall that on a standard understanding of the risk-benefit profile a trial presents to its participants, the benefits include prospective benefits to future patients. Thus, a trial of this kind could present a favorable risk-benefit profile to its participants, but not be in their best medical interests. Plainly, in such a case, the principle of equipoise is not satisfied and the requirements for informed consent should be more demanding than those appropriate for standard clinical care. A more interesting case to consider is one in which the risk-benefit profile presented by the trial is not known to be contrary to the best medical interests of its participants. Here, we might imagine a beneficent physician being unsure whether participation in the trial is in the best medical interests of her patient when compared to receipt of standard care outside of the trial. Providing that the patient in consultation with her physician is free to withdraw from the trial at any time and receive the standard care, a case could be made that participation in the trial satisfies the principle of equipoise and hence does not trigger the more demanding consent requirements.

A substantial measure of caution is in order here, however. In standard clinical practice, patients can confront treatment decisions in which the alternative treatment options are on a par with respect to medical benefits and risks.

[47] Robert Truog et al., "Is Informed Consent Always Necessary for Randomized, Controlled Trials?" *New England Journal of Medicine* 340, no. 10 (1999): 804–7.

[48] Franklin Miller and Scott Kim, "Personal Care in Learning Health Care Systems," *Kennedy Institute of Ethics Journal* 25, no. 4 (2015): 423.

From the standpoint of medical best interests, the treatment options may appear to be equally good, such that a well-trained physician would have no reason to recommend one option over the others. But a patient's medical interests are just a part of her overall interests and she may have reasons of her own to prefer one of the alternative treatments. Standard medical care is oriented toward the health of the patient, but it is "health, ultimately in the service of the patient's well-being," that is the ultimate goal.[49] Medical contexts in which shared decision-making between physicians and patients is appropriate are contexts in which there is reason to believe that the best medical treatment for one patient may not be the best one for other patients with the same or similar medical condition. In these contexts, the medical duty of beneficence requires the physician to engage with her patients to determine the treatment that would be best for them. These points pertain to clinical trials that provide participants with standard therapy and an experimental intervention. Even if the option to receive standard therapy outside of the trial and the option to receive standard therapy within the trial in conjunction with an experimental agent were in equipoise in the abstract, it would not follow that a beneficent physician would be indifferent between them. Such a physician might reasonably judge that it was in her patient's best interests overall to make an informed choice between them as opposed to being randomly assigned to one option over the other. When that is the case, and it might be the case in most trials in this category,[50] then the trials under consideration would trigger the more demanding requirements of informed consent.[51]

Let me turn, lastly, to early-phase oncology trials with no good options. These are heart-wrenching examples, as patients enter these trials out of desperation. Having exhausted available treatment modalities, patients turn to experimental interventions as their last hope. Nearly everyone agrees that participation in these trials requires a demanding form of informed consent, but how does this judgment relate to the principle of clinical equipoise? One answer is that if a trial offers its participants no reasonable chance of benefit, then it is not offering them treatment at all. Phase 1 oncology trials are designed to test the safety and toxicity of dosage levels of experimental agents for participants. This is not providing them with treatment. Participants in these trials might be thought to be analogous to healthy individuals who volunteer to participate in research for altruistic reasons. High-grade consent is required, because no treatment is provided. Yet, while early-phase trials are not designed to provide treatment,

[49] Dan Brock, "The Ideal of Shared Decision Making between Physicians and Patients," *Kennedy Institute of Ethics Journal* 1, no. 1 (1991): 44.

[50] As Jeremy Menikoff, "The Unbearable Rightness of Being in Clinical Trials," *Hastings Center Report* (2013): S31, observes: "[I]t is likely a relatively rare study where there are genuinely no good reasons for a patient or doctor to prefer one treatment over the other."

[51] Here, it might be objected that it is not equipoise that triggers the need for a more demanding form of informed consent, but rather some other duty of medical beneficence, such as the duty to engage in shared decision-making with the patient, that does the work. But recall that equipoise imposes two requirements: an honest null hypothesis and no inferior treatment. It is the second of these requirements that is not met when a physician judges that his patient, given her values and concerns, might be better off not participating in the pragmatic clinical research at issue.

it does not follow that they offer no prospect for medical benefit to their participants. The prospective benefit is not known.

There may be some evidence, though, that clinical trials of this kind in general or on average provide participants with a nonnegligible prospect for benefit. This aggregate evidence may make it reasonable—or at least not irrational—to believe that participation in a given trial is one's best bet for responding to one's cancer.[52] The issue is whether this kind of "reasonable hope" for benefit should factor into judgments of equipoise. Could such reasonable hopes for benefit counterbalance the risks and costs of trial participation, thereby making participation in the trial a medically indicated option? Put in this way, the answer seems to be no. The prospective benefits of an experimental option should be more objective than reasonable hope if they are to figure in a risk-benefit calculation. To determine whether treatment is being provided, we need to ask whether it would it be reasonable to expect a benefit from the intervention, as opposed to asking whether a reasonable patient could hope for benefit from it. Once an experimental agent in an early-phase oncology trial meets that objective benefit threshold, it could count as treatment and as benefit. But in such a case, the trial presumably should be stopped and the agent should be made available to cancer patients generally as standard therapy.

Equipoise and anti-exploitation

This last point underlines a dilemma presented by the claim that pragmatic clinical research serves the interests of the patients who participate in it. If a research component is embedded within standard clinical care, we can ask whether the inclusion of the research component benefits the patient. If the answer is no and if the research component presents some risk or cost to participants, then the practice as a whole—that is, the package of standard care and research—is best viewed as research. Its orienting purpose is to generate knowledge for the good of future patients. If the answer is yes, then it is unclear why the research component should not itself be considered clinical care. The way out of the dilemma is to appeal to the uncertainty that the research is intended to resolve. That uncertainty is a matter of objective clinical knowledge and not a matter of a subjective assessment or hunch.

Early critics of the principle of equipoise charged it with conceptual incoherence. It is a principle, they objected, that seeks to assess the ethics of clinical research by a standard appropriate for beneficent medical care. There is something right about this critique, but we should not forget Fried's point. Equipoise can silence the exploitation concern. When equipoise is understood as an anti-exploitation norm or as a component of an anti-exploitation norm, it avoids the incoherence of applying a norm of clinical care to the practice of clinical research. When a pragmatic research practice fails the equipoise test, the relationship between the physician-investigator and patient is altered. It is no longer a relationship oriented in the first instance toward the good of the patient

[52] Miller and Joffe, "Benefit in Phase 1 Oncology Trials."

and that change in the nature of the relationship should affect the kind of informed consent that is required to justify the interaction.

Pragmatic clinical research is ethically challenging because it obscures, perhaps deliberately, the nature of the relationship between the relevant parties. The solution is not to abandon pragmatic clinical research. Its proponents are right to call attention to its potential for improving health care over time. Nor is the solution to abandon the research-practice distinction and to develop substantially new ethical frameworks for thinking about consent as it applies to these practices. The solution, rather, is to keep our eye on the ball as to when an instance of integrated care and research crosses the line from beneficent medical care to experimental research for the good of others and to adjust the standards of informed consent accordingly. The much-maligned principle of clinical equipoise can find new life in helping us to discharge that crucial task.

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