Vanderbilt Law Review

Volume 58 | Issue 2 Article 1

3-2005

Duties to Subjects in Clinical Research

Carl H. Coleman

VANDERBILT LAW REVIEW

VOLUME 58 MARCH 2005 NUMBER 2

Duties to Subjects in Clinical Research

*Carl H. Coleman**

I. INTRODUCTION 388
II. BACKGROUND 392
III. THE UNDERLYING CONFLICT IN CLINICAL RESEARCH 396
IV. THE INADEQUACY OF AN ALL-OR-NOTHING APPROACH TO THE PROBLEM: WHY THE OBLIGATIONS OF RESEARCHERS MUST BE DIFFERENT FROM THOSE OF EITHER TREATING PHYSICIANS OR PURE SCIENTIFIC INVESTIGATORS 403
A. *Equating the Duties of Researchers with Those of Treating Physicians* 404
B. *The Other Extreme: Researchers as "Scientists Only"* 413
V. BRIDGING THE GAP: FIDUCIARY LAW AS A MODEL FOR THE RESEARCHER-SUBJECT RELATIONSHIP 421
A. *Loyalty and Consent in Fiduciary Relationships* 424
B. *Fiduciary Principles Applied to the Researcher-Subject Relationship* 431
1. Are Researchers Fiduciaries? 431
2. Determining the Appropriate Level of Scrutiny 435

* Professor of Law and Director, Health Law & Policy Program, Seton Hall Law School. B.S.F.S., Georgetown University; A.M., J.D., Harvard University. I would like to thank Kathleen Boozang, Timothy Glynn, Rachel Godsil, Tristin Green, John Jacobi, Solangel Maldonado, Jerry Menikoff, Haavi Morreim, and Charles Sullivan for helpful comments on previous drafts of this Article, and Andrea Brown and August Heckman for their valuable research assistance.

VI. A FIDUCIARY LAW APPROACH TO THE CONFLICTS INHERENT IN CLINICAL RESEARCH 442
VII. CONCLUSION 448

I. INTRODUCTION

Physicians who conduct clinical research with human subjects face a profound conflict in professional roles. As physicians, they are committed to promoting the best interests of current patients. As researchers, however, their goal is to produce generalizable knowledge by studying the effects of interventions in broad cohorts of subjects.[1] Because producing generalizable knowledge often requires actions that are inconsistent with the best interests of the individuals enrolled in a study, these dual objectives often come into conflict. In such situations, where should the physician-researcher's loyalties lie?

While this question has long been of interest to physicians and bioethicists, it has largely escaped the attention of lawyers. A recent wave of lawsuits against clinical researchers,[2] however, is likely to change this situation. In evaluating these claims, courts will have to determine whether researchers owe subjects the same duty of care that physicians owe to their patients, or whether the researcher-subject relationship involves a different set of legal obligations—and, if it does, how those obligations should be defined.[3]

---

1. Some commentators have begun using the term "participant" to describe individuals enrolled in medical research, rather than the word "subject," in order to "reinforce the aspiration to involve participants more directly in research and its oversight." COMM. ON ASSESSING THE SYS. FOR PROT. HUMAN RESEARCH SUBJECTS, INST. OF MED., PRESERVING PUBLIC TRUST: ACCREDITATION AND HUMAN RESEARCH PARTICIPANT PROTECTION PROGRAMS 34 (2001); *see also* Benedict Carey, *The Subject . . . Is Subjects*, N.Y. TIMES, June 15, 2004, at F1 (discussing guidelines by the American Psychological Association that reject the term "subject" as "too impersonal, stripping people of their individuality, their humanity" and that urge the use of the word "participant," which "implies consent"). For two reasons, this Article does not adopt that terminology. First, it is inconsistent with the language used in the federal regulations governing human "subject" protections. *See* 21 C.F.R. § 50.3(g) (2004) ("Human subject means an individual who is or becomes a participant in research"); 45 C.F.R. § 46.102(f) (2004) ("Human subject means a living individual about whom an investigator (whether professional or student)" conducts research). Second, it ignores the fact that individuals who enroll in research enter into a situation fraught with disparities of knowledge and power. Rather than empowering these people, describing them as "participants" may increase their vulnerability by creating the false impression that their relationship with researchers is no different from ordinary arm's-length transactions.

2. *See infra* notes 29-32 and accompanying text.

3. This Article assumes that lawsuits against researchers would not be governed by strict liability, as research is unlikely to fit within the definition of an "abnormally dangerous" activity. *See* RESTATEMENT (SECOND) OF TORTS § 520 (1977) (listing factors used to determine when an activity is "abnormally dangerous"). Whether a no-fault administrative compensation system should be established for injured research subjects is beyond the scope of this Article. *Cf.* COMM. ON ASSESSING THE SYS. FOR PROT. HUMAN RESEARCH PARTICIPANTS, INST. OF MED., NAT'L

At one extreme, courts might conclude that researchers have the same therapeutic obligations to subjects in clinical trials that physicians owe patients receiving ordinary medical treatment, a position advanced by several commentators in the medical and bioethics literature.[4] According to this approach, researchers providing potentially therapeutic interventions[5] in the context of clinical trials may not deviate from the best interests of individual subjects, because to do so would violate the physician's professional obligation to promote the patient-subject's wellbeing.[6]

As explained below, however, the methodological demands of clinical trials often pose unavoidable conflicts with the medical interests of individual subjects.[7] Thus, if taken seriously, the view that researchers' duties are equivalent to those of treating physicians would require a virtual prohibition of clinical research. Moreover, the approach ignores the fact that some individuals might rationally choose to sacrifice the therapeutic commitment of a physician-patient relationship in exchange for other possible benefits of a clinical trial.

Alternatively, courts could take the opposite position—i.e., that because clinical trials do not constitute a form of medical treatment, researchers have no obligation to promote subjects' individual medical

---

ACADS., RESPONSIBLE RESEARCH: A SYSTEMS APPROACH TO PROTECTING RESEARCH PARTICIPANTS 188-94 (Daniel D. Federman et al. eds., 2003) [hereinafter RESPONSIBLE RESEARCH] (proposing such a system). Even if such a system were created, it is unlikely that it would eliminate subjects' right to sue for damages if legal fault could be established. *See* David M. Studdert & Troyen A. Brennan, *Toward A Workable Model of "No-Fault" Compensation for Medical Injury in the United States*, 27 AM. J.L. & MED. 225, 230 (2001) (suggesting that it would be "legally and politically unrealistic to anticipate that any state would undertake wholesale replacement of tort law with a no-fault scheme").

4. *See* discussion *infra* Part III.A.

5. Selecting a term to describe the drugs and other medical interventions offered to subjects in clinical trials is not easy. On the one hand, because these interventions have the potential to improve the subjects' medical conditions, it is tempting to refer to them as "medical treatments." Certainly, many research subjects view them that way, given that individuals often enroll in clinical trials as a means of receiving "cutting-edge" therapies. *See infra* note 101 and accompanying text. Moreover, in some cases, subjects actually receive the same drugs or procedures given to patients outside of research – for example, in studies designed to determine the relative efficacy of two or more standard treatments, or when subjects in a control group receive standard treatment as a basis for comparing the results of an investigational intervention. On the other hand, describing research interventions as medical treatments is potentially misleading, because it obscures the differences between being a research subject and receiving a physician's individualized attention in the context of an ordinary physician-patient relationship. *See* discussion *infra* Part II. Whenever possible, therefore, this Article avoids the term "medical treatments" in describing the interventions offered to subjects in clinical trials. Instead, aspects of research that may provide direct medical benefits to subjects are described as "potentially therapeutic interventions," while aspects that do not offer potential direct benefits to subjects are described as "nontherapeutic" interventions.

6. *See infra* note 90 and accompanying text.

7. *See infra* notes 38-54 and accompanying text.

interests.[8] Such an approach would emphasize the researcher's commitment to producing scientifically valid data, a consideration not relevant when physicians provide care outside of research. Because producing scientifically valid data often requires actions inconsistent with subjects' medical interests, courts might conclude that it is illogical to hold researchers to the same therapeutic obligations as treating physicians. Commentators who endorse this approach argue that protecting subjects' individual interests is the function of the informed consent process and that subjects who have consented to participate in a study should not rely on the researcher to look out for their individual needs.[9]

While this position avoids the restrictiveness of the first approach, the view that researchers have no obligation to protect subjects' medical interests errs too far in the opposite direction. Its reliance on informed consent as the primary mechanism for protecting subjects' welfare ignores the fact that the process of informed consent suffers from significant limitations. In addition, even when the validity of subjects' consent cannot reasonably be doubted, the process of human experimentation implicates interests beyond those of the individuals who agree to be subjects. Regulatory oversight of research addresses some of these issues, but these oversight mechanisms are not designed to identify specific individuals for whom enrolling or continuing in a study poses unacceptable risks.

Accordingly, this Article develops an alternative vision of the researcher-subject relationship, one that neither holds researchers to the same therapeutic obligations as treating physicians nor absolves researchers from any obligation to attend to subjects' individual medical needs. As a basis for such an approach, this Article examines legal principles applicable to individuals in relationships governed by fiduciary principles, including trustees, corporate directors, and partners. Fiduciary principles provide a useful framework for thinking about the relationship between researchers and subjects because they recognize that relationships characterized by trust and dependency create an unusually high danger of exploitation and abuse. To minimize these risks, the fiduciary is charged with an obligation to protect the best interests of the beneficiary of the relationship and is presumptively prohibited from pursuing her own interests or those of someone else. Yet, fiduciary principles also accommodate the possibility that deviations from the exclusive pursuit of the beneficiary's best interests can sometimes be appropriate; thus,

8. *See* discussion *infra* Part III.B.

9. *See infra* notes 109-110 and accompanying text.

the fiduciary's obligation to refrain from pursuing conflicting interests can, under some circumstances, be limited or waived. Notably, however, the beneficiary's consent is generally insufficient to justify a fiduciary's pursuit of interests potentially adverse to those of the beneficiary. Instead, in most contexts, the law imposes additional requirements to ensure that the fiduciary's actions are objectively fair.

Admittedly, there are important differences between the researcher-subject relationship and the types of relationships traditionally governed by fiduciary principles. However, the point of examining fiduciary principles is not to show that the researcher-subject relationship necessarily *is* a fiduciary relationship, but instead to suggest how a duty to protect a vulnerable party's interests can co-exist with actions that simultaneously may threaten that party's overall needs. After explaining why it makes sense to apply a fiduciary law framework to clinical research, this Article explains how fiduciary principles can accommodate the tension between the pursuit of scientific knowledge and subjects' individual needs.

This Article does not explore the financial conflicts of interest that increasingly pervade the world of biomedical research, such as the conflicts that arise when researchers have financial stakes in the companies sponsoring a study.[10] Unlike the issues discussed in this Article, those conflicts are not inherent in the nature of clinical research. Instead, they stem from the particular way that research is financed, and, at least theoretically, could be eliminated by developing alternative financing mechanisms. By contrast, the conflicts explored in this Article are inherent in the nature of clinical trials, as they stem from unavoidable tensions between the pursuit of generalizable knowledge and the best interests of individual subjects.[11]

---

10. *See generally* Mark Barnes & Patrik S. Florencio, *Investigator. IRB and Institutional Financial Conflicts of Interest in Human Subjects Research: Past, Present, and Future*, 32 SETON HALL L. REV. 525 (2002) (advocating increased counterincentives to fight increasing financial influences in research); Mark Barnes & Patrik S. Florencio, *Financial Conflicts of Interest in Human Subjects Research: The Problem of Institutional Conflicts*, 30 J.L. MED. & ETHICS 390 (2002) (providing a framework to conceptualize and manage institutional conflicts of interest); Thomas Bodenheimer, *Uneasy Alliance: Clinical Investigators and the Pharmaceutical Industry*, 342 N. ENG. J. MED. 1539 (2000) (discussing the impact of financial incentives on drug studies); Jesse A. Goldner, *Dealing with Conflicts of Interest in Biomedical Research: IRB Oversight as the Next Best Solution to the Abolitionist Approach*, 28 J.L. MED. & ETHICS 379 (2000) (advocating regulatory changes to encourage IRBs to better address conflicts of interest).

11. *But cf.* Deborah Hellman, *Evidence, Belief, and Action: The Failure of Equipoise to Resolve the Ethical Tension in the Randomized Clinical Trial*, 30 J.L. MED. & ETHICS 375, 379 (2002) (arguing that "tbe randomized clinical trial is not the only way to gather information about which therapies are effective," and that "[o]ther methods that also offer useful information may pose less ethical strain").

Part II of this Article provides general background on clinical research with human subjects, including a brief discussion of the existing oversight mechanisms for research and the growing wave of litigation against researchers seeking compensation for research-related harms. Part III explores the conflicts inherent in clinical research, including the methodological features of clinical trials that can compromise individual subjects' medical needs. Part IV then considers two possible approaches to the relationship between researchers and subjects in clinical trials – at one extreme, the view that researchers have the same obligations as treating physicians, and at the other, the view that researchers have no obligation to promote subjects' medical welfare. After explaining the problems with each of these positions, Part V turns to the law governing fiduciary relationships as a model to conceptualize the legal relationship between researchers and subjects. It begins by examining the legal principles applicable to traditional fiduciaries, including trustees, corporate directors, and partners. Then, it goes on to examine the implications of these principles for the relationship between researchers and subjects in clinical trials. Finally, Part VI applies a framework grounded in fiduciary law principles to a hypothetical case involving a subject injured in a clinical trial, explaining how the framework would regulate the extent to which researchers could deviate from subjects' medical needs.

II. BACKGROUND

Although activities that could be characterized as human experimentation have existed at least since the time of Hippocrates, research as we know it did not emerge until the early nineteenth century, when physicians "began to evaluate the effectiveness of therapeutic techniques statistically."[12] This effort to apply statistical methods to the evaluation of medical interventions is the essence of the research enterprise. Thus, when a physician tries out a completely new way of treating a patient based on a hunch that deviating from standard treatment will produce a better result, in some sense one might say that she is conducting an "experiment" on the patient, but she is not engaged in "research" as that term is commonly used. Instead, the term "research" describes activities "designed to test an hypothesis, permit conclusions to be drawn, and

12. PAUL STARR, THE SOCIAL TRANSFORMATION OF AMERICAN MEDICINE 54-55 (1982).

thereby to develop or contribute to generalizable knowledge."[13] The development of generalizable knowledge is thus both the underlying goal of research and the basis for distinguishing research from ordinary medical care.[14]

Human subjects are used in many different types of research, ranging from surveys and focus groups, to reviews of identifiable medical records or human tissue samples, to clinical trials evaluating new therapies or drugs.[15] A clinical trial is defined as a "controlled study involving human subjects, designed to evaluate prospectively the safety and effectiveness of new drugs or devices or of behavioral interventions."[16] The "gold standard" for clinical research is the randomized controlled trial, in which one group of subjects is randomly assigned to receive an investigational intervention while one or more other groups receive either a different intervention or a placebo. To the extent feasible, randomized controlled trials are "double-masked," meaning that neither the investigators nor the subjects know who is receiving the experimental intervention and who is in the control group until the study has concluded.[17]

Each of these methodological features of clinical trials is designed to promote the statistical validity of the resulting data. Dividing the subjects into different groups, each of which is treated identically—except that one group receives the experimental intervention and the others do not—reduces the likelihood that confounding variables will affect the validity of the results. Assigning subjects to each group randomly is seen as "an essential element of experimental research because it makes more likely the probability that differences observed between subject groups are the result of the experimental intervention," as opposed to differences in the character-

13. NAT'L COMM. FOR THE PROT. OF HUMAN SUBJECTS OF BIOMED. AND BEHAVIORAL RESEARCH, U.S. DEP'T OF HEALTH, EDUC., & WELFARE, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH (1978) [hereinafter BELMONT REPORT]; *see also* 45 C.F.R. § 46.102(d) (2004) (defining "research" as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge").

14. *See generally* Nancy M.P. King, *The Line Between Clinical Innovation and Human Experimentation*, 32 SETON HALL L. REV. 573 (2002) (discussing the often-nebulous distinction between research and treatment).

15. *See generally* RESPONSIBLE RESEARCH, *supra* note 3, at 32-36 (describing the broad range of activities that constitute research with human subjects).

16. OFFICE FOR PROT. FROM RESEARCH RISKS, DEP'T OF HEALTH & HUMAN SERVS., INSTITUTIONAL REVIEW BOARD GUIDEBOOK: HUMAN SUBJECT PROTECTIONS ch. 4 [hereinafter IRB GUIDEBOOK], *available at* http://www.hhs.gov/ohrp/irb/irb_chapter4.htm (last visited May 5, 2005).

17. *Id.*

istics of the various groups.[18] Finally, the use of double-masking seeks to prevent the expectations of researchers or subjects from influencing their interpretation of the events that occur during the study, while also attempting to reduce the potential impact of the placebo effect.[19]

Most clinical trials, as well as other forms of human subject research, are subject to extensive regulatory oversight by federal agencies. The primary federal regulations governing human subject research are known as the "Common Rule," which derives its name from the fact that it has been adopted in identical form by over a dozen agencies that conduct or support research with human subjects.[20] In addition to the Common Rule, the Food and Drug Administration (FDA) has promulgated its own regulations governing human subject research that are similar to the Common Rule in most respects.[21] The Common Rule and the FDA regulations apply to most human subject research in this country, although some research remains exempt from regulatory scrutiny.[22]

Both the Common Rule and the FDA regulations require proposals for human subject research to be reviewed and approved by institutional review boards ("IRBs"), committees comprised of both researchers and lay members, most of whom serve as volunteers.[23] The IRB's most important functions are to weigh the risks and benefits of research protocols and to ensure that the researchers have developed adequate plans for obtaining the subjects' informed

---

18. *Id.*

19. The placebo effect refers to improvements or side effects that "reflect imagination or anticipation rather than actual power of a drug." *Id.*

20. *See* 1 NAT'L BIOETHICS ADVISORY COMM'N, U.S. DEP'T OF COMMERCE, ETHICAL AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS 156 (2001) [hereinafter NAT'L BIOETHICS ADVISORY COMM'N] (noting that the Common Rule covers eighteen federal agencies). Because most human subject research is conducted or supported by the Department of Health and Human Services (DHHS), citations to the Common Rule typically refer to the DHHS version of the regulations, which are codified at 45 C.F.R. part 46 (2004).

21. 21 C.F.R. pt. 56 (2004).

22. The regulations apply to all research conducted or supported by the federal government, as well as to all research related to the development of drugs or medical devices, regardless of whether federal funding is involved. In addition, most institutions that conduct federally-funded research have signed "assurances" with the federal government, in which they agree to comply with the federal regulations in all of their research with human subjects. *See* Jesse A. Goldner, *An Overview of Legal Controls on Human Experimentation and the Regulatory Implications of Taking Professor Katz Seriously*, 38 ST. LOUIS U. L.J. 63, 99-100 (1993) (discussing these federal "assurances"). However, "[a]n unknown amount of nonfederally funded research is completely unregulated under the federal system." NAT'L BIOETHICS ADVISORY COMM'N, *supra* note 20, at 46 (observing that unregulated research "may include experimental surgical techniques, research on reproductive technologies, some uses of approved drugs and medical devices, and research use of private, identifiable data").

23. *See* 45 C.F.R. §§ 46.107-109 (2004) (specifying requirements for IRBs' membership and functioning).

consent.[24] The regulations contain specific requirements for obtaining informed consent to human subject research, related both to the substantive information that must be disclosed to subjects and the manner in which the subject's consent must be documented.[25]

In addition to IRBs, some studies, particularly those involving multiple sites, employ data safety monitoring boards ("DSMBs") to provide ongoing monitoring of clinical trials as the study proceeds.[26] In addition to reviewing reports of adverse events that occur during a trial, DSMBs can monitor the data emerging from the study to determine whether there are sufficiently significant differences between the results in the experimental and control groups to warrant stopping the trial.[27] However, the federal regulations do not require the use of DSMBs in most situations, leaving the decision whether to convene one up to the trial's sponsor.[28]

Until recently, the role of litigation has been quite limited in the area of human subject research, but in recent years this has begun to change.[29] A new wave of litigation against researchers and research institutions has emerged, based on a variety of legal theories, including informed consent violations, claims related to the inappropriate enrollment of subjects or the improper monitoring of subjects' health during the course of a study, and theories related to researchers' alleged fraudulent conduct or conflicts of interest.[30] As one recent survey of this litigation observes, "Because the recent spate of clinical trials cases is still working its way through the courts, there are few published opinions that allow us to gauge the evolution of the

---

24. The IRB's obligations are set forth in 45 C.F.R. § 46.111 (2004).

25. 45 C.F.R. §§ 46.116-117 (2004).

26. *See* Sharona Hoffman, *Continued Concern: Human Subject Protection, the Institutional Review Board, and Continuing Review*, 68 TENN. L. REV. 725, 762-66 (2001) (discussing the role of DSMBs).

27. *See id.* at 763 (discussing various reasons that a DSMB may suggest trial modifications or termination). For example, a placebo-controlled trial of drug designed to treat heart failure in African-Americans was recently halted after a DSMB concluded that "it would be unethical to continue giving some patients a placebo because those getting the drug were living significantly longer." Andrew Pollack, *Drug Approved for Heart Failure in Black Patients*, N.Y. TIMES, July 20, 2004, at C1.

28. *See* Hoffman, *supra* note 26, at 764 (noting that DSMBs are not required unless the research is conducted in an emergency setting).

29. *See* Alice Dembner, *Lawsuits Target Medical Research Patient Safeguards, Oversight Key Issues*, BOSTON GLOBE, Aug. 12, 2002, at A1 (noting that "[f]or years medical researchers were largely immune from lawsuits" but that a new upsurge in suits "is sending shivers through the research community").

30. *See* Michelle M. Mello et al., *The Rise of Litigation in Human Subjects Research*, 139 ANNALS OF INTERNAL MED. 40, 41 (2003) (discussing the trend of bringing "routine informed consent claim[s]" under a variety of other legal theories).

common law in this area."[31] One of the primary unresolved issues relates to the standard of care that courts will apply in this context and the relationship of that standard to both the federal regulations governing human subject research and to "garden-variety medical malpractice cases."[32] In order to understand the complexity of that issue, it is first necessary to examine the differences between research and ordinary medical treatment.

III. THE UNDERLYING CONFLICT IN CLINICAL RESEARCH

At the heart of clinical research lies a fundamental conflict. On the one hand, clinical research involves the provision of medications or other interventions to individuals in need of medical attention—activities that look a great deal like traditional medical treatment.[33] In fact, individuals often participate in clinical trials out of a desire to obtain state-of-the-art medical therapy,[34] and to do so they often must forego other treatments available outside the study. On the other hand, despite the close resemblance of clinical research to ordinary treatment, the goals of the physician-researcher are strikingly different from those of physicians who treat patients in a nonresearch setting. Unlike treating physicians, who are expected to be guided solely by the best interests of individual patients,[35] physicians in clinical trials are not seeking to achieve the best medical outcome for each subject in the study. Instead, the underlying goal of research is the production of generalizable knowledge,[36] i.e., data that can be used to improve the medical care available for patients in the future. To achieve this goal, researchers must be concerned primarily with the implications of their actions for the validity of the data, not the consequences for any particular subject's medical needs.

While producing generalizable knowledge does not always conflict with the best interests of individual subjects, certain conflicts

31. *Id.* at 43.

32. *Id.*

33. Because this Article focuses on clinical research with individuals in need of medical attention, it does not directly address the duties researchers owe to "normal healthy volunteers." *See generally* IRB WORKGROUP, NEW YORK STATE DEP'T OF HEALTH, SAFEGUARDING HEALTHY RESEARCH SUBJECTS: PROTECTING VOLUNTEERS FROM HARM, *available at* http://www.health.state.ny.us/nysdoh/provider/volunteer/intro.htm (discussing the use of healthy subjects in biomedical research) (last visited Feb. 2, 2005).

34. *See infra* notes 101 and accompanying text.

35. *See* Donna T. Chen et al., *Clinical Research and the Physician-Patient Relationship*, 138 ANNALS OF INTERNAL MED. 669, 669 (2003) ("Clinical practice is oriented toward providing patients with individualized care by physicians who are dedicated primarily to their patients' best interests.").

36. *See supra* note 13 and accompanying text.

between the subjects' best interests and the goals of a study are unavoidable. Many such conflicts result from the demands of sound research methodology, particularly the randomized, double-masked, controlled clinical trial, which, as discussed above, is generally considered the "gold standard" for testing new drugs or medical procedures.[37] Such trials depend on a variety of techniques that can undermine the medical best interests of individual subjects.

The first such technique is the process of randomization. In clinical practice, physicians faced with a choice between two or more treatments decide which is most appropriate based on a variety of factors, including evidence from the medical literature (if any exists), personal experience and that of their colleagues, and patient preferences about the different risks and benefits associated with each option.[38] In a clinical trial, by contrast, subjects are assigned to different interventions randomly. Randomized assignments are not necessarily harmful to patients; in fact, in the absence of clear evidence about which intervention is preferable, the flip of a coin may be as good a way as any to determine which one a particular patient should receive.[39] However, even if it is impossible to determine which of two interventions is objectively preferable for patients in general, there may be good grounds for particular individuals to prefer one over the other. Outside of research, physicians are expected to uncover such reasons by carefully investigating the patient's unique circumstances.[40] The randomized trial deliberately avoids this degree of individualized assessment, potentially providing subjects with interventions that are inferior in light of the subject's particular needs.[41]

---

37. *See supra* note 17 and accompanying text.

38. *See* Paul B. Miller & Charles Weijer, *Rehabilitating Equipoise*, 13 KENNEDY INST. ETHICS J. 93, 109 (2003) (discussing factors physicians consider in making treatment recommendations).

39. *See* Howard Mann & Benjamin Djulbegovic, *Letter to the Editor*, HASTINGS CENTER REP., Sept.-Oct. 2003, at 5 (arguing that when there is genuine uncertainty about the relative merits of two treatments, "randomization offers the participant the best chance (fifty-fifty odds) of getting the best intervention, if one is subsequently shown to be superior"); *cf.* Steven M. Grunberg & William T. Cefaul, *The Integral Role of Clinical Research in Clinical Care*, 348 N. ENG. J. MED. 1386, 1387 (2003) (suggesting that physicians who maintain that randomization violates their Hippocratic obligation to promote patients' best interests have failed "to recognize the limitations of their own knowledge").

40. Of course, the statement in the text describes the ideal situation; in reality, the nature and extent of physician-patient communication often falls short of this ideal. *See, e.g.*, Peter H. Schuck, *Rethinking Informed Consent*, 103 YALE L.J. 899, 903-05 (1994) (describing the wide gap between informed consent "idealists" and "realists").

41. In an influential essay published in 1974, Charles Fried argued that, even in the absence of firm evidence favoring one treatment over another, the failure to tailor each subject's

Consider, for example, the debate over whether to provide radiation to women who have stage two breast cancer with three or fewer malignant lymph nodes.[42] Some evidence suggests that providing radiation to these women could reduce the risk that they will have a recurrence of cancer, but it is unclear whether the reduced cancer risk would translate into a greater chance of long-term survival. At the same time, radiation involves nontrivial discomforts, risks, and costs, making the decision to use it in these circumstances a difficult choice. Yet, even in the absence of clear evidence about the utility of radiation, some women might have strong feelings about whether undergoing radiation is appropriate for them. Women who are particularly concerned about avoiding a recurrence of cancer might want to receive radiation regardless of its potential impact on the length of their lives. Other women might prefer to forego the unproven benefits of radiation in exchange for a better quality of life in the present. A clinical trial that randomly assigned women to "radiation" or "no radiation" arms would make it impossible to take into account these individualized assessments of radiation's benefits and risks.[43]

Second, once a subject has been assigned to a particular arm of a study, the specifics of the regimen—for example, the dosages of drugs, the timing of interventions, and the duration of treatments—are dictated by the terms of the protocol, with little or no room for variation based on the individual subject's circumstances.[44] Outside of research, by contrast, physicians are free to structure all aspects of treatment based on the individual patient's situation, making necessary adjustments as more information is learned about the patient's reaction to the chosen interventions. For example, if a

---

treatment to his or her particular circumstances amounts to a "sacrifice" of the individual for the good of the experiment:

> One might say that the individual patient has perhaps not been sacrificed in the crude sense that the best available treatment has been withheld from him, but he has been sacrificed in that for the sake of the experimental design his interest in having his particular circumstances investigated has been sacrificed. But this amounts to the same thing.

Charles Fried, *Medical Experimentation: Personal Integrity and Social Policy*, *in* 5 CLINICAL STUDIES 53 (A.G. Bearn et al. eds., 1974).

42. *See* Laurie Tarkan, *A Debate on Radiation in Breast Cancer*, N.Y. TIMES, Feb. 24, 2004, at F1 (discussing the debate over radiation's impact on survival rates).

43. Such studies were, in fact, attempted, but they ended due to the inability to attract a sufficient number of subjects. *See id.* (quoting a doctor saying that there have been "several randomized studies").

44. *See* JESSICA W. BERG ET AL., INFORMED CONSENT: LEGAL THEORY AND CLINICAL PRACTICE 282 (2d ed. 2001) (explaining how the rigidities of scientific protocols severely restrict the capacity for individual decisionmaking).

patient taking antidepressants experiences difficulty sleeping, the physician may recommend lowering the dosage; if the drug does not appear to be working, a different drug may be tried. In a clinical trial, these options are rarely available.[45] In most cases, the only way a subject can receive treatment in a manner that deviates from the protocol is to withdraw from the study.[46] This option is undesirable for the researcher, who has an interest in maintaining sufficient enrollment to generate usable data, and also may be undesirable for subjects, particularly those who have difficulty obtaining access to alternative sources of care.[47]

Third, in many clinical trials, a variety of interventions are performed solely for the purpose of gathering data, without any direct benefit to the subject's own care.[48] While many of these interventions are only minimally burdensome, such as additional blood draws or physical examinations, others can pose more substantial risks. For example, in some studies subjects are given lumbar punctures (spinal taps) to withdraw cerebrospinal fluid for analysis,[49] a procedure that, while usually safe, can lead to persistent headache and "serious neurological sequelae."[50]

Placebos are a specific type of nontherapeutic intervention used in clinical trials that are especially difficult to reconcile with the physician's traditional commitment to promoting an individual's medical best interests. Placebos are usually inert interventions given to subjects in a control group "to determine whether improvement and

---

45. Some commentators argue that the rigidity of research protocols is not substantially different from the use of practice guidelines outside of research. *See, e.g.*, Grunberg and Cefalu, *supra* note 39, at 1387 (arguing that "the logical extension" of concerns about the rigidity of protocols "would be that one should object to the growing body of evidence-based treatment guidelines and follow-up outcome measures that are becoming part of standard medical care"). However, practice guidelines are simply advisory documents; physicians are not required to follow them in the same manner that researchers are required to adhere to a protocol. It is true that practice guidelines are sometimes used as evidence of the standard of care in medical malpractice cases, but deviation from the guidelines has never been found to constitute negligence per se. Michelle M. Mello, *Of Swords and Shields: The Role of Clinical Practice Guidelines in Medical Malpractice Litigation*, 149 U. PA. L. REV. 645, 672 n.124 (2001).

46. *See* E. Haavi Morreim, *Medical Research Litigation and Malpractice Tort Doctrines: Courts on a Learning Curve*, 4 HOUS. J. HEALTH L. & POL'Y 1, 16 ("Commonly a drug dosage cannot be raised or lowered even when such a change might suit the patient better, unless explicitly permitted by the protocol.").

47. *See infra* note 107 and accompanying text.

48. *See* Chen et al., *supra* note 35, at 669 (noting that "participation in some trials may include medication washout periods, biopsies, overnight hospital stays, imaging studies, blood draws, and questionnaires").

49. *See, e.g.*, Stephan Haimowitz et al., *Uninformed Decisionmaking: The Case of Surrogate Research Consent*, HASTINGS CENTER REP., Nov.-Dec. 1997, at 9, 11-13 (defending the nontherapeutic use of lumbar punctures in research involving suicidal teenagers).

50. Editorial, *Lumbar Puncture and Headache*, 316 BRIT. MED. J. 1018, 1018 (1998).

side effects may reflect imagination or anticipation rather than actual power of a drug."[51] While some subjects may actually do better after receiving placebos,[52] the purpose of placebos in research is not to benefit the subject. Moreover, even though placebos are generally harmless substances,[53] subjects who receive them bear the risks of foregoing active interventions for the condition being investigated. These risks, which can be considerable, are imposed because of the placebo's potential usefulness to the quality of the data, not because of any expected benefits to the individuals involved.

Finally, double-masked trial designs, in which neither the investigator nor the subject knows which intervention the subject is receiving, can compromise the best medical care of the subjects in the study. This is particularly true when subjects experience adverse reactions during the course of clinical research. Uncertainty about the cause of the subject's reaction may make it difficult to determine how best to respond.[54]

Ultimately, the most significant source of the conflict between the pursuit of generalizable knowledge and the medical best interests of individual subjects has less to do with any of these specific methodological features of clinical trials than with the differing *goals* of researchers and treating physicians. Outside of research, physicians' primary goal is to promote the individual patient's welfare. While other factors also can come into play—for example, financial incentives to limit treatment under managed care arrangements,[55] or the need to use patients as teaching opportunities for residents in academic medical centers[56]—the treatment of individual patients is

---

51. IRB GUIDEBOOK, *supra* note 16.

52. *See generally* Kathleen M. Boozang, *The Therapeutic Placebo: The Case for Patient Deception*, 54 FLA. L. REV. 687 (2002) (discussing evidence suggesting that, in some circumstances, placebos can produce better results than conventional treatments).

53. Placebos are not always harmless, however. *See generally* Ruth Macklin, *The Ethical Problems with Sham Surgery in Clinical Research*, 341 NEW ENG. J. MED. 992 (1999) (criticizing the use of sham brain surgery as a placebo control in a study evaluating the efficacy of fetal tissue transplants for Parkinson's disease).

54. Another risk of research is that the investigational intervention will turn out not to work, or that it will actually cause harm to the subjects. That risk, however, also exists when physicians provide unproven therapies to patients in the ordinary clinical setting. It is therefore not a risk inherent in the methodological design of clinical research, as are the risks discussed in the text, but instead a risk associated with the use of unproven interventions in any context.

55. *See, e.g.*, Barry R. Furrow, *Managed Care Organizations and Patient Injury: Rethinking Liability*, 31 GA. L. REV. 419, 465-73 (1997) (discussing conflicts of interest in managed care arrangements).

56. *See* Atul Gawande, *Education of a Knife*, *in* COMPLICATIONS: A SURGEON'S NOTES ON AN IMPERFECT SCIENCE 11, 24 (2002) (discussing the ethical conflicts inherent in the training of surgical residents, and noting that, "[w]hen an attending physician brings a sick family member in for surgery, people at the hospital think hard about how much to let trainees participate").

still the *raison d'être* of physicians' activities. In research, by contrast, physicians judge themselves, and are judged by their peers, on the quality of their data, not on whether they have provided the best possible medical care to each person in a trial. Moreover, outside of research, it is in everyone's interests for each patient to get better. To prove a new treatment successful, however, the researcher must show a statistically significant difference in outcomes between the different arms of the study. Thus, if all of the subjects experience equally good outcomes, those seeking to demonstrate the superiority of the new intervention will consider the study to have been a failure.

The differing motivations of the researcher and the treating physician are especially relevant at two junctures in a study. The first is the initial decision by the researcher to enroll a particular individual as a subject in a trial. While there are some situations in which enrolling in a clinical trial can be in an individual's best interests,[57] physicians committed exclusively to the welfare of individual patients are likely to be cautious about research, given the inherent risks of clinical trials outlined above. Even when a physician believes that the experimental intervention offers particular promise to a patient, it may be possible to gain access to the intervention outside of the study,[58] allowing the patient to receive the benefits of the intervention without the loss of individualized care. Researchers eager to enroll as many subjects as possible, however, have an incentive to discount the risks of research enrollment, and to overlook factors that might make it appropriate to recommend that an individual receive treatment outside of the study.[59]

After the study begins, the differing motivations of the researcher and clinician may also affect how physicians react when subjects fail to respond to treatment or experience discomfort or other adverse reactions to particular interventions. A physician concerned solely with the best interests of the individual subject might recommend that the subject drop out of the protocol, find out which of the various interventions she has been receiving, and receive individually-tailored treatment outside of the study. The researcher concerned about maintaining enrollments, by contrast, has an

---

57. *See infra* notes 100-103 and accompanying text.

58. *See* Jerry Menikoff, *The Hidden Alternative: Getting Investigational Treatments Off-Study*, 361 LANCET 63, 65 (2003) (noting that physicians have "a broad range of discretion in offering a patient an unproven treatment when the doctor thinks that doing so may be in the patient's best interest," and that, as a result of this discretion, it is often possible to gain access to experimental interventions outside of a study).

59. *See id.* at 64-65 (criticizing researchers for failing to inform subjects about the possibility of obtaining investigational interventions outside of a clinical trial).

incentive to keep each subject in the study as long as possible, even if doing so is inconsistent with a particular subject's wellbeing.

The potential impact of the researcher's decisions on the welfare of subjects should not be underestimated. Despite extensive oversight of clinical research by IRBs and DSMBs,[60] those entities cannot identify every individual for whom enrolling or continuing in a study poses unacceptable risks. While the IRB must approve the study's general inclusion and exclusion criteria, the IRB's focus is on the risks and benefits of a study for broad categories of potential subjects, not on the desirability of enrolling in research for any particular person.[61] Moreover, under the federal regulations, IRBs are directed to weigh the risks of research against "the anticipated benefits, if any, to subjects, *and the importance of the knowledge that may reasonably be expected to result*."[62] Thus, it is possible for a risky study to be approved by an IRB even when *no* benefits are anticipated for any of the subjects, based solely on the knowledge the study is expected to produce.

As for problems that emerge in the course of the study, existing oversight mechanisms provide only limited protection for individual subjects. Although IRBs are required to conduct "continuing review" of ongoing studies,[63] these reviews take place infrequently,[64] and many IRBs treat them as a low-priority task.[65] Moreover, most continuing reviews focus on an analysis of statistical reports, not a detailed examination of individual subjects' experiences.[66] Oversight by DSMBs suffers from similar limitations. In addition, the use of DSMBs is generally optional, and some commentators believe that DSMBs are prone to conflicts of interest due to their financial ties to research sponsors.[67] While both of these entities serve important oversight functions, effective monitoring of the day-to-day experience of individual subjects depends on the persons who are actually

60. *See supra* notes 23-28 and accompanying text.

61. *See* 45 C.F.R. § 46.111 (2004) (setting forth IRBs' obligations).

62. 45 C.F.R. § 46.111(a)(2) (emphasis added).

63. *See* 45 C.F.R. § 46.109(e).

64. *See id.* (providing that continuing reviews he conducted "at intervals appropriate to the degree of risk, but not less than once per year").

65. *See* Hoffman, *supra* note 26, at 735 (explaining that "[f]ederal administrative agencies cannot realistically monitor every activity of each IRB and cannot guarantee the welfare of all trial participants").

66. *See id.* at 735 (noting criticisms that "continuing reviews are generally limited to the reading of reports submitted by investigators, and IRBs do not conduct on-site inspection or receive feedback from research subjects").

67. *Id.* at 765-66.

conducting the study – i.e., the principal investigator and other members of the research team.

IV. THE INADEQUACY OF AN ALL-OR-NOTHING APPROACH TO THE PROBLEM: WHY THE OBLIGATIONS OF RESEARCHERS MUST BE DIFFERENT FROM THOSE OF EITHER TREATING PHYSICIANS OR PURE SCIENTIFIC INVESTIGATORS

The conflict between the methodological demands of the controlled clinical trial and the therapeutic interests of individual subjects has not escaped the attention of physicians and bioethicists. Many commentators have attempted to deal with the problem by searching for a way to reconcile the conflict, so that physicians can conduct research without sacrificing their commitment to promoting the individual subjects' medical best interests.[68] Underlying this effort is the assumption that clinical researchers are first and foremost physicians, subject to the same therapeutic obligations to individual subjects that treating physicians owe to their patients.

At the other extreme, there have been occasional suggestions that physicians conducting research should not be held to any of the obligations of treating physicians because they are acting as "scientists only."[69] According to this approach, researchers' primary obligation is to the integrity of their data, not to promoting the best medical interests of the subjects in a trial. Thus, as long as the subjects have provided informed consent to participate in the study, the researcher has no obligation to ensure that the study promotes individual subjects' medical needs.

Each of these positions takes an all-or-nothing view of researchers' obligations: either researchers have the same duty to provide individualized medical attention as treating physicians, or they have no duty whatsoever to promote subjects' medical needs. This Part argues that each of these extreme positions is untenable. Equating the duties of researchers with those of treating physicians ignores the fact that research is not treatment and that subjects have consented to enter into a relationship in which advancing their medical interests is not the primary goal. However, the view that researchers have no duty to attend to the medical best interests of individual subjects errs too far in the opposite direction. In addition to being inconsistent with the expectations of most individuals who

68. *See infra* notes 70, 72-81, 89-93 and accompanying text.

69. *See infra* notes 109-110 and accompanying text.

enroll in clinical trials, it undermines important societal interests in overseeing the risks that subjects are asked to accept.

A. Equating the Duties of Researchers with Those of Treating Physicians

Despite the significant differences between research and ordinary treatment, some commentators maintain that "the ethics of the physician-patient relationship must govern" clinical trials, and that "physicians who conduct these trials have a 'therapeutic obligation' to patients enrolled in them."[70] This view obviously presents a challenge to researchers, given the inherent conflicts in clinical research outlined above.[71]

The most influential attempt to answer this challenge was an essay published by the physician Benjamin Freedman in 1987.[72] Freedman's goal was to respond to the claim that physicians cannot ethically randomize individuals between different arms of a study if there is any reason to believe that one of the arms offers treatment that is superior to the others. As Freedman notes, such a position would make it difficult to conduct any randomized clinical trial, as even "a slight accretion of evidence favoring one arm of the trial"[73] would make it unethical to subject individuals to the risk of randomization. Taken to its extreme, it would preclude randomization "as soon as the investigator perceives a difference between the alternatives—whether or not any genuine difference exists."[74] Such a perception might be based on personal experience, preliminary data that emerge during the course of a study, or even a "'gut feeling' or 'instinct' resulting from (or superimposed on) other considerations."[75]

Freedman's response was not to challenge the critics' underlying assumption—i.e., that it is unethical to randomize subjects if the interventions used in one arm of the study are preferable to those used in the other arms—but to reformulate the criteria for determining when a genuine difference in the interventions actually exists. According to Freedman, the relevant question is not whether a

---

70. Franklin G. Miller & Howard Brody, *A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials*, HASTINGS CENTER REP., May-June, 2003, at 19, 20. As discussed below, Miller and Brody do not themselves accept this position. *See infra* notes 156-160 and accompanying text.

71. *See* discussion *supra* Part II.

72. Benjamin Freedman, *Equipoise and the Ethics of Clinical Research*, 317 N. ENG. J. MED. 141 (1987).

73. *Id.* at 143.

74. *Id.*

75. *Id.*

particular physician has some reason to believe that treatment A is preferable to treatment B. Instead, what matters is whether there is "an honest, professional disagreement among expert clinicians about the preferred treatment," a state of affairs that Freedman referred to as "clinical equipoise."[76] If there is no consensus in the professional community about which treatment is preferable, a physician can ethically ask individuals to submit to randomization—even if the physician has a "decided preference" for one of the treatments and would choose to receive that treatment herself if she were in the subject's position. This standard of clinical equipoise is appropriate, Freedman argued, because the quality of medical care is judged by physicians' conformity to customary practice, not by their adherence to their personal hunches or beliefs.[77]

While Freedman's goal was to defend the randomized clinical trial against ethical challenges, his insistence on clinical equipoise as a prerequisite to randomization presents a barrier to some types of studies that physicians might want to conduct. For example, Freedman noted that his approach would preclude a study evaluating the efficacy of a discredited treatment, such as laetrile:[78] "[W]hen there is no support for a treatment regimen within the expert clinical community, the first ethical requirement of a trial—clinical equipoise—is lacking; it would therefore be unethical to conduct such a trial."[79] In addition, the principle of clinical equipoise would preclude conducting a placebo-controlled trial when effective treatment for a

---

76. *Id.* at 144.

77. *Id.* The role of professional custom in determining the standard of medical care is discussed further *infra* note 267 and accompanying text.

78. Laetrile, a derivative of apricot pits, was a popular alternative treatment for cancer in the 1970s. Andrew Vickers, *Alternative Cancer Cures: "Unproven" or "Disproven"?*, 54 CA: A CANCER J. FOR CLINICIANS 110, 114 (2004). The FDA, finding that laetrile was not generally recognized as safe and effective, refused to authorize the interstate distribution of the drug. The Supreme Court upheld the FDA's determination. United States v. Rutherford, 442 U.S. 544, 546, 551 (1979); *see also* C.G. Moertel et al., *A Clinical Trial of Amygdalin (Laetrile) in the Treatment of Human Cancer*, 306 N. ENG. J. MED. 201, 201 (1982) (concluding that laetrile "is a toxic drug that is not effective as a cancer treatment").

79. Freedman, *supra* note 72, at 145. Some commentators who accept the importance of clinical equipoise have questioned whether the principle should apply when a treatment, although discredited by mainstream physicians, is used by the public on the advice of alternative practitioners. Under these circumstances, a study definitely disproving the efficacy of the treatment could protect consumers from unnecessary risk. *See* Kathleen M. Boozang, *National Policy on CAM: The White House Commission Report*, 31 J.L. MED. & ETHICS 251, 258 (2003) (suggesting that the problem is in part "a definitional quandary – does a disagreement between medical doctors and [complementary and alternative medicine] practitioners establish clinical equipoise?").

particular condition exists.[80] In such circumstances, there is no uncertainty in the professional community about the merits of foregoing active treatment and receiving a placebo. Thus, if clinical equipoise is an absolute requirement for ethically acceptable research, placebo-controlled trials would be permitted only when no treatment for a condition already exists, or in populations for whom the available treatments have proven ineffective or intolerable.[81]

To the extent Freedman's goal was to reconcile clinical research with the patient-centered ethos of the medical profession, his principle of clinical equipoise is only partially successful. At best, Freedman's analysis demonstrates that randomized clinical trials do not *always* conflict with the medical best interests of individual subjects. Yet, even when all of the arms of a study are in a position of clinical equipoise, the risks and benefits of each arm are not necessarily equivalent for every individual subject. As discussed above, a particular arm of the study may be preferable for certain individuals;[82] even if this is not known at the outset of the study, it may become clear after a subject experiences negative reactions once the study has begun. Randomization can compromise the best interests of these particular subjects, regardless of whether clinical equipoise exists for the study population as a whole.[83] Moreover, even when randomization itself is unproblematic, numerous other aspects of clinical trials can undermine the welfare of subjects, including the inflexibility of treatment protocols, the administration of risky

80. *See* Benjamin Freedman, *Placebo-Controlled Trials and the Logic of Clinical Purpose*, 12 IRB: A REVIEW OF HUMAN SUBJECTS RESEARCH, Nov.-Dec. 1990, at 1.

81. *Id.* This standard raises the question of whether "existing treatments" include all treatments theoretically available, or only those treatments actually available to the particular patient population. Freedman accepted that, if "validated optimal treatment is not made freely available to patients, because of cost constraints or otherwise," a placebo-controlled trial of a new treatment could be ethically justified, but he cautioned that this principle "may only be applied when background conditions of justice prevail within the health care system in question." *Id.* at 5; *cf.* David Orentlicher, *Universality and Its Limits: When Research Ethics Can Reflect Local Circumstances*, 30 J.L. MED. & ETHICS 403, 406 (2002) (arguing that, because "[t]he best available therapy varies from country to country," it was ethically justifiable to conduct a placebo-controlled trial in Kenya testing the use of AZT to reduce the risk of HIV transmission from pregnant women to their offspring, despite the fact that the use of AZT in those circumstances was then the standard of care in the United States, because the researchers "were obligated to provide the best therapy available in Kenya, not the best therapy available anywhere in the world.").

82. *See supra* notes 43-47and accompanying text.

83. *See* Miller and Weijer, *supra* note 38, at 112 (arguing that clinical equipoise does not answer the questions, "Is trial participation an appropriate alternative for this particular patient? Should this patient, in light of her condition and accruing medical evidence, continue to participate in this study?").

nontherapeutic interventions, and the use of double-masked trial designs.[84]

The real problem with clinical equipoise, however, is not that it fails to achieve the goals that motivated Freedman's analysis, but that the goals themselves are misguided. In other words, the problem is with the underlying assumption that researchers' duties are equivalent to those of treating physicians, and that researchers therefore owe subjects the same duty of therapeutic beneficence that physicians owe patients when providing ordinary treatment. Not only is this assumption unrealistic, given the inherent conflicts in clinical research discussed above,[85] but it also ignores the fact that individuals who enroll in clinical trials *consent* to assume the role of a subject in an experiment.[86] It is true that the quality of the informed consent process in many studies leaves much to be desired,[87] and, as discussed in the next Section, there are reasons to prohibit certain risks even when the quality of the subjects' consent is not in dispute.[88] Nonetheless, in most circumstances, the law permits individuals to decide for themselves the nature and extent of the risks to which they are willing to be subjected. Thus, rather than starting with the assumption that any deviation from the best interests of subjects is inherently unacceptable, the more logical starting point is to presume that such deviations are permissible as long as they are consensual. Prohibitions on consensual deviations from subjects' best interests should be regarded as exceptional situations, not as a general rule to be applied to clinical trials in all cases.

---

84. *See supra* notes 44-54 and accompanying text. Oddly, some commentators who believe in the importance of clinical equipoise are not opposed to the use of risky nontherapeutic interventions in clinical trials. For example, Charles Weijer argues that interventions that "are administered with a therapeutic warrant," such as drugs and surgical procedures, must satisfy the test of clinical equipoise because physicians' ethical obligations prevent them from providing treatments known to be inferior to the standard of care. Charles Weijer, *The Ethical Analysis of Risk*, 28 J.L. MED. & ETHICS 344, 355-56 (2000). Yet, the only limit he would place on "nontherapeutic procedures" – even those that are "invasive or otherwise fraught with risk" – is that their risks must be balanced by the study's potential contribution to knowledge. *Id.* It is difficult to understand why he considers it inherently unethical to provide potentially therapeutic interventions if they are in any way suboptimal, when he accepts the use of nontherapeutic procedures that may actually involve much greater risks.

85. *See* discussion *supra* Part II.

86. The federal regulations permit research without the subject's informed consent only if consent is provided by the subject's "legally authorized representative," 45 C.F.R. § 46.116 (2004), or if the IRB waives the consent requirement. 45 C.F.R. § 46.116(c)-(d). The option of waiving the consent requirement is available only in specific categories of minimal-risk research, 45 C.F.R. § 46.116(d), and research related to certain types of emergency medical treatments, 21 C.F.R. § 50.24 (2004).

87. *See infra* notes 116-124 and accompanying text.

88. *See infra* notes 132-148 and accompanying text.

Some commentators have suggested that relying on consent to justify deviations from subjects' best interests would violate the principle that individuals generally may not waive the right to sue for medical negligence.[89] For example, two bioethicists, observing that "[c]onsent alone is an insufficient defense when a physician fails to act according to the established standard," argue that "[p]rospective research subjects should not be invited to consent to what by law would constitute negligence in the practice of medicine."[90] The premise of their argument appears to be that the courts' unwillingness to enforce agreements to assume the risks of medical negligence means that physicians' cannot deviate from the patient's or subject's best interests whether or not they have obtained informed consent.[91]

To the extent these commentators are claiming that the duty to act non-negligently should be no more waivable in research than it is in ordinary treatment, their argument should not be controversial. The nonwaiveability of the right to be free from medical negligence stems from public policy judgments about the unequal bargaining power between physicians and patients, combined with the societal interest in ensuring competent medical care by establishing minimum standards of treatment below which physicians may not fall.[92] These principles apply as strongly in medical research as they do in ordinary treatment. Indeed, the federal regulations governing human subject research explicitly prohibit asking subjects to waive their right to sue for negligently-caused injuries.[93]

---

89. *See, e.g.*, Kathleen Cranley Glass & Duff Waring, *Effective Trial Design Need Not Conflict with Good Patient Care*, 2 AM. J. BIOETHICS 25, 26 (2002). The arguments for refusing to enforce agreements not to sue for medical negligence are discussed at length in *Tunkl v. Regents of the University of California*, 383 P.2d 441 (Cal. 1963), which found that agreements to release a hospital from liability for negligence are void as against public policy.

90. Glass & Waring, *supra*, note 89, at 26.

91. Samuel Hellman and Deborah Hellman have similarly argued against relying on consent to justify deviations from subjects' medical interests:

> [O]ne might suggest that the patient has abrogated the rights implicit in a doctor-patient relationship by signing an informed-consent form. We argue that such rights cannot be waived or abrogated. They are inalienable. The right to be treated as an individual deserving the physician's best judgment and care, rather than to be used as a means to determine the best treatment for others, is inherent in every person. This right, based on the concept of dignity, cannot be waived.

Samuel Hellman & Deborah S. Hellman, *Of Mice But Not Men: Problems of the Randomized Clinical Trial*, 324 N. ENG. J. MED. 1585, 1587 (1991).

92. *See Tunkl*, 383 P.2d at 446-47 (arguing that "[t]he public policy of this state has been, in substance, to posit the risk of negligence upon the actor; in instances in which this policy has been abandoned, it has generally been to allow or require that the risk shift to another party better or equally able to bear it, not to shift the risk to the weak bargainer").

93. *See* 45 C.F.R. § 46.116 (2004) ("No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative . . . appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.").

Yet, even if researchers have a nonwaivable obligation to avoid negligent behavior, the concept of negligence does not mean the same thing in clinical research that it does in ordinary treatment. Because negligence means exposing people to risks that are not reasonable under the circumstances, it is essential to take into account the context of an activity when determining the acceptability of the risks it involves. In an ordinary clinical interaction, the sole purpose of the activity is to benefit the patient; thus, risks that are not necessary to promote the patient's medical interests are negligent because they undermine the very reason the activity is being conducted. In research, by contrast, the primary goal of the activity is to develop generalizable knowledge; even in studies that have the potential to benefit the subjects directly, the pursuit of knowledge is ultimately the reason the study is being done. Thus, in research it is not necessarily negligent to deviate from subjects' medical interests, provided that doing so can be justified by a sufficiently important scientific goal.

This interpretation of negligence does not mean that the subject's consent plays no role in justifying the risks associated with research. On the contrary, if subjects (or their representatives) did not provide informed consent to research, any deviations from their best interests would be difficult to defend.[94] However, consent need not be viewed as an agreement to waive the right to sue when a researcher acts negligently, but instead as evidence that, in the context of a clinical trial, certain deviations from the subjects' medical interests do not constitute negligence at all.

That consent can legitimize risks that might otherwise be considered unacceptably dangerous is the premise behind the doctrine of "primary implied assumption of risk," a principle of tort law often applied to activities like participatory sports and amusement park rides.[95] Unlike other forms of assumption of risk, which operate as defenses to activities that have already been determined to be negligent, primary implied assumption of risk is not a defense to negligence but a tool for determining when negligence has occurred. According to the doctrine, an individual who imposes risks on others that might normally be considered unjustifiably dangerous will not be

94. The limited circumstances in which IRBs may waive the informed consent requirement, *see supra* note 86, are consistent with this assumption, as they limit waivers to situations involving either minimal risk, 45 C.F.R. § 116(d), or life-threatening conditions that "necessitate[] intervention," where available treatments are "unproven or unsatisfactory" and the risks of the research interventions are "reasonable." 21 C.F.R. § 50.24(a)(1), (a)(3)(iii).

95. *See, e.g.*, Davenport v. Cotton Hope Plantation Horizontal Prop. Regime, 508 S.E.2d 565, 568-71 (S.C. 1998) (explaining the differences between various types of assumption of risk).

found negligent if: (1) the risks were an inherent part of the activity in which those exposed to the risks were voluntarily participating; and (2) it was reasonable for the person imposing the risks to assume that those participating in the activity knowingly accepted the dangers involved. For example, it is not negligent to accidentally trip a player in a game of tackle football, as the possibility of falling down is an inherent part of the game, and each player can reasonably assume that the others are aware of this danger and have agreed to accept it. It would, however, be negligent to run down the sidewalk in a manner likely to knock down pedestrians, both because causing pedestrians to fall is not necessary to the activity of using the sidewalk and because it is unreasonable to assume that a pedestrian has voluntary accepted the risk of being knocked down.

A similar analysis can be applied to the risks of providing medical interventions in a manner that potentially compromises the best interests of the individuals receiving them. Just as it can be reasonable to run into a participant in a football game but not a pedestrian, providing medical interventions that do not promote the recipient's best interests can be reasonable in a clinical trial but not in ordinary medical care.[96] In both cases, the critical questions are whether the risks are necessary components of the underlying activity, and whether it is reasonable to assume that those participating in the activity have knowingly agreed to be exposed to the risks that are involved.

The discussion in Part II established the first of these requirements, i.e., that deviating from the best interests of individual subjects is often unavoidable when conducting a randomized controlled trial.[97] As for the second requirement, written consent forms provide some evidence that individuals who enroll in clinical trials are aware of the dangers, but a signature on a form does not necessarily mean that the subjects genuinely understood or accepted all of the risks.[98] Aside from the consent form, however, several other

96. Consent also can alter the nature of physicians' obligations outside of research. For example, in *Schneider v. Revici*, 817 F.2d 987 (2d Cir. 1987), the court found sufficient evidence to allow the jury to consider assumption of risk as a defense to a malpractice claim against a physician who treated a cancer patient with unconventional therapy. In that case, however, the purpose of the treatment was to benefit the patient, and, in addition to providing unconventional treatment, the physician expressly advised the patient to have her tumor surgically removed. *Id.* at 989. Because the physician was seeking to promote the medical interests of the individual patient, the court did not have to consider whether consent could ever justify tradeoffs between the patient's best interests and broader societal goals.

97. *See* discussion *supra* Part II.

98. *See infra* notes 116-124 and accompanying text. Outside of research, signed informed consent forms can sometimes establish a presumption that the patient provided informed consent, but the presumption is rebuttable. *See, e.g.*, OHIO REV. CODE ANN. § 2317.54 (2004). Ar-

factors make it reasonable to believe that at least some subjects enroll in clinical trials with knowledge of the risks and a willingness to accept them. Identifying such subjects requires understanding the factors that can make enrolling in clinical trials a rational choice.

First, in many cases, the risks associated with deviating from the subject's best interests are not very significant.[99] In a study comparing a new drug and a placebo for the treatment of a minor condition like mild heartburn, for example, there is little reason to be concerned that subjects in the placebo arm will have to forego treatment for the condition during the course of the study. Even if standard treatment for the condition is available, the only risk associated with foregoing standard treatment is likely to be minor, short-term discomfort.

At the same time, subjects may receive medical benefits from participating in research that make the loss of a therapeutic relationship an acceptable tradeoff. For example, while it is often possible to receive experimental interventions outside of a protocol,[100] sometimes participating in research may be the only way to obtain access to a promising new drug or therapy.[101] In addition, there is some evidence that simply participating in a clinical trial can lead to better medical outcomes – even for individuals who are randomized

---

guably, if a subject's explicit agreement to accept the inherent risks of research can be established, whether through the consent form or otherwise, the analytical framework would shift from primary implied assumption of risk to express assumption of risk. As discussed above, under primary implied assumption of risk, the plaintiff's willingness to participate in an inherently dangerous activity is used as a factor to consider in assessing the reasonableness of the defendant's behavior. *See supra* note 95 and accompanying text. Under express assumption of risk, by contrast, the reasonableness of the activity is not relevant, since the plaintiff has essentially contracted away the right to be treated non-negligently. *See Davenport*, 508 S.E.2d at 570 (explaining that "the rule remains that express assumption of risk continues as an absolute defense in an action for negligence"). However, courts will not apply express assumption of risk in situations where allowing individuals to contract away the right to be treated non-negligently would violate public policy. *See* RESTATEMENT (SECOND) OF TORTS, § 496B (1965). As argued in Part III.B. *infra*, there are strong public policy reasons to limit the risks to which human subjects are exposed, regardless of whether particular individuals might be willing to accept those risks if asked to do so. *See infra* notes 136-148 and accompanying text. Thus, the application of express assumption of risk would be unwarranted in this context.

99. Most research is actually not very risky. *See* ROBERT J. LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH 39 (2d ed. 1988) (arguing that, in most cases, "it is not particularly hazardous to be a research subject").

100. Menikoff, *supra* note 58, at 63-64.

101. For example, if a drug has not been approved by the Food and Drug Administration for any purpose, the only way to obtain access to the drug would be to participate in a clinical trial. *Id.* at 66.

into a placebo control arm.[102] Although a recent study suggests that this "inclusion benefit" applies in only a small minority of trials,[103] the fact that it exists at all suggests that foregoing a therapeutic relationship with a treating physician does not always reduce one's chances of achieving a good medical result.

Even when subjects do not receive medical benefits from participating in research, they may welcome the opportunity to do something altruistic.[104] While altruistic motivations for participating in research can exist in a variety of circumstances, they are especially likely in certain types of situations. For example, in studies of conditions that have a genetic component, even subjects who do not stand to receive a direct medical benefit from participating may be motivated to participate by the prospect of future benefits to their family members.[105] In addition, individuals with medical conditions around which social or political advocacy movements have emerged, such as HIV/AIDS or breast cancer, may feel a special affinity with others who have the same condition. The same may be true for individuals with rare diseases, particularly when many of the individuals who have the disease know one another through support groups or other connections. This shared sense of purpose may lead to a desire to do something beneficial for the affected community, even if doing so involves taking on some risk.[106]

Another reason some people participate in clinical trials is simply to gain access to some form of health care.[107] In a society without universal health care access, clinical trials, which are typically subsidized by the sponsors of the research, may be the least expensive way to get medical attention, particularly for people without

---

102. John D. Lantos, *The "Inclusion Benefit" in Clinical Trials*, 134 J. PEDIATRICS 130, 130 (1999) (suggesting that such benefits may be due to factors such as "selection bias, placebo effects, and adherence to well-defined protocols").

103. Jeffrey M. Peppercorn et al., *Comparison of Outcomes in Cancer Patients Treated Within and Outside Clinical Trials: Conceptual Framework and Structured Review*, 363 LANCET 263, 267-69 (2004).

104. Nancy E. Kass et al., *Trust: The Fragile Foundation of Contemporary Biomedical Research*, HASTINGS CENTER REP., Sept.-Oct. 1996, at 25, 27 (noting that some individuals cite altruism as an important factor in their decision to become research subjects). It is possible that some individuals who attribute their decisions to altruism are actually driven by more self-interested motivations. *See* Claus Wedekind, *Give and Ye Shall Be Recognized*, 280 SCIENCE 2070, 2070-71 (1998) (using game theory to explain why it is often in an individual's best interests to engage in presumably altruistic behavior). Nonetheless, "[a] substantial body of evidence" suggests that genuine altruism "is prevalent among humans." Julia D. Mahoney, *The Market for Human Tissue*, 86 VA. L. REV. 163, 175 n.39 (citing sources).

105. See Kass et al., *supra* note 104, at 25, 27.

106. *See id.* at 27 (quoting survey respondent with a hereditary condition who expressed a desire to participate in research in order to help others in her family).

107. *See* NAT'L BIOETHICS ADVISORY COMM'N, *supra* note 20, at 87.

health insurance. That some people assume the risks of research primarily because they lack other options for obtaining medical treatment is certainly troubling.[108] However, until this country develops a more equitable health care system, participating in a clinical trial, despite the inherent risks, may be a rational decision for persons who otherwise would go without any medical care at all.

That is not to say that the limited health care options available to some subjects should be ignored in assessing the appropriateness of deviating from subjects' best interests. On the contrary, the fact that some subjects have few viable alternatives to participating in research underscores the importance of supplementing the consent requirement with other mechanism for safeguarding subjects' wellbeing. However, a blanket policy of precluding individuals from consenting to deviations from their best interests would do more harm than good for those who depend on the availability of clinical trials as a means of obtaining free or low-cost medical attention. For such individuals, the risks of foregoing the undivided attention of a treating physician are more theoretical than real, and they may pale in comparison to the risks of going entirely without any medical care.

If, as the preceding discussion suggests, deviations from the best interests of individual subjects can sometimes be justified, there is no need to reconcile clinical trials with the therapeutic obligations of treating physicians. This conclusion has two important implications. First, it suggests that clinical equipoise should not be considered a prerequisite for all types of research. If subjects can consent to deviations from their best interests under at least some sets of circumstances, it is not essential that subjects always receive interventions that are at least as promising as the existing standard of care. Second, if we reject the physician-patient relationship as a model for defining researchers' obligations, it becomes necessary to define researchers' duties in some other way. The next Part considers, and ultimately rejects, one such model, which takes a position diametrically opposed to the approach described above.

B. The Other Extreme: Researchers as "Scientists Only"

If researchers need not be exclusively committed to subjects' best interests, may they simply ignore them? In other words, if we reject the physician-patient relationship as the model for defining

108. *Cf.* Gina Kolata and Kurt Eichenwald, *For the Uninsured, Drug Trials Are Medicine*, N.Y. TIMES, June 22, 1999, at A1 (pointing out that individuals who enroll in clinical trials because they lack other health care options may find that the benefits they receive are "fleeting or nonexistent").

researchers' duties, is the alternative to view the researcher-subject relationship as an arm's-length transaction, in which neither party has any obligation to look out for the other's individual needs? A few commentators appear to endorse such an approach. One researcher, for example, maintains that "[t]here is a divergence in the goals of the physician and the researcher, *because the latter is not obligated to act in the best interests of the subject.*"[109] According to this commentator, researchers' duties are limited to promoting "scientific correctness . . . tempered by many features such as informed consent, no duress, and freedom to withdraw."[110] In this view, as long as the subjects' consent is informed and voluntary, the researcher is free to focus exclusively on the pursuit of generalizable knowledge, without any concern for individual subjects' medical needs.

Unlike the view of research ethics described in the previous Section, this "scientific correctness" approach recognizes that research is different from ordinary medical treatment. However, its conclusion that researchers have *no* obligation to act in the best interests of subjects errs too far in the opposite direction. The point of the previous Section was that consensual deviations from subjects' best interest should be presumptively acceptable, not that consent *always* justifies actions that undermine subjects' medical needs.

There are two reasons to be skeptical about the use of consent to justify any conceivable deviation from subjects' medical interests. First, the process of informed consent to research suffers from significant limitations.[111] Going through the ritual of consent[112] is therefore no guarantee that a subject's agreement to enroll in a study is actually informed in any meaningful sense. In addition, even when the validity of subjects' consent to participate in a study cannot reasonably be doubted, the process of human experimentation implicates interests beyond those of the individuals who agree to be subjects.[113] Just as the law places limits on the enforceability of consensual transactions in other situations,[114] there are important

109. C. Barbara Mueller, *Breast Cancer Trials on Trial: A Case of Conflicting Ethical Interests*, 75 CANCER 2403, 2404 (1995) (emphasis added).

110. *Id.*

111. *See infra* notes 116-124 and accompanying text.

112. *Cf.* Paul Root Wolpe, *The Triumph of Autonomy in American Bioethics: A Sociological View*, *in* BIOETHICS AND SOCIETY: SOCIOLOGICAL INVESTIGATIONS OF THE ENTERPRISE OF BIOETHICS 38, 50 (Raymond DeVries & Hanardan Subedi eds.,1998) (describing the process of informed consent as a "ritual of trust" that has taken on greater importance as genuine trust between physicians and patients has eroded).

113. *See infra* notes 132-146 and accompanying text.

114. *See infra* notes 141-146 and accompanying text.

public policy reasons to limit the nature and extent of the risks that human subjects are asked to accept.

First, the fact that individuals may rationally consent to the inherent risks of research in some situations[115] does not mean that everyone who agrees to be a research subject genuinely understands what he or she is being asked to do. Part of the problem is that the process of obtaining informed consent to research is often poorly conducted. In many studies, the primary focus is on getting individuals to sign a piece of paper, with little real interaction between prospective subjects and members of the research team.[116] Yet, even when the consent process is carried out more conscientiously, subjects often fail to grasp what enrolling in a clinical trial really means. A variety of studies have documented that individuals routinely fail to understand the distinction between research and ordinary medical treatment, even after receiving accurate information during the process of informed consent.[117] For example, even when subjects seem to understand the concept of randomized treatment assignments in the abstract, they may refuse to believe that their own treatment will actually be assigned based on the flip of a coin. In general, many subjects harbor a "therapeutic misconception"[118] about the nature of research; they believe that, despite the disclaimers, clinical trials are really designed to promote subjects' own medical interests, in addition to producing knowledge for the potential benefit of patients in the future.[119]

It is not difficult to understand why subjects might have such a mistaken perspective about the nature and goals of biomedical research.[120] The process of informed consent to research does not occur in a vacuum; instead, it takes place in a society that views

---

115. *See supra* notes 99-108 and accompanying text.

116. BERG ET AL., *supra* note 44, at 287.

117. *See id.* at 288-90.

118. *Id.* at 288.

119. *Id.*; *see also* Nancy M. P. King, *Defining and Describing Benefit Appropriately in Clinical Trials*, 28 J.L. MED. & ETHICS 332, 334-36 (2000) (discussing subjects' tendency to overestimate the therapeutic benefits they will receive from research). In a recent empirical study of the therapeutic misconception, 61.8 percent of subjects were found to have exhibited the phenomenon; 31.1 percent "expressed inaccurate beliefs regarding the degree of individualization of their treatment," while 51.1 percent "manifested an unreasonable belief in the nature or likelihood of benefit, given the methods of the study in which they were enrolled." Paul S. Appelbaum et al., *Therapeutic Misconception in Clinical Research: Frequency and Risk Factors*, IRB: ETHICS IN HUM. RES., Mar.-Apr. 2004, at 1, 4-5.

120. In fact, it is quite common for individuals to underestimate the risks and overestimate the benefits of potentially dangerous activities. *See generally* Paul Slovic, *Trust, Emotion, Sex, Politics, and Science: Surveying the Risk Assessment Battlefield*, 1997 U. CHI. LEGAL F. 59 (discussing common cognitive biases that tend to distort individuals' evaluations of risk).

physicians as "single-mindedly devoted to advancing one's health."[121] Under these circumstances, a subject encountering a physician—typically someone dressed in a white coat, wearing a stethoscope, and working in a hospital—may find it difficult to accept that what is going on is not actually designed to promote the subject's medical wellbeing.[122] This is particularly true for people who are referred to clinical trials as a means of obtaining state-of-the-art therapy, as is the case for many patients with cancer or AIDS, conditions for which participation in clinical trials has effectively become part of the standard of care.[123] In these circumstances, even the most carefully designed informed consent process may be incapable of overcoming subjects' expectation that enrolling in research is part of their individualized care.

In addition to increasing subjects' expectation of receiving benefits from research, the therapeutic misconception also may lead subjects to underestimate the risks that clinical research involves. Many people assume that physicians would not expose them to serious health risks, an assumption that can lead subjects to discount the possibility of experiencing an injury.[124] As such, despite the disclosure of risks as part of the informed consent process, it is unreasonable to assume that subjects necessarily appreciate the potential for harm.

Scholars and policymakers have proposed a variety of approaches to dealing with the therapeutic misconception. For example, some have proposed the use of "consent monitors" in particularly complicated or high-risk studies, to help ensure that the subject actually understands what the study entails.[125] Others have suggested that subjects in clinical trials should be paid to participate, so that they realize that they are providing a service rather than

---

121. Paul S. Applebaum, *Clarifying the Ethics of Clinical Research: A Path Toward Avoiding the Therapeutic Misconception*, AM. J. BIOETHICS, Spring 2002, at 22, 23.

122. *See* Kass et al., *supra* note 104, at 26 (noting that, according to surveys of research subjects, many individuals "placed a good deal of trust in the hospitals in which they were receiving care" and believed that, "if they're conducting this research at that hospital, it must be state-of-the-art").

123. In fact, for certain conditions, individuals may "have little access to interventions of any sort outside research." King, *supra* note 119, at 339 (noting that "most children with cancer are enrolled in research because the community of practice agreed to develop an all-encompassing research agenda in order to make progress against the disease"). As Rebecca Dresser argues, patient advocacy organization also may unintentionally contribute to the therapeutic misconception by implying that enrolling in a study is the best way for patients to receive cutting-edge treatment. REBECCA DRESSER, WHEN SCIENCE OFFERS SALVATION: PATIENT ADVOCACY AND RESEARCH ETHICS 47-48 (2002).

124. BERG ET AL., *supra* note 44, at 289.

125. *See, e.g.*, RESPONSIBLE RESEARCH, *supra* note 3, at 153-54.

receiving standard medical care.[126] Yet, despite the potential benefits of these proposals, individuals' expectations about the role of physicians appear to be too deeply ingrained to assume that these changes would eliminate subjects' tendency to conflate research with ordinary medical care.

Some commentators have suggested that researchers' own sense of obligation to promote subjects' medical interests is partly to blame for subjects' confusion about the nature of clinical research. Jay Katz, for example, criticizes researchers for acting as if they were entering into physician-patient relationships with subjects, despite the fact that the researcher-subject relationship is not designed to address the subject's medical needs.[127] In so doing, researchers "unwittingly become double agents with conflicting loyalties,"[128] making it difficult for subjects to understand the difference between research and clinical care. Katz suggests that the way to remedy this problem is for researchers to "see themselves as scientists only and not as doctors."[129] By changing their self-perception to one that more accurately reflects their true relationship with subjects, Katz argues, researchers can help subjects understand what enrolling in a clinical trial is really about.

Katz's proposal is similar to the view that the researcher's duty is limited to the promotion of "scientific correctness."[130] However, it is motivated not by a desire to free researchers from the burdens of therapeutic obligations, but by an effort to ensure that subjects' consent is genuinely voluntary and informed. Yet, the danger is that, unless the approach is completely successful—i.e., unless researchers' efforts to see themselves as "scientists only" completely disabuse subjects of their expectation of individualized therapeutic attention—it may simply make research more dangerous for subjects. Given the deeply-ingrained nature of the therapeutic misconception, subjects would likely continue to conflate research with a therapeutic relationship, but their expectations would be even more misguided, as researchers would now be making a conscious effort to abandon any sense of obligation to promote subjects' medical needs.[131]

---

126. *See* Miller & Brody, *supra* note 70, at 19, 26. For additional suggestions of methods to reduce the therapeutic misconception, see Rebecca Dresser, *The Ubiquity and Utility of the Therapeutic Misconception*, 19 SOC. PHIL. & POL'Y 271 (2002).

127. Jay Katz, *Human Experimentation and Human Rights*, 38 ST. LOUIS U. L.J. 7, 28-29 (1993).

128. *Id.* at 28.

129. *Id.*

130. *See supra* notes 110 and accompanying text.

131. In addition, "[a] complete purging of the therapeutic milieu of clinical research would likely undercut the motivation of patients to volunteer" for clinical trials, as well as making clini-

Freeing researchers from any obligation to promote subjects' medical welfare also ignores the larger societal interests in overseeing clinical trials. While informed consent is certainly an important criterion in determining the ethical acceptability of human subject research, it is not the only consideration. In the *Belmont Report*,[132] an influential document published in 1979 by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research, the emphasis on informed consent was accompanied by an equally strong recognition of other important values. For example, the report emphasized the importance of beneficence, a principle that would prohibit "brutal or inhumane treatment" regardless of consent.[133] It also stressed that justice requires a fair distribution of the benefits and burdens of research, which may require that "some classes of potential subjects . . . may be involved as research subjects, if at all, only on certain conditions,"[134] again notwithstanding those individuals' willingness to consent. Similarly, the Nuremberg Code states that "[n]o experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects."[135] These upper limits on risk do not depend on the presence or absence of consent.

As an example of a situation in which consent might be an insufficient justification for deviating from a subject's medical interests, consider a subject who experiences severe and persistent headaches after receiving a lumbar puncture.[136] Despite the painful and potentially dangerous implications of this adverse reaction, the subject may still want to continue in the study—even if doing so means receiving additional lumbar punctures—because she is sincerely committed to helping the research succeed. Nonetheless, even if this subject actually understands and accepts the risks of continuing in the study, there are a variety of public policy reasons for overriding her consent.

First, allowing subjects to proceed in a study after experiencing significant adverse reactions has implications not only for the

---

cal research "less attractive" for those physician-investigators who are genuinely concerned about promoting subjects' medical wellbeing. Franklin G. Miller et al., *Professional Integrity in Clinical Research*, 280 J. AM. MED. ASS'N 1449, 1451 (1998).

132. BELMONT REPORT, *supra* note 13.

133. *Id.*

134. *Id.*

135. Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No. 10 § 5 (1946-1949) [NUREMBERG CODE], *available at* http://www1.umn.edu/humanrts/instree/nuremberg.html.

136. *See supra* notes 48-50 and accompanying text..

individual subjects but also for society at large. Just as one of the legacies of the notorious Tuskegee syphilis study has been a deep-seated distrust of physicians by African-Americans,[137] knowledge that researchers sometimes perform painful interventions on subjects past the point of serious injury may cause the public to lose trust in the integrity of the medical profession. If the result is that some people become reluctant to seek medical attention, the consequences would be serious for both those individuals' own health and, potentially, the health of the public, to the extent that some people forego treatment for communicable diseases. In addition, it could exacerbate the public's already growing distrust of the safety of research,[138] making it difficult to generate adequate enrollments even in studies that do not pose significant risks.[139]

Second, there are non-utilitarian reasons for limiting the risks imposed on individuals in the name of scientific progress. As Richard Garnett has argued, "Dignity may require respecting autonomy-as-free-choice in some circumstances, but at the same time it may also require objective limits on practices, behaviors, procedures, and institutions which are in themselves inconsistent with the dignity of persons."[140] The notion that certain rights are too significant to be alienated by agreement is a consistent theme running through many areas of law. To list just a few examples, consent is not a defense to most crimes,[141] courts will not enforce agreements that violate public policy,[142] and certain statutory rights are not waivable by the

---

137. James H. Jones, *The Tuskegee Legacy: AIDS and the Black Community*, HASTINGS CENTER REP., Nov.- Dec. 1992, at 38. In the Tuskegee study, researchers observed hundreds of poor African-American men with syphilis over several decades to determine the natural course of the disease. Not only did the researchers fail to offer treatment to the men, even when penicillin became widely available, but they also actively sought to prevent the men from obtaining treatment from other sources. *See generally* Allan M. Brandt, *Racism and Research: The Case of the Tuskegee Syphilis Study*, HASTINGS CENTER REP., Dec. 1978, at 21.

138. *See* Giselle Corbie-Smith et al., *Distrust, Race, and Research*, 162 ARCHIVES INTERNAL MED. 2458, 2460 (2002) (finding that nearly 80 percent of African-Americans and 52 percent of Caucasian-Americans believed that they or "people like them" could be used as "guinea pigs" for medical research without their consent).

139. *See* Goldner, *supra* note 10, at 381 (arguing that the loss of public trust in research "has implications for the willingness of individuals to participate as subjects in research, for the public to financially support research efforts, and ultimately for our very ability to continue to alleviate suffering, conquer disease, and treat painful medical conditions").

140. Richard W. Garnett, *Why Informed Consent? Human Experimentation and the Ethics of Autonomy*, 36 CATH. LAW. 455, 488 (1996).

141. *See* Paul H. Robinson, *The Criminal-Civil Distinction and the Utility of Desert*, 76 B.U. L. Rev. 201, 204 n.21 (1996) ("[C]onsent is rarely a defense in criminal law.").

142. *See* RESTATEMENT (SECOND) OF CONTRACTS § 178(1) (1981) ("A promise or other term of an agreement is unenforceable on grounds of public policy if legislation provides that it is unenforceable or the interest in its enforcement is clearly outweighed in the circumstances by a public policy against the enforcement of such terms.").

individual.[143] Some of these limits on consent are designed partly to prevent individuals from making rash decisions they may later regret,[144] while others, such as the federal prohibition on the sale of human organs,[145] reflect a desire to avoid the commodification of the human body and, ultimately, of persons.[146] In general, these limits demonstrate that public policy in this country does not support unbridled autonomy; in some cases, acceding to individuals' choices may conflict with other values that society holds dear.

A final justification for placing limits on consent to particularly dangerous activities is the difficulty of identifying which individuals' decisions are genuinely informed and voluntary. Even assuming that some subjects would genuinely understand and accept the risks of continuing in a study after experiencing serious adverse reactions, many other subjects' consent would undoubtedly be influenced by the therapeutic misconception—i.e., the assumption that research is guided by the same patient-centered ethos as ordinary medical care.[147] Refusing to accept anyone's consent under these circumstances can be justified by the difficulty of accurately distinguishing the former group from the latter. In other words, a refusal to accept consent to serious deviations from subjects' medical interests serves a prophylactic function; although potentially overinclusive, it guarantees that no one will be exposed to significant risks based on misguided expectations rather than authentic consent. While such a rule might frustrate the autonomous choices of a small group of people, it can be justified when the danger of inadequate consent is particularly high.[148]

---

143. For example, the consumer's right to a three-day rescission period for certain transactions governed by the federal Truth in Lending Act is generally not waivable. *See* 15 U.S.C. § 1635 (2000).

144. For example, policies precluding pregnant women from making binding agreements to give up their babies for adoption are based largely on this rationale. *See, e.g.*, Sullivan v. Mooney, 407 So.2d 559, 563 (Ala. 1981); Anonymous v. Anonymous, 439 N.Y.S.2d 255, 259-60 (Sup Ct. 1981).

145. 42 U.S.C. § 274e (2004).

146. *See* Mark F. Anderson, *The Future of Organ Transplantation: From Where Will New Donors Come, To Whom Will Their Organs Go?*, 5 HEALTH MATRIX 249, 294-301 (1995) (outlining arguments against developing a market in organs). *See generally* Anthony T. Kronman, *Paternalism and the Law of Contracts*, 92 YALE L.J. 763 (1983) (arguing that "[s]ome paternalistic limitations on contractual freedom are best explained by considerations of economic efficiency and distributive fairness, others by the idea of personal integrity, and a third set of limitations by the familiar, though poorly understood, notion of sound judgment").

147. *See supra* notes 120-124 and accompanying text.

148. Similar concerns about the difficulty of distinguishing between authentic and inauthentic consent are one of primary justifications for prohibitions on physician-assisted suicide. *See* Carl H. Coleman, *The "Disparate Impact" Argument Reconsidered: Making Room for Justice in the Assisted Suicide Debate*, 30 J.L. MED. & ETHICS 17, 18-23 (2002) (weighing the risks of inauthentic consent to assisted suicide against the potential benefits of the practice); *cf.* Margaret

Having rejected both the physician-patient relationship and the pure scientific investigator as models for defining the obligations of researchers, where does that leave us? The next Section attempts to answer that question by examining the law's treatment of other types of relationships characterized by a similarly high degree of trust and dependency. This examination provides the basis for constructing a middle ground between the two all-or-nothing positions outlined above.

V. BRIDGING THE GAP: FIDUCIARY LAW AS A MODEL FOR THE RESEARCHER-SUBJECT RELATIONSHIP

Recognizing the inadequacy of the all-or-nothing approaches described in the previous Sections, a few commentators have called for a more balanced definition of researchers' obligations. Franklin Miller and colleagues, for example, write that "[w]e need to cultivate a conception of the moral identity of the physician-investigator that integrates the roles of the clinician and the scientist without giving predominance to the one or the other."[149] Thus, researchers "should be prepared to sacrifice scientific rigor when necessary to protect patient volunteers from exposure to severe suffering or disproportionate risks of harm,"[150] but they also should be permitted to ask subjects to tolerate "minor risks and mild-to-moderate discomfort . . . to conform to scientific protocols."[151]

Elsewhere, Miller and Howard Brody have suggested that, rather than modeling researchers' duties to subjects on either the physician-patient relationship or the ethical obligations of scientific investigators, the emphasis should be on avoiding the "exploitation" of human research subjects.[152] Drawing on ethical principles for research developed by a group of bioethicists at the National Institutes of Health,[153] Miller and Brody suggest that this "non-exploitation framework" requires assurances of "scientific or social value and scientific validity," "fair subject selection," "favorable risk-benefit ratio," and "independent review, informed consent, and respect for enrolled research participants."[154]

Jane Radin, *Market Inalienability*, 100 HARV. L. REV. 1849, 1909-11 (1987) (discussing prophylactic justifications for prohibitions on consensual sales).

149. Miller et al., *supra* note 131, at 1452.

150. *Id.* at 1453.

151. *Id.*

152. Miller & Brody, *supra* note 70, at 26.

153. *See generally* Ezekiel J. Emanuel et al., *What Makes Clinical Research Ethical?* 283 J. AM. MED. ASS'N 2701 (2000) (setting forth seven basic principles for ethical research).

154. Miller & Brody, *supra* note 70, at 26-27.

These commentators' efforts to construct a new definition of researchers' obligations that recognizes both the differences and similarities between clinical research and ordinary medical treatment is a welcome development. However, their principle of "non-exploitation," while useful as a general description of the ideals to which researchers should aspire in their interactions with human subjects, provides little guidance for resolving specific situations in which the pursuit of scientific integrity and the best interests of individual subjects collide. Many of their principles simply incorporate the existing regulatory requirements that IRBs apply in reviewing research protocols, including the regulatory standard for risk-benefit assessment, under which risks to subjects are balanced against the potential *societal* benefits associated with particular studies.[155] For example, in defending a placebo-controlled trial of an antidepression medication, Miller and Brody comment that "risks to participants . . . were justifiable by the anticipated value of the knowledge to be gained from the research."[156] Yet, if we take seriously the notion that physician-researchers may not completely abdicate their responsibility for the best interests of individual subjects—a position implicit in Miller's insistence that researchers "integrate the roles of the clinician and the scientist"[157]—the critical issue is determining when risks become unacceptable *despite* a study's potential to generate valuable knowledge. To the extent Miller and Brody address this question, it is in their directive to ensure "respect for enrolled research participants" by, for example, adopting "procedures for monitoring subjects for possible risk of harm."[158] This requirement suggests that researchers have some obligation to promote subjects' best interests even when doing so may undermine the pursuit of generalizable knowledge. However, the meaning of "respect," and its relationship to the regulatory standard for risk-benefit assessment, is never made clear.

We are thus left with a dilemma: on the one hand, if clinical research is different from ordinary medical treatment, researchers' deviation from the best interests of individual subjects is not necessarily problematic, provided there are valid reasons for conducting the study and the subjects voluntarily agree to assume the risks of foregoing individualized medical care. On the other hand, deficiencies in the process of informed consent to research, combined

155. *See supra* note 62 and accompanying text.

156. Miller & Brody, *supra* note 70, at 27.

157. Miller et al., *supra* note 131, at 1452.

158. Miller & Brody, *supra* note 70, at 27.

with the societal interest in overseeing the conduct of medical professionals, suggest that researchers should not be permitted to completely ignore the best interests of individual subjects, even if protecting subjects' welfare may impede the production of generalizable knowledge. The challenge is to define researchers' duties in a manner that both recognizes subjects' presumptive authority to consent to deviations from their best interests, while carving out a limited duty of therapeutic attentiveness to which all researchers must adhere.

Fortunately, this type of challenge is not unique to human subject research. The function and limits of consent in relationships characterized by trust and dependency also is a familiar theme in the regulation of financial transactions, where the issue frequently arises in dealings between individuals in fiduciary relationships.[159] Consider, for example, a young adult who inherits property in the form of a trust, which will be managed by a trustee until the beneficiary reaches a certain age. The beneficiary stands in a highly vulnerable position vis-à-vis the trustee, given that the trustee has legal title to the property and the authority to manage it, while the beneficiary may lack the maturity, financial acumen, or access to information necessary to determine whether the trustee is managing the property appropriately. The law regulates such situations to ensure that the trustee does not pursue interests at odds with those of the beneficiary, in part by limiting the legal effectiveness of the beneficiary's consent. For example, if the trustee sells trust property to a business in which she has significant interests—potentially benefiting the trustee at the expense of getting the best price for the property—the transaction may be voidable even if the beneficiary consented to it.[160] The law does not bar beneficiaries from consenting to transactions in which trustees pursue conflicting interests, but it requires additional indicia of fairness before the transaction will be upheld.[161] In other fiduciary relationships, the law similarly imposes limits on the beneficiary's power to authorize transactions in which the fiduciary is pursuing competing interests, although the nature and extent of those constraints differs depending on the type of relationship involved.[162]

Admittedly, there are differences between the conflicts that typically arise in relationships governed by fiduciary principles and

159. For a definition of fiduciary relationships, see *infra* notes 171-178.

160. *See infra* note 186-188, 198 and accompanying text.

161. *See id.*

162. *See infra* notes 190-201 and accompanying text.

the conflicts inherent in clinical research. In traditional fiduciary relationships, the underlying purpose of the relationship is to benefit the beneficiary; in research, the primary goal is to develop generalizable knowledge. In addition, conflicts in traditional fiduciary relationships usually involve the fiduciary's effort to derive *personal* advantages at the expense of the beneficiary; in research, the conflict involves the researchers' pursuit of *societal* benefits in a manner that compromises the subject's medical needs.[163] Nonetheless, the law's treatment of the pursuit of self-interest by fiduciaries in financial relationships provides a model for thinking about the power and limits of consent in dependent relationships more generally. For one thing, it calls into question the assumption that individuals in vulnerable relationships are inherently incapable of consenting to actions that are potentially inconsistent with their overall best interests. At the same time, the fact that the legal effectiveness of consent is limited in fiduciary relationships suggests that consent is not necessarily a sufficient safeguard to protect vulnerable individuals from exploitation and abuse. Ultimately, fiduciary principles can help bridge the gap between the all-or-nothing views of researchers' obligations outlined in Part III of this Article, by providing a framework in which consent, while important, becomes just one of several conditions necessary to justify deviations from the pursuit of subjects' medical wellbeing.

The remainder of this Part begins by examining the legal principles governing fiduciary relationships in three contexts—trusts, corporations, and partnerships—particularly as applied to agreements in which the beneficiary of the relationship seeks to authorize the fiduciary to act in a manner that potentially conflicts with the beneficiary's economic interests. It then considers how these principles might be extrapolated to apply to the relationship between researchers and subjects when conflicts arise between the pursuit of scientific knowledge and subjects' medical wellbeing. Part V then turns to the implications of a fiduciary approach to the researcher-subject relationship for litigation in which subjects seek compensation for research-related harms.

A. Loyalty and Consent in Fiduciary Relationships

Although fiduciary principles underlie numerous areas of the law, they are "widely regarded as among the most indefinite,

163. These differences are explored in more detail *infra* text accompanying 242-243.

imprecise, and elusive legal abstractions."[164] At its heart, a fiduciary relationship obligates one party to act "for the benefit of the other party to the relation as to matters within the scope of the relation."[165] A fiduciary relationship is therefore fundamentally different from an ordinary arm's-length transaction, in which neither party has any obligation to protect the other party's interests.[166] Fiduciary obligations typically arise in one of four circumstances:

> (1) when one person places trust in the faithful integrity of another, who as a result gains superiority or influence over the first; (2) when one person assumes control and responsibility over another; (3) when one person has a duty to act for or give advice to another on matters falling within the scope of the relationship; or (4) when there is a specific relationship that has traditionally been recognized as involving fiduciary duties, as with a lawyer and a client.167

Traditional examples of fiduciary relationships include "trustee-beneficiary, principal-agent, guardian-ward, attorney-client, executor-estate beneficiary, partner-partner, director-corporation and shareholders, and majority shareholder-minority shareholder."[168] Fiduciary principles also have been applied to several "nontraditional" relationships, including insurer-insured, priest-penitent, and bank-customer.[169] When fiduciary principles are applied to these nontraditional relationships, "[a] common theme . . . is the relaxation of one party's self-interested vigilance or independent judgment in favor of the other party's protection, because the circumstances justify the belief that the other is acting in the first party's best interests."[170]

Fiduciary obligations are usually divided into two components. The first is the "duty of care," which requires fiduciaries to exercise diligence in making decisions on behalf of the beneficiary.[171] The second is the "duty of loyalty," which obligates the fiduciary to act in a manner that promotes the best interests of the beneficiary, as opposed

---

164. Alan M. Weinberger, *Expanding the Fiduciary Relationship Bestiary: Does Concurrent Ownership Satisfy the Family Resemblance Test?* 24 SETON HALL L. REV. 1767, 1779 (1994).

165. 1 AUSTIN W. SCOTT & WILLIAM F. FRATCHER, THE LAW OF TRUSTS § 2.5 (4th ed. 1987).

166. *See, e.g.*, Meinhard v. Salmon, 164 N.E. 545, 546 (N.Y. 1928) (holding that partner had a duty to inform his copartner of a business opportunity arising out of their venture).

167. Karen E. Boxx, *The Durable Power of Attorney's Place in the Family of Fiduciary Relationships*, 36 GA. L. REV. 1, 16 (2001) (citing BLACK'S LAW DICTIONARY 640 (7th ed. 1999)).

168. *Id.*

169. *Id.* (noting that fiduciary principles have been applied to such relationships only under limited circumstances).

170. *Id.* at 22.

171. *See, e.g.*, Smith v. Van Gorkom, 488 A.2d 858, 872-73 (Del. 1985) (holding that directors violated their duty of care in evaluating a merger proposal and were therefore not entitled to protection by the business judgment rule).

to the fiduciary's own interests or those of another person or entity.[172] The duty of loyalty is most relevant to the present discussion; like the physician's duty to promote the patient's medical best interests, the fiduciary's duty of loyalty constrains the fiduciary's ability to take actions that potentially conflict with the beneficiary's wellbeing.[173]

While all fiduciaries are obligated to promote the beneficiary's best interests, the nature and scope of that obligation depends on the type of relationship. At one extreme is the relationship between trustee and beneficiary, in which self-dealing by the trustee—a paradigmatic example of a breach of the duty of loyalty—is "virtually prohibited."[174] Although the common law's absolute prohibition on self-dealing transactions by trustees has been relaxed in some contexts,[175] the circumstances in which trustees may pursue their own interests at the potential expense of those of the beneficiary remain extremely limited. Under Delaware law, for example, "a court will uphold [a self-interested] transaction against a beneficiary's challenge only if the trustee can show that the transaction was fair and that the beneficiaries consented to the transaction after receiving full disclosure of its terms."[176] Under this standard, even an objectively fair transaction can be set aside if the beneficiary did not consent to it,[177] and even with consent, a self-interested transaction will be voidable if the trustee "failed to disclose material facts, used her position of influence inappropriately, or conducted [the] transaction unfairly."[178]

---

172. *See, e.g.*, Cede & Co. v. Technicolor, 634 A.2d 345, 361 (Del. 1993) ("Essentially, the duty of loyalty mandates that the best interest of the corporation and its shareholders takes precedence over any interest possessed by a director, officer or controlling shareholder and not shared by the stockholders generally."). The Delaware Supreme Court refers to a "triad of fiduciary duties," in which a "duty of good faith" is added to the more common duties of care and loyalty. *See, e.g.*, Emerald Parts. v. Berlin, 787 A.2d 85, 90 (2001) (outlining the triad of duties). Despite this formulation, however, "it is difficult to see how good faith as a concept is not encompassed within the other legs of the 'triad' – i.e., how a director might be found to bave breached his duty of good faitb without being either disloyal or insufficiently careful." DAVID A. DREXLER ET AL., DELAWARE CORPORATE LAW AND PRACTICE § 15.02 (1989).

173. *See supra* note 172.

174. Stegemeier v. Magness, 728 A.2d 557, 563 (Del. 1999) (placing the burden to prove the fairness of a self-interested transaction on the trust executor).

175. *See, e.g., id.*

176. *Id.* (citing Oberly v. Kirby, 592 A.2d 445, 466 (Del. 1991)).

177. Boxx, *supra* note 167, at 20 n.132 (citations omitted).

178. *Id.* at 20 n.127 (citations omitted). As stated by the drafters of the Restatement, Second, of Trusts:

> If the trustee acquires . . . an interest [in the trust property] with the consent of the beneficiary, the transaction cannot be set aside by the beneficiary if the beneficiary was not under an incapacity, and had knowledge of his legal rights and of all material facts which the trustee knew or should have known unless the trustee reasonably believed that the beneficiary knew them, and was not induced by the trustee by undue

Traditionally, the rules governing other fiduciaries, including directors of corporations and members of partnerships, reflected the common-law prohibition on self-dealing by trustees. Thus, in the corporate context, some early cases stated that self-interested transactions by corporate directors were "per se voidab[le]," regardless of their underlying fairness to the corporation,[179] although more recent decisions by the Delaware Supreme Court suggest that the common-law prohibition was never actually that strict.[180] However, the enactment of Section 144 of the Delaware General Corporation Law,[181] combined with decisions by the Delaware Supreme Court,[182] have made it clear that a rule of per se voidability, to the extent it ever applied, no longer is the standard for self-interested transactions by corporate directors. Instead, Section 144 now provides that a director's conflicting interest in a corporate transaction will not be grounds for voiding the transaction if: (1) a majority of the disinterested directors approve the transaction after full disclosure; (2) a majority of the disinterested shareholders approve the transaction after full disclosure;[183] or (3) the transaction is "fair to the corporation as of the time it is authorized, approved or ratified."[184] Although only the third factor under Section 144 explicitly requires an assessment of the fairness of the transaction, the Delaware courts have emphasized that transactions approved by the disinterested directors and, in at least some cases, transactions approved by the disinterested shareholders, also remain subject to a fairness test.[185]

---

influence or other improper means to enter into the transaction, and the transaction was fair and reasonable. If any of these factors is not present, however, the beneficiary can set aside the transaction. The relation between the trustee and the beneficiary being a fiduciary relation, the standard of conduct required of the trustee is higher than that required of persons who are not in a fiduciary relation.

RESTATEMENT OF THE LAW (SECOND) TRUSTS § 170 cmt. w (1959).

179. *See, e.g.*, Rothenburg v. Franklin Washington Trust Co., 13 A.2d 667, 671 (N.J. Ch. 1940).

180. Marciano v. Nakash, 535 A.2d 400, 404 (Del. 1987).

181. DEL. CODE ANN. tit. 8, § 144 (2004).

182. *See* Weinberger v. UOP, Inc., 457 A.2d 701, 710-15 (Del. 1983) (en banc) (advocating a wide ranging "entire fairness" inquiry into the actions of corporate directors).

183. Although the statute does not specifically refer to "disinterested" shareholders, such a requirement has effectively been read into the statute. *See, e.g., In re* Wheelabrator Tech., Inc. S'holders Litig., 663 A.2d 1194, 1203 (Del. Ch. 1995) (stating that directors' decision to enter into a transaction is protected by the business judgment rule when it has been ratified by a majority of the disinterested shareholders); Fliegler v. Lawrence, 361 A.2d 218, 221-22 (Del. Ch. 1976) (same).

184. DEL. CODE ANN. tit. 8, § 144(a)(3) (2004).

185. *See, e.g., In re* Wheelabrator, 663 A.2d at 1203; Weinberger, 457 A.2d at 710-15; Fliegler, 361 A.2d at 221-22. However, approval by the disinterested directors or shareholders "shifts the burden of proof on the issue of fairness from the controlling or dominating shareholder

While self-interested transactions by corporate directors remain subject to legal scrutiny under Section 144, the restrictions on self-dealing by corporate directors are far less rigorous than those applicable to trustees. As one prominent treatise on Delaware corporate law emphasizes, "the distinction between directors and trustees is not merely 'technical.' "[186] Instead, while "the role of a trustee requires a nigh-single-minded, selfless dedication to the interest of the trust estate and its beneficiaries," directors of corporations "are not required by their duty of loyalty to eschew self-interest entirely."[187]

The duty of loyalty required of partners also has its origins in the strict fiduciary obligations applicable to trustees. Indeed, Judge Cardozo's famous description of the obligations of partners—"[n]ot honesty alone, but the punctilio of an honor the most sensitive, is then the standard of behavior"[188]—drew explicitly on trust law principles.[189] The modern view of partners' fiduciary obligations, however, is more relaxed. For example, under the Revised Uniform Partnership Act, partners may contractually modify their fiduciary duties to one another, including by placing limits on the scope of the duty of loyalty.[190] They may agree, *ex ante*, on "specific types or categories of activities that do not violate the duty of loyalty,"[191] and they "may determine the standards by which the performance of the obligation [of good faith and fair dealing] is to be measured."[192] Partners also have the option of authorizing or ratifying a specific transaction "that otherwise would violate the duty of loyalty," provided full disclosure of all material facts is made.[193] Nonetheless, the Revised Act retains some limitations on partners' ability to modify their fiduciary duties to one another. For example, *ex ante* modifications of the duty of loyalty and the duty of good faith and fair dealing will be upheld only if they are "not manifestly unreasonable."[194] Moreover, while partners may

---

to the challenging shareholder-plaintiff." Kahn v. Lynch Communication Sys., Inc., 638 A.2d 1110, 1117 (1994).

186. DREXLER ET AL., *supra* note 172, § 15.02.

187. *Id.*

188. Meinhard v. Salmon, 164 N.E. 545, 546 (N.Y. 1928).

189. *See id.* ("A trustee is held to something stricter than the morals of the marketplace.").

190. *See* Allan W. Vestal, *Fundamental Contractarian Error in the Revised Uniform Partnership Act*, 73 B.U.L. REV. 523, 534, 539-544 (1993) (describing and criticizing the Act's shift to a "contractarian" regime).

191. REVISED UNIFORM PARTNERSHIP ACT § 103(b)(3)(i) (1997).

192. *Id.* § 103(b)(5).

193. *Id.* § 103(b)(3)(ii).

194. *Id.* § 103(b)(3)(i), (b)(5).

contractually modify the duties of loyalty, and of good faith and fair dealing, those duties "may not be eliminated" entirely.[195]

Thus, the concept of a fiduciary relationship is not a one-size-fits-all category. Instead, the meaning of fiduciary obligations varies depending on the type of relationship at issue, with significant differences in the fiduciary's ability to pursue interests that potentially conflict with those of the beneficiary. For example, under trust law, the beneficiary's consent to a self-interested transaction by the trustee is essential;[196] under corporate law, by contrast, self-dealing by a director is acceptable even without the consent of the disinterested directors or shareholders if the transaction is fair to the corporation at the time it is approved.[197] The function of consent also is different under the various legal standards. Under trust law, even consensual self-dealing is unacceptable if the transaction is "conducted unfairly,"[198] and the trustee bears the burden of proving the fairness of the transaction.[199] Under corporate law, however, the approval of the disinterested directors or the shareholders shifts the burden of persuasion to the party challenging the transaction, who must convince the trier of fact that the transaction was not objectively fair.[200] Modern partnership law also makes it difficult to challenge consensual modifications of the duty of loyalty. *Ex ante* modifications of the duty of loyalty are voidable only if they are "manifestly unreasonable," and specific consent to "known past or anticipated violation of duty" essentially immunizes the transaction from challenge regardless of whether it is fair.[201]

Yet, despite the "variations in intensity"[202] of fiduciary relationships, certain core features of fiduciary obligations are similar

---

195. *Id.* § 103(b)(3), (b)(5); *see also id.* § 103 cmt. 4 (noting that the prohibition on eliminating the duties of loyalty and of good faith and fair dealing "are intended to ensure a fundamental core of fiduciary responsibility").

196. *See supra* note 174 and accompanying text.

197. *See supra* note 183-184 and accompanying text.

198. *See supra* note 178 and accompanying text.

199. *See* Stegemeier v. Magness, 728 A.2d 557, 563 (Del. 1999) ("Under current Delaware law, an interested transaction is not void but is voidable, and the court will uphold such a transaction against a beneficiary only if the trustee can show that the transaction was fair." (citing Oberly v. Kirby, 592 A.2d 445, 466 (Del. 1991) (internal citations omitted)); *cf.* Schock v. Nash, 732 A.2d 217, 226 (Del. 1999) (holding that, in breach of fiduciary duty suit against attorney-in-fact acting under power of attorney, attorney-in-fact bears the burden of persuasion).

200. *See supra* note 183-184 and accompanying text.

201. *See* REVISED UNIFORM PARTNERSHIP ACT § 103 cmt. 6 (noting that "consent to a known past or anticipated violation of duty" is a method by which partners can "validate conduct that might otherwise not satisfy the 'manifestly unreasonahle' standard" that is normally applicable to breaches of the duty of loyalty).

202. Weinberger, *supra* note 164, at 1782.

in all circumstances. First, fiduciaries are presumptively required to pursue only the best interests of the beneficiary; unlike a party in an arm's-length transaction, the fiduciary is not supposed to pursue her own interests or those of someone else. Second, the prohibition on pursuing interests that potentially conflict with those of the beneficiary is a presumptive obligation only. Even trustees, who are subject to the strictest fiduciary obligations, are permitted to pursue other interests if the beneficiary consents and the transaction is ultimately fair.[203] Finally, the beneficiary's consent is generally insufficient, in and of itself, to justify the fiduciary's pursuit of interests potentially adverse to those of the beneficiary. While the substantive standards and burdens of proof vary depending on the nature of the relationship, in all fiduciary contexts consensual self-dealing by the fiduciary is voidable under at least some circumstances, ranging from the strict limits on the pursuit of self-interest by trustees to the more relaxed rules applicable to corporate directors and partners.

That some self-interested transactions by fiduciaries are voidable even if the beneficiary has consented suggests that fiduciary obligations are not, as some commentators have argued,[204] simply implied contractual terms, or gap-filling provisions designed to mirror what the parties would have agreed to had they actually negotiated about the details of their mutual obligations.[205] Instead, in many situations, the obligation to promote the beneficiary's best interests constrains the fiduciary's actions even when the beneficiary has expressly authorized the fiduciary to pursue conflicting goals. These constraints promote valuable societal purposes that a purely contractual approach to fiduciary obligations would be incapable of protecting. For example, that the duty of loyalty generally cannot be completely eliminated by contract reinforces beneficiaries' ability to trust that their interests will be protected despite the fiduciary's disproportionate power and control over matters within the scope of

---

203. *See supra* note 176 and accompanying text.

204. *See, e.g.*, Frank H. Easterbrook & Daniel R. Fischel, *Contract and Fiduciary Duty*, 36 J.L. & ECON. 425, 426 (1993) (arguing that the fiduciary "package" is contractual because the "principal and agent enter into this understanding for a gain").

205. *See* Melvin A. Eisenberg, *Corporate Law and Social Norms*, 99 COLUM. L. REV. 1253, 1275 (1999) ("[I]f the duty of loyalty was contractual, it would follow that the duty could be not only limited but completely waived by agreement. Generally speaking, however, it cannot be."). The fact that corporations may not limit or eliminate directors' personal liability for breaches of the duty of loyalty, *see, e.g.*, DEL. CODE ANN. tit. 8, § 102(b)(7) (2004) (stating that a certificate of incorporation may limit directors' personal liability, "provided that such provision sball not eliminate or limit the liability of a director: (i) for any breach of the director's duty of loyalty to the corporation or its shareholders"), further supports the view that core fiduciary obligations exist independent of the parties' implicit or explicit intentions.

the relationship.[206] Similarly, this constraint avoids the danger of "exploitation and abuse" that might arise if the law granted beneficiaries an absolute right to "opt out of fiduciary duties" with no limits on the enforceability of the beneficiary's consent.[207]

At the same time, by permitting beneficiaries to consent to some transactions that might otherwise be considered breaches of the fiduciary's duty of loyalty, the law appropriately recognizes that the fiduciary's pursuit of conflicting interests need not always cause the beneficiary harm. Moreover, refusing to enforce any consensual deviations from the single-minded pursuit of the beneficiary's best interests would be inconsistent with the emphasis on individual autonomy that animates our entire legal system.[208] Respect for autonomy suggests that even individuals in the type of vulnerable relationships that trigger fiduciary obligations should have the freedom to sacrifice the fiduciary's undivided loyalty, provided they have full information and there are no reasons to believe that the transaction is unfair. Permitting parties to structure their relationships free of excessive limitations also arguably enhances efficiency, by facilitating socially beneficial transactions that a more restrictive regime would preclude.

B. Fiduciary Principles Applied to the Researcher-Subject Relationship

1. Are Researchers Fiduciaries?

The closest a court has come to holding that the researcher-subject relationship imposes fiduciary obligations is the Maryland Supreme Court's decision in *Grimes v. Kennedy Krieger Institute*,[209] which found that researchers conducting a study on lead paint poisoning in inner-city households most likely had a duty to warn children in the households when blood tests revealed that the children had elevated lead levels. In reaching this decision, the court found that, in addition to a contractual duty to warn stemming from agreements signed by the researchers, a duty also might exist based

206. *See* Eisenberg, *supra* note 205, at 1275 ("[T]he critical role of trust in the success of the corporate system would be significantly undermined if the law sent a message that the duty of loyalty was essentially a contractual duty, not a duty imposed by law.").

207. Vestal, *supra* note 190, at 562.

208. As one commentator notes, "[t]he altruistic norm of fiduciary duty runs counter to cherished principles of rugged individualism." Weinberger, *supra* note 164, at 1780-81.

209. 782 A.2d 807, 858 (Md. 2001).

on the "special relationship" that "normally exists between researcher and subject."[210]

A "special relationship" is a tort-law concept used to determine when one person has an affirmative duty to protect others from risks not of the person's own creation.[211] For example, the special relationship between lifeguards and beach-goers explains why a lifeguard has a duty to rescue a drowning swimmer, while a person sunbathing on the beach is free to stand around and watch the swimmer drown.[212] While the *Grimes* court's use of the term "special relationship" indicates that researchers have a heightened duty to protect the best interests of subjects, the concept of a "special relationship" and a "fiduciary obligation" are not necessarily the same. An innkeeper, for example, has a special relationship-based duty to come to the aid of an injured guest on the premises,[213] but does not have a fiduciary-based duty of loyalty to pursue solely the guest's interests and eschew personal gain.

Two other courts have discussed the application of fiduciary principles to biomedical research, but both of those cases involved situations distinguishable from the clinical trials with which this Article is concerned. The first, *Moore v. Regents of the University of California*,[214] held that a physician who extracted tissue from his patient in the course of medical treatment had a fiduciary obligation to inform the patient that some of the tissue would be used for biomedical research that could lead to significant profits for the physician.[215] Because that case involved a physician treating a patient in a non-research setting, it does not resolve the question of whether a fiduciary relationship exists between researchers and subjects in clinical trials. The second case, *Greenberg v. Miami Children's Hospital Research Institute*,[216] rejected a breach-of-fiduciary-duty claim brought by individuals who donated tissue to

210. *Id.* at 858. *See generally* Diane E. Hoffman & Karen H. Rothenberg, *Whose Duty Is It Anyway? The Kennedy Krieger Opinion and Its Implications for Public Health Research*, 6 J. HEALTH CARE L. & POL'Y 109 (2002) (focusing on "the legal duty of researchers and the role of tort law in mediating between the need for advances in public health research and compensating injured research subjects").

211. *See* RESTATEMENT (SECOND) OF TORTS § 314A (outlining several categories of relationships giving rise to a duty to protect).

212. *See, e.g.*, S & C Company v. Horne, 235 S.E.2d 456, 459-61 (Va. 1977) (finding defendant apartment complex liable for the death of a swimmer where a lifeguard employee did not notice the drowning because he was talking with his friends by the side of the pool).

213. *See* RESTATEMENT (SECOND) OF TORTS, § 314A (1977) (specifically listing innkeepers as an example of a special relationship giving rise to a duty to protect).

214. 793 P.2d 479 (Cal. 1990).

215. *Id.* at 480-83.

216. 264 F. Supp.2d 1064 (S.D. Fla. 2003).

researchers who were seeking to uncover the genetic mutations associated with Canavan Disease. The tissue donors sued after learning that the researchers had obtained a patent on their discoveries and were using the patent to restrict public access to Canavan disease testing, rather than keeping the fruits of the research in the public domain.[217] Because the tissue donors never received any medical interventions, the case was distinguishable from clinical trials, which involve the provision of drugs or other forms of medical care.[218]

Despite the absence of directly-applicable precedent, a few commentators have concluded that the researcher-subject relationship is fiduciary in nature. Richard Delgado and Helen Leskovac, for example, have argued that "researchers, whether physicians or not, are like other professionals charged with fiduciary duties."[219] In reaching this conclusion, they point out that prospective research subjects are "likely to view the relationship in terms of expectations derived from the typical physician-patient relationship."[220] In addition, they note that research subjects are often "poorly equipped to evaluate the researcher's performance," that "[t]hey frequently depend upon the greater skill or knowledge of the researcher to fulfill their goals," and that "they must trust the researcher to protect their interests."[221] Other commentators have likewise concluded that the researcher-subject relationship has fiduciary characteristics.[222]

---

217. *Id.* at 1067-68.

218. Indeed, the court expressly distinguished tissue donors from "objects of human experimentation." *Id.* at 1071. This distinction is at odds with the federal regulations on human subject research, under which individuals donating tissue directly to a researcher would clearly fit within the definition of a "human subject." *See* 45 C.F.R. § 46.102(f) (2004) (defining "human subject" as "a living individual about whom an investigator . . . conducting research obtains . . . data through intervention or interaction with the individual").

219. Richard Delgado & Helen Leskovac, *Informed Consent in Human Experimentation: Bridging the Gap Between Ethical Thought and Current Practice*, 34 UCLA L. REV. 67, 110 (1986).

220. *Id.* at 109.

221. *Id.*

222. *See, e.g.*, Angela R. Holder, *Do Researchers and Subjects Have a Fiduciary Relationship?* IRB: A REVIEW OF HUMAN SUBJECTS RESEARCH, Jan. 1982, at 6 (answering yes to the question posed in the title); Richard S. Saver, *Critical Care Research and Informed Consent*, 75 N.C. L. REV. 205, 222 (1996) ("Although the case law has not specifically addressed the question, the medical researcher likely has a fiduciary relationship to the subject just as the doctor has to his or her patient."); *cf.* Henry S. Richardson and Leah Belsky, *The Ancillary-Care Responsibilities of Medical Researchers: An Ethical Framework for Thinking about the Clinical Care that Researchers Owe Their Subjects*, HASTINGS CENTER REP., Jan.-Feb. 2004, at 25 (arguing that, as an ethical matter, researchers have "limited but substantive fiduciary obligations" to subjects, which in some circumstances obligate the researcher to diagnose and possibly provide care for conditions unrelated to the research).

Some commentators, by contrast, have criticized the application of fiduciary principles to the researcher-subject relationship, emphasizing that the *purpose* of the relationship is not to promote the best interests of the subject.[223] Certainly, the fact that the purpose of research is to produce generalizable knowledge distinguishes the researcher-subject relationship from traditional fiduciary situations. For example, trust relationships are created *in order to* manage the beneficiary's property, and corporate directors serve *in order to* benefit the corporation's affairs. However, the application of fiduciary principles does not always turn on whether the more powerful party enters into the relationship primarily for the protection of the weaker party. Instead, as Karen Boxx observes, "Some courts have defined the required element as 'justifiable trust,' in other words, where one party has justifiably put trust in another to watch out for the first party's interests."[224] As an example, Boxx cites a case suggesting that an adoption agency might have a fiduciary obligation to inform prospective parents about a child's prior mental and physical problems.[225] Adoption agencies do not exist primarily to promote the best interests of the prospective parents; their main goal is to promote the child's interest in finding a good home. Nonetheless, the court emphasized that the relationship between the agency and prospective parents "would reasonably lead the adoptive parents to place a great degree of trust in the agency," and that the agency's "superior position" created a duty to look out for the prospective parents' needs.[226] In this case, the critical issue was whether the parents' expectation of protection from the agency was reasonable under the circumstances; after finding that it was, the court applied

223. *See, e.g.*, Morreim, *supra* note 46, at 45 (arguing that "the very nature of research precludes a fiduciary relationship between investigators and subjects" because "by definition the researcher's *goal* is not the betterment of any particular participant" (emphasis added)). For similar reasons, Miller and Brody also reject the application of fiduciary principles to the researcher-subject relationship:

> [T]he investigator, in contrast to the treating physician, cannot be seen as having a fiduciary relationship with research subjects, including those who have a prior physician-patient relationship with the investigator. In research, the investigator cannot in good faith promise fidelity to doing what is best medically for the patient-subject.

Howard Brody & Franklin G. Miller, *The Clinican-Investigator: Unavoidable But Manageable Tension*, 13 KENNEDY INST. ETHICS J. 329, 336 (2003).

224. Boxx, *supra* note 167, at 22.

225. *Id.* (citing Taeger v. Catholic Family & Cmty. Servs., 995 P.2d 721 (Ariz. Ct. App. 1999)).

226. *Taeger*, 995 P.2d at 727.

fiduciary principles to ensure that these expectations would be appropriately enforced.[227]

In any event, the critical question is not whether the researcher-subject relationship necessarily *is* a fiduciary relationship, but whether it is sufficiently *similar* to fiduciary relationships to warrant the application of a comparable legal approach. As discussed in Part III, the relationship between researchers and subjects is characterized by the same type of vulnerability, trust, and expectation of protection that underlie the relationship between fiduciaries and beneficiaries. These similarities make fiduciary principles an appropriate model for defining researchers' duties to subjects, even if the researcher-subject relationship is different from traditional fiduciary relationships in certain respects.

2. Determining the Appropriate Level of Scrutiny

As discussed above, the nature of fiduciary obligations varies considerably across different relationships, ranging from the strict constraints on the pursuit of conflicting interests by trustees[228] to the more liberal rules allowing contractual modifications of the duty of loyalty among partners.[229] This Section considers the appropriate level of scrutiny to apply when researchers engage in actions that potentially compromise individual subjects' medical best interests. Part V applies this analysis by proposing a specific standard to guide litigation brought by subjects who experience research-related harms.

Several aspects of the researcher-subject relationship suggest that researchers should be held to relatively strict obligations to subjects in clinical trials, similar to the fiduciary duties imposed on trustees. Even more than beneficiaries of trusts, research subjects are in a highly vulnerable position. Many subjects are dealing with serious illnesses, which put them in perhaps the quintessential state of extreme vulnerability. Often, subjects have either exhausted standard treatment options or have been unable to obtain standard treatment because of inadequate access to health care.[230] Thus, they may feel that enrolling in research is their only real option, making them reluctant to question whether participation is actually in their best interests. In addition, the therapeutic misconception leads many

227. *See* Boxx, *supra* note 167, at 22 (arguing that courts should apply fiduciary principles for "prescriptive purpose[s]," *i.e.*, to establish expectations about appropriate conduct for others in the future).

228. *See supra* notes 174-178.

229. *See supra* notes 190-195 and accompanying text.

230. *See supra* notes 107-108 and accompanying text.

subjects to harbor unrealistic expectations about the benefits they will receive from a clinical trial, as well as to ignore the fundamental differences between research and ordinary medical care.[231] As discussed in Part III, the process of informed consent is often insufficient to overcome these mistaken beliefs.[232]

The vast disparity in knowledge between researchers and subjects further increases subjects' vulnerability. In general, the relative knowledge and sophistication of the parties in a fiduciary relationship is a significant factor in determining the extent to which a fiduciary will be permitted to pursue conflicting goals. For example, the relative freedom given to partners to limit the nature and scope of fiduciary obligations under the Revised Uniform Partnership Act is based in part on the assumption that partners are typically sophisticated businesspeople operating on relatively equal footing.[233] While the premise that individuals entering into partnerships are necessarily savvy businesspeople is debatable,[234] it is probably true that partners are more likely to be in a position of relative equality than beneficiaries of trusts vis-à-vis a trustee. The model of sophisticated businesspeople negotiating agreements from a relatively equal position is clearly inapplicable to the researcher-subject relationship, given the inherent complexity of research and the fact that most prospective subjects are not medically trained.

An additional reason for holding researchers to relatively strict fiduciary duties is their relative independence from day-to-day oversight in their interactions with human subjects. In general, the more a fiduciary's actions are subject to external control or oversight, the less the need for scrutinizing consensual transactions. Thus, the fact that trustees exercise extensive independent authority[235] is one reason that the law is reluctant to accept the beneficiary's consent to

---

231. *See supra* notes 117-124 and accompanying text.

232. *See supra* notes 115-124 and accompanying text.

233. *See* Vestal, *supra* note 190, at 541 (criticizing the "contractarian" nature of the R.U.P.A. because it jeopardizes those who are not sophisticated business people). Some commentators, citing the supposed sophistication of individuals entering partnerships, would go farther than the Revised Act and let partners completely eliminate the duties of loyalty and good faith and fair dealing. *See, e.g.*, Larry E. Ribstein, *A Mid-Term Assessment of the Project to Revise the Uniform Partnership Act*, 46 BUS. LAW. 111, 137 n.98 (1990) ("Waivers in the partnership context are normally negotiated by knowledgeable parties at arms' length. This is hardly a situation in which mandatory rules are necessary to protect unwary parties.").

234. *See* Vestal, *supra* note 190, at 562 (noting the "ubiquitous presence of the partnership form" and "the widespread participation of relatively unsophisticated individuals in partnerships").

235. As Boxx notes, the trustee "holds legal title to fiduciary property and acts independently of direction except from the trust document, although the trust beneficiaries have the opportunity to observe the trustee and complain about breaches of duty." Boxx, *supra* note 167, at 19.

conflicted transactions without some additional assurances of fairness.[236] The trustee's relative independence can be contrasted with the role of an agent in a principal-agency relationship. Unlike a trustee, who can disregard the beneficiary's instructions if they appear to be inconsistent with the terms of the trust instrument,[237] an agent must follow the principal's instructions and is subject to dismissal by the principal at any time.[238] The principal's ability to supervise and terminate the actions of an agent explains why "the agent owes a somewhat less rigorous duty of loyalty than a trustee."[239]

While researchers do not have quite the degree of autonomy as a trustee charged with managing a beneficiary's property, most of the mechanisms for overseeing research do not apply to researchers' day-to-day interactions with subjects. Instead, they apply to research at the macro level—for example, the IRB's initial review of the protocol, or the DSMB's review of data that come in as the study proceeds.[240] It is true that, like the principal's ability to terminate an agent, subjects have the right to withdraw from clinical trials at any time.[241] However, because most subjects lack the information or expertise to determine whether continuing in a study is in their best interests, they are likely to depend on the researcher's guidance to determine whether it is advisable to withdraw from a study. In many principal-agent relationships, by contrast, the principal has either independent knowledge or access to disinterested advisors who can help determine whether the agent is remaining faithful to the principal's needs.

Nonetheless, while the relationship between researchers and subjects exhibits many similarities to the trustee-beneficiary relationship, there are important differences between the two situations that also must be taken into account. The primary

---

236. *See id.*:

> The greater the independent authority to be exercised by the fiduciary, the greater the scope of his fiduciary duty. Thus, a trustee is under a stricter duty of loyalty than is an agent upon whom limited authority is conferred or a corporate director who can act only as a member of the board of directors or a promoter acting for investors in a new corporation.

237. Because the trustee must remain faithful to the settlor's intentions, she is duty-bound to reject instructions by the beneficiary that depart from the settlor's goals. *See id.* at 20 (explaing that "the duty of a trustee [is] to carry out the terms of the trust in the best interests of the beneficiaries, ratber than obeying the beneficiaries' instructions").

238. *Id.*

239. *Id.*

240. *See supra* notes 23-28 and accompanying text.

241. *See* 45 C.F.R. § 46.116(a)(8) (2004) (stating that subjects must be told that they "may discontinue participation at any time without penalty or loss of benefits to which the subject was otherwise entitled").

difference has to do with the nature of the competing interests that potentially undermine the fiduciary's pursuit of the beneficiary's welfare. In the trust context, as well as in the corporate and partnership conflicts of interests discussed in the previous Section, the typical problem is the fiduciary's pursuit of personal interests at the potential expense of the beneficiary. Although fiduciaries can be subject to competing interests in situations not involving self-interested transactions—for example, when a trustee must balance the interests of one beneficiary with a life estate in trust property against the interests of another beneficiary who will inherit the property when the first beneficiary dies[242] – those situations still involve tradeoffs between two or more individuals' economic best interests. In research, by contrast, the underlying conflict stems from the researcher's pursuit of *societal* benefits, as opposed to either her own economic interests or those of someone else.[243] How, if at all, should this distinction affect the type of scrutiny the law applies to actions that potentially undermine a subject's medical needs?

If the corporate law standard applied in this context, the answer would be clear: corporate law draws a sharp distinction between a director's pursuit of societal or charitable purposes and self-interested transactions, with only the latter seen as a potential violation of the duty of loyalty. A corporate board's decision to donate money to charity, for example, will almost always be reviewed under the extremely deferential business judgment rule,[244] rather than the "intrinsic fairness" standards applicable to a director's pursuit of personal gain. However, corporate donations to charity do not necessarily conflict with shareholders' individual interests; even if the shareholders must forego immediate profits or dividends, they are likely to benefit from the good will the corporation ultimately receives.[245] In research, by contrast, the potential conflict between the pursuit of societal benefits and the best interests of subjects is

242. *See* Estate of Hamill, 410 A.2d 770, 773 (Pa. 1980) (citing AUSTIN WAKEMAN SCOTT, THE LAW OF TRUSTS § 232 (3d ed. 1967) and noting that the trustee's obligation under such circumstances is to make the trust property productive for the life beneficiary while simultaneously preserving the trust property for successive beneficiaries).

243. Economic conflicts of interest also arise in clinical research, but, as emphasized at the outset, those conflicts are beyond the scope of this Article. *See supra* notes 10-11 and accompanying text.

244. *See generally* A.P. Smith Mfg. Co. v. Barlow, 98 A.2d 581 (N.J. 1953) (holding that a corporate donation to Princeton University was not a violation of a corporation's fiduciary duty to its shareholders), *appeal dismissed*, 346 U.S. 861 (1953).

245. *See id.* at 590 (noting that the corporation's donation to Princeton University "was voluntarily made in the reasonable belief that it would aid the public welfare *and advance the interests of the plaintiff as a private corporation* . . . ." (emphasis added)).

undeniable, making the deferential corporate law standard entirely inapt.

However, even if we reject the corporate law standard for actions motivated by researchers' desire to pursue societal benefits, it is still arguable that the law should be more deferential when the fiduciary is not motivated by the potential for personal gain. In fact, outside the research context, Marc Rodwin argues, the law has been reluctant to apply broad fiduciary principles to the physician-patient relationship,[246] in part because of "the idea that physicians *should* serve . . . interests beyond those of their individual patients."[247] For example, the law requires doctors to breach confidentiality and report patients who threaten identifiable individuals with immediate danger, or who have communicable diseases that pose a danger to the public health. In addition, managed care organizations, acting with the support of courts and policymakers, encourage physicians to think not only about the individual patient's welfare but also about the fair allocation of resources. While these examples may appear to conflict with the physician's primary duty of loyalty to the individual patient, Rodwin argues, the law also reflects the idea that "doctors and medical organizations must also act in the interests of the *populations* they serve."[248]

Yet, the fact that research is motivated by the pursuit of societal benefits rather than personal interests does not mean that the potential for overreaching by researchers is necessarily reduced. There have been enough examples of abuses of human subjects in the

---

246. Marc A. Rodwin, *Strains in the Fiduciary Metaphor: Divided Physician Loyalties and Obligations in a Changing Health Care System*, 21 AM. J. L. & MED. 241 (1995). Rodwin argues that fiduciary law principles have been applied to physicians only for very limited purposes. *Id.* at 247-48. These include requiring that physicians not abandon patients, keep information they learn confidential, obtain patient's informed consent to treatment, and in one case, disclose to patients any financial interest in clinical research. *Id.* Aside from these limited circumstances, physicians – as clinicians – are not held to fiduciary standards, especially with respect to financial conflicts of interest. *Id.*

247. *Id.* at 253. Similarly, some commentators have argued that broad fiduciary law principles should not always be applied to lawyers. *See, e.g.*, *Developments in the Law – Conflicts of Interest*, 94 HARV. L. REV. 1244, 1463-64 (1981) (arguing that, despite the lawyer's usual fiduciary law duty to accept favorable settlement offers, lawyers should be permitted to pursue public interest objectives by entering into binding agreements with clients that, "absent unforeseen circumstances, the litigation will be prosecuted as a test case").

248. Rodwin, *supra* note 246, at 254 (emphasis added). An example of such a balancing is the recent announcement that the American Academy of Pediatrics and the American Academy of Family Physicians will soon recommend that doctors stop treating most ear infections in children with antibiotics. As one member of the committee reviewing the guidelines stated, "We are making a societal trade-off – at the individual level, some kids may have a little bit longer course of their infection, but for society as a whole, we will be better served if we don't give them." Associated Press, *Groups Urging No Antibiotics for Earaches*, N.Y. TIMES, Mar. 3, 2004.

name of scientific progress to establish that researchers' altruistic motivations do not prevent the exploitation of subjects. In fact, it is arguable that altruistically-motivated deviations from the subject's best interests pose even greater dangers than actions motivated by the fiduciary's desire for personal gain. When a fiduciary engages in a self-interested transaction, there is at least the potential that feelings of guilt (or fear of being caught) will limit the extent to which she will sacrifice the beneficiary's best interests. A researcher struggling to find a cure for a life-threatening illness, by contrast, is likely to feel justified by the nobility of her altruistic mission. In the midst of promising research, it simply may not *feel* wrong to increase the dose of a drug for a subject who has reported discomforting side effects—as compared, for example, to when a trustee skims interest from a beneficiary's account, obviously well aware that her actions are wrong.

Moreover, it is important not to exaggerate the distinction between the pursuit of societal benefits and personal gain. While most researchers are genuinely motivated by the desire to do good for society, the researcher whose study is successful will also reap personal and professional rewards, including prestige, job security, and easier access to grants.[249] The fact that the primary *goal* of research is to produce generalizable knowledge does not mean that researchers' *motivations* are necessarily limited to the pursuit of societal good.

Nonetheless, the unique nature of the conflicts inherent in clinical trials makes the researcher-subject relationship different from traditional fiduciary situations in one critical respect. In a typical fiduciary conflict, we can presume that the beneficiary would be unwilling to accept *any* reduction in her economic welfare simply to help the fiduciary profit. When a researcher is pursuing societal benefits, by contrast, some subjects may genuinely want to help the researcher's mission for altruistic reasons.[250] Even subjects not motivated by altruism may have other rational reasons for accepting some sacrifice of individualized medical care.[251] The problem arises when researchers deviate *too much* from subjects' medical interests to pursue societal benefits—i.e., when their weighing of the value of generalizable knowledge and subjects' best interests is insufficiently protective of subjects' medical welfare – not that subjects may

249. *See* Norman G. Levinsky, *Nonfinancial Conflicts of Interest in Research*, 347 N. ENG. J. MED. 759, 759 (2002) (observing that "[t]hese dual motives, advancement of medical science and personal benefits from publications and acquisition of grants, have not changed over the past 40 years as clinical research has burgeoned").

250. *See supra* notes 104-106 and accompanying text.

251. *See supra* notes 100-103, 107-108 and accompanying text.

sometimes receive somewhat less individualized benefit than if researchers were not motivated by the pursuit of generalizable knowledge at all.[252]

The fact that subjects might not necessarily be opposed to some tradeoffs between their personal interests and the pursuit of societal benefit has significant implications for defining researchers' obligations to subjects. In traditional fiduciary contexts, when the law scrutinizes a fiduciary's self-interested transaction, the goal is to ensure that the fiduciary's conflict of interest did not cause the value of the beneficiary's assets to drop below what it might have been if the conflict were absent.[253] While the standard for self-interested transactions by corporate directors is somewhat more relaxed than that applicable to trustees,[254] the concept of fairness remains tied to the value the corporation would have received in the absence of a conflict of interest.[255]

This interpretation of "fairness" or "reasonableness" is inappropriate in clinical research. Because subjects may rationally choose to sacrifice some degree of individualized medical attention in order to participate in research, the goal should not be to compare the subject's experience with the type of individualized treatment a patient would receive in a traditional physician-patient relationship.[256] Instead, the law should seek to protect subjects from *excessive* deviations from their medical interests, without requiring

---

252. Delgado and Leskovac use the phrase "conflict of value" to describe the diverging goals of researchers and subjects. Delgado & Leskovac, *supra* note 219, at 100. Unlike a "conflict of interest," which refers to one individual's effort to gain personal benefits at the expense of another, Delgado and Leskovac write, a conflict of value "arises when two or more participants in a human venture place different values either on the outcomes or objectives of their common effort, or on the means to be employed in achieving those outcomes or objectives." *Id.*

253. *See, e.g.*, *In re* Estate of Rothko, 372 N.E.2d 291, 297-98 (N.Y. 1977) (noting that when a trustee engages in a self-dealing transaction, the general rule in assessing damages is that "beneficiaries are entitled to be put in the position that they would have occupied if no breach of duty bad been committed" (quoting 3 AUSTIN WAKEMAN SCOTT, THE LAW OF TRUSTS § 205 (4th ed. 1988))).

254. *See, e.g.*, HMG/Courtland Props., Inc. v. Gray, 749 A.2d 94, 117 (Del. Ch. 1999) (indicating that "fairness is often a range, rather than a point, so that a transaction involving a payment by the corporation may be fair even though it is consummated at the high end of the range" (quoting AM. L. INST., PRINCIPLES OF CORP. GOVERNANCE: ANALYSIS AND RECOMMENDATIONS pt. 5, at 202 (1994))) .

255. *See, e.g.*, 3 REVISED MODEL BUS.CORP. ACT ANN. 1142.39 (3d ed. 1993):

> It has long been settled tbat a 'fair' price is any price in a broad range which an unrelated party might have been willing to pay or willing to accept . . . for the property, following a normal arm's-length business negotiation, in the light of the knowledge that would have been reasonably acquired in the course of such negotiations, any result within that range being 'fair.'

256. Such a standard would essentially replicate the first view of research ethics discussed in Part III.A. of this Article.

researchers to provide the same level of therapeutic attentiveness they would in ordinary clinical care. Part V takes up that challenge by proposing a specific standard to govern cases in which a researcher's pursuit of scientific benefits allegedly compromises the quality of care that a subject receives.

VI. A FIDUCIARY LAW APPROACH TO THE CONFLICTS INHERENT IN CLINICAL RESEARCH

Consider a study that randomizes subjects between standard treatment and an investigational drug for the treatment of stage IV pancreatic cancer, a condition for which available treatments are not very helpful. After the study begins, one subject experiences severe nausea and has difficulty keeping down food. While other subjects have also experienced some similar symptoms, this subject's experience is particularly severe. Because the study is double-masked, no one knows whether the subject is receiving standard treatment or the investigational drug. If the subject drops out of the study, she can receive individually-tailored treatment that might pose fewer side effects—although it is possible that, if she has been randomized into the standard treatment arm, the treatment she would receive outside the study might not differ greatly from what she is currently receiving. If she continues in the study, however, her nausea and discomfort are likely to continue.

The IRB may well have acted appropriately in authorizing this study, assuming a favorable balance between the study's overall risks and benefits.[257] Nonetheless, the IRB's approval does not free the researcher from considering the implications of continuing in the study for the subject's wellbeing. If the subject continues in the study, suffers increasing discomfort, and ultimately sues the researchers for causing her injuries, a fiduciary law approach suggests the following framework for evaluating her claim:

First, the plaintiff would have to show that the decision to continue in the study posed a conflict between her medical best interests and the pursuit of scientific knowledge. In other words, as in a traditional breach-of-fiduciary-duty claim, the plaintiff would have the burden of showing that the researcher was actually faced with a conflict of interest.[258] If no such conflict existed, any claim for breach of the researcher's duties would necessarily fail.

---

257. *See supra* notes 61 and accompanying text (explaining the standard IRBs apply in evaluating the risks and benefits of research).

258. *See, e.g.*, Cede & Co. v. Technicolor, Inc., 634 A.2d 345, 363 (Del. 1993) (noting that the plaintiff has the burden of demonstrating the existence of a self-dealing transaction).

Assuming the plaintiff can make such a showing (which should not be difficult under the hypothetical presented above), the burden of persuasion would shift to the researcher to demonstrate that the subject consented to continue in the study after being fully informed about the risks and alternatives.[259] This requirement mirrors the approach used in breach-of-fiduciary-duty cases involving trustees, both in that it treats consent as an absolute requirement in all situations and that it shifts the burden of persuasion to the defendant once the plaintiff has established that a conflict existed.[260] The trustee approach is appropriate in this context because, as discussed above, the researcher-subject relationship exhibits at least as much vulnerability and dependency as the relationship between trustee and beneficiary.[261]

However, even if the researcher can establish that the subject was given adequate information and expressed her willingness to continue, the inquiry would not end there. Just as a trustee may not engage in unfair transactions even if the beneficiary has consented,[262] the researcher should have a duty to avoid unreasonable risks to the subject's medical interests regardless of whether the subject has knowingly accepted those risks. In other words, under some circumstances the researcher should be required to override a subject's decision to continue in a study, if continuing would pose unreasonable risks to the subject's wellbeing.

The critical question, of course, is giving content to the concept of "reasonableness" in this context. As discussed above,[263] the standard used in traditional breach-of-fiduciary-duty claims, which focuses on what might have occurred in the absence of the fiduciary's conflict of interest, is inappropriate in research, given that some subjects might reasonably accept some deviations from their medical interests in order to pursue other legitimate goals. Instead, the reasonableness inquiry should turn on the *extent* to which the decision compromised the subject's medical interests in order to pursue the potential for generalizable knowledge. This interpretation of reasonableness would prevent researchers from taking unfair

259. *Cf.* Dave Wendler and Jonathan Rackoff, *Consent for Continuing Research Participation: What Is It and When Should It Be Obtained?*, IRB: ETHICS & HUM. RES., May-June 2002, at 1 (discussing when researchers should approach subjects for "reconsent" after a study has begun).

260. *See supra* note 176 and accompanying text.

261. *See supra* note 230-243 and accompanying text.

262. *See supra* notes 177 and accompanying text.

263. *See supra* notes 260.

advantage of subjects without denying individuals the autonomy to participate in research for reasons that are important to them.

To achieve this goal, the fact-finder should consider a variety of factors that affect individuals' decisions about participating in research. Thus, it should take into account the possibility that some individuals are genuinely motivated by altruism, as well as the other factors that might lead a reasonable person to continue in a study even when doing so involves risks to their medical well-being.[264] At the same time, it should consider the vulnerability inherent in the researcher-subject relationship, as well as the impact of the therapeutic misconception on the process of consent. Ultimately, the purpose of the inquiry should be to determine whether the decision to continue in the study reflects a reasonable tradeoff between the individuals' medical interests and other goals that a reasonable person might plausibly pursue.

If the researcher cannot satisfy this reasonableness standard, and the plaintiff can show that she actually experienced an injury, the researcher should be permitted to escape liability only by demonstrating that the subject's injuries were not proximately caused by the researcher's deviation from the subject's medical interests. Putting the burden on the researcher to disprove the causal link between the breach of fiduciary duty and the damages suffered by the plaintiff is again modeled on the approach used in cases involving trustees.[265] Essentially, the plaintiff's burden is simply to demonstrate the existence of the conflict and a physical injury; at that point, the defendant bears the burden of persuasion on the elements of consent, reasonableness, and proximate cause.

An important aspect of this approach is that the reasonableness of tradeoffs between the pursuit of generalizable knowledge and the protection of subjects' welfare would be based on a lay community standard, i.e., on the fact-finder's assessment of the tradeoffs a reasonable person would be likely to accept. The use of a lay standard is appropriate in this context because the acceptability of tradeoffs between pursuing generalizable knowledge and protecting subjects' medical interests is primarily a question about ethics and values, which are not matters about which researchers can claim special expertise.[266] Thus, these cases are not like malpractice cases

264. *See supra* notes 100-108 and accompanying text.

265. *See supra* note 200 and accompanying text.

266. However, the testimony of researchers or other experts would still be required to identify the risks and expected benefits of the particular study. In addition, expert standards of care would remain applicable in cases alleging ordinary medical negligence committed in the course of a clinical trial, such as the faulty insertion of a catheter.

involving ordinary medical treatment, in which the law has traditionally deferred to the medical profession's own assessment of the standard of care.[267] When physicians provide treatment to patients in a non-research setting, the risks and benefits all relate to the consequences of the treatments for the individual patient. Physicians can plausibly claim special expertise in determining the type of treatments most likely to promote the health of their patients, but researchers know nothing more than the rest of us about the ethical acceptability of sacrificing subjects' medical interests for the larger social good.[268]

This distinction between expert professional matters and ordinary questions of reasonableness has already been recognized in the law of informed consent. In *Canterbury v. Spence*,[269] one of the first cases to hold that physicians must inform patients about the risks, benefits, and alternatives that a "reasonable patient" would consider material to a decision, the court emphasized that the professional standard of care should be limited to questions that bring the physician's "medical knowledge and skills peculiarly into play."[270] In rejecting the professional standard for questions related to the disclosure of information, the court found that "[t]he decision to unveil the patient's condition and the chances as to remediation . . . is ofttimes a non-medical judgment."[271] The same can be said for

---

267. In ordinary malpractice cases, the standard of care has traditionally been based on the custom of the medical community, although many jurisdictions now give juries greater discretion to decide what they believe a "reasonable practitioner" would have done under the circumstances. *See* Philip G. Peters, *The Quiet Demise of Deference to Custom: Malpractice Law at the Millennium*, 57 WASH. & LEE L. REV. 163, 164 (2000):

> [J]udicial deference to physician customs is eroding. Gradually, quietly and relentlessly, state courts are withdrawing this legal privilege. Already, a dozen states have expressly rejected deference to medical customs and another nine, although not directly addressing the role of custom, have rephrased their standard of care in terms of the reasonable physician, rather than compliance with medical custom.

268. Haavi Morreim similarly argues that the standards of care used in malpractice cases provide an inadequate basis for evaluating negligence claims against researchers. Yet, she would still rely extensively on professional opinions, including those of "the broader scientific community" and "the bioethics community." Morreim, *supra* note 46, at 40. The approach proposed in this Article, by contrast, rejects the idea that determining the acceptability of tradeoffs between individual medical benefits and societal interests are "expert" decisions. *Cf.* Bethany J. Spielman, *Professionalism in Forensic Bioethics*, 30 J.L. MED. & ETHICS 420 (2002) (examining whether bioethicists have sufficiently clear and distinct professional standards to warrant their use as expert witnesses in litigation).

269. 464 F.2d 772 (D.C. Cir. 1972), *cert. denied*, 409 U.S. 1064 (1972).

270. *Id.* at 785.

271. *Id.* States are now "nearly divided" between this "reasonable patient" approach to physicians' disclosure obligations and the more traditional "reasonable practitioner" approach. BARRY R. FURROW ET AL., HEALTH LAW: CASES, MATERIALS AND PROBLEMS 406 (3d ed. 1997).

decisions about balancing the pursuit of generalizable knowledge and individual subjects' medical needs.

Applying a lay standard in this context would also create appropriate incentives for researchers. When pursuing scientific rigor poses potential risks to individual subjects, the researcher would have to consider not just her own views on the matter, or the views of her professional colleagues, but how a lay decision-maker is likely to view the reasonableness of asking a subject to accept the particular tradeoff. At the same time, because the standard incorporates the possibility that reasonable people might accept risks to their medical interests under some sets of circumstances, it would not preclude the use of methodological features that require deviations from the medical best interests of subjects, provided those deviations satisfy a reasonableness test.

One potential drawback of this approach is that it might reduce researchers' incentives to obtain subjects' informed consent to aspects of research that potentially jeopardize subjects' medical interests. Because the approach would allow even fully informed subjects to claim that their consent was "unreasonable" and therefore legally ineffective, researchers might decide that providing information to subjects is simply not worth the trouble. In fact, they may conclude that full disclosure would actually do more harm than good, to the extent it ends up scaring some subjects away from a study. Of course, researchers have incentives other than fear of litigation to comply with their informed consent obligations,[272] but those incentives have so far done little to ensure that subjects are adequately informed.[273]

In order to create appropriate incentives for researchers to provide sufficient information to subjects, it would therefore be useful to provide an additional remedy for subjects who were never given the opportunity to consent. Such an additional remedy would be consistent with the law applicable to trustees, under which conflicting transactions are voidable by the beneficiary, regardless of their fairness, if the trustee did not obtain the beneficiary's consent.[274] The analogous situation in the research setting would be a right to recover dignitary damages when researchers engage in nonconsensual deviations from the subject's medical interests—even if a reasonable

272. For example, investigators who are found to have "repeatedly or deliberately" failed to comply with FDA regulations may be prohibited from conducting further research with investigational drugs. *See* 21 C.F.R. § 312.70 (2004) (outlining the procedure for disqualification of clinical research investigators).

273. *See, e.g.*, RESPONSIBLE RESEARCH, *supra* note 3, at 40 (discussing widespread deficiencies in the process of informed consent to research).

274. *See supra* note 177 and accompanying text.

person would have consented to the deviation if given the opportunity, and even if the subject did not experience physical harm.

Some scholars have proposed a similar remedy for failure to obtain informed consent to ordinary medical treatment. For example, Aaron Twerski and Neil Cohen, criticizing the emphasis on causation in prevailing informed consent jurisprudence, argue that informed consent doctrine should instead focus on protecting "the decision rights of the plaintiff which the defendant destroyed by withholding adequate information."[275] Under such an approach, a plaintiff could recover damages for violation of her right to participate in the decisionmaking process, without having to prove that she would have made a different decision if adequate information had been disclosed.[276] Although the courts have never adopted this approach in cases involving standard medical treatment, it is possible that they might take a different view in the context of clinical trials.

In fact, a federal district court approved a settlement of a class action against researchers premised on just such a theory.[277] The plaintiffs in that case were women who alleged that, while they were pregnant and receiving care at a county hospital, they were subjected to repeated amniocentesis testing as part of a study, without ever having been told that they were participating in research. The plaintiffs' theory was that, even though they did not suffer any physical injuries, the repeated testing constituted a violation of their dignitary interests. Although the court's approval of the settlement does not mean that it would have ruled for the plaintiffs on the merits, the case is nonetheless notable as the first litigation to have "produced a substantial monetary recovery to a class of human subjects of biomedical research in the absence of any claim of physical injury."[278]

The argument for recognizing a cause of action based on the failure to obtain proper consent, even when that failure was not the proximate cause of any physical harm, is stronger in research than in ordinary clinical treatment. In the clinical setting, obtaining informed consent is certainly an important ethical and legal requirement, but it is not the only basis for justifying a physician's provision of medical treatment. In addition to the patient's consent, the physician's actions

---

275. Aaron D. Twerski & Neil B. Cohen, *Informed Decision Making and the Law of Torts: The Myth of Justiciable Causation*, 1988 U. ILL. L. REV. 607, 609.

276. *Id.* at 608; *see also* Marjorie Maguire Shultz, *From Informed Consent to Patient Choice: A New Protected Interest*, 95 YALE L.J. 219 (1985) (calling for the courts to recognize a legally-protected interest in "patient autonomy").

277. Diaz v. Hillsborough County Hosp. Auth., No. 8:90-CV-120-T-25B, 2000 U.S. Lexis 14061, at *3 (M.D. Fla. Aug. 7, 2000).

278. *Id.* at *7.

are justified by the principle of beneficence: by providing treatment that meets the prevailing standard of care, the physician is helping to promote the patient's medical wellbeing. In research, by contrast, informed consent is the primary justification for performing risky interventions that have no potential to benefit the subject's individual medical interests. With a few narrow exceptions,[279] imposing risks on subjects for the benefit of others, without the informed consent of the subjects or their legally authorized representatives, would be a flagrant violation of individual dignity.[280] Thus, nonconsensual research is a far greater violation of personal dignity than nonconsensual treatment, and therefore justifies a remedy even if one does not exist for nonconsensual treatment that does not directly cause physical harm.

In addition, providing a remedy for the failure to inform subjects of aspects of studies that potentially compromise their interests would create a greater incentive for researchers to *identify* situations where the pursuit of generalizable knowledge threatens subjects' medical welfare. Thus, researchers may be more likely to engage in active monitoring of subjects' experience during clinical trials. Additional monitoring may ultimately lead to fewer situations in which subjects experience physical harm.

VII. CONCLUSION

The approach proposed in this Article is designed to provide a middle ground between the two extreme positions that have dominated contemporary discourse on the ethics of clinical research. In place of either requiring researchers to adhere to the same duties of therapeutic beneficence that physicians owe patients, or permitting any deviations from subjects' medical interests as long as the subject consents, the proposed approach would base researchers' obligations on a fiduciary law framework. Under this framework, informed consent would be a necessary but not sufficient justification for aspects of research that deviate from the subject's medical interests. In addition to consent, researchers would have the burden of

279. *See supra* note 86.

280. *Cf.* Hans Jonas, *Philosophical Reflections on Experimenting with Human Subjects*, *reprinted in* JAY KATZ, EXPERIMENTATION WITH HUMAN BEINGS: THE AUTHORITY OF THE INVESTIGATOR, SUBJECT, PROFESSIONS AND STATE IN THE HUMAN EXPERIMENTATION PROCESS 667, 668 (1972) (arguing that the "'wrong'" of human experimentation – making the subject "a passive thing merely to be acted on" – can be rectified only "by such authentic identification with the cause that it is the subject's as well as the researcher's cause," which is possible only if the subject's decision to enroll in research is "autonomous and informed").

demonstrating that their actions were objectively reasonable, with reasonableness determined according to a lay point of view.

By rejecting the physician-patient relationship as the model for researchers' duties, the proposed approach would permit reasonable deviations from subjects' medical interests in order to pursue potentially valuable knowledge. At the same time, by treating consent as a necessary but not sufficient justification for such deviations, it acknowledges the vulnerability of subjects and the potential for abuse. Ultimately, this approach recognizes the impossibility of eliminating the tension between clinical research and the medical interests of subjects. It therefore seeks to manage the tension to the maximum extent possible, so that valuable research can continue without exposing human subjects to unreasonable risks.

***

Corporate Voting and the Takeover Debate

Paul H. Edelman
Randall S. Thomas
58 Vand. L. Rev. 453 (2005)

For many years academics have debated whether it is better to permit hostile acquirers to use tender offers to gain control over unwilling target companies, or to force them to use corporate elections of boards of directors in these efforts. The Delaware courts have expressed a strong preference for shareholder voting as a change of control device in hostile acquisitions. To force acquirers to accept their preferences, the Delaware courts have developed a jurisprudence permitting the effective classified board (ECB), a poison pill combined with a classified board, to protect target company management from removal by a hostile tender offer alone, or through a single corporate election. For companies with ECBs, this means that a determined acquirer must engage in two corporate elections over a period of two years to force entrenched managers to give up power.

In this Article, Professors Edelman and Thomas cxamine whether proxy contests, tender offers, or combined proxy contest/tender offers are more likely to result in value maximizing outcomes for shareholders when target companies are able to deploy defensive tactics. The authors begin by showing that prior work suffers from serious flaws involving the use of voting models that are inappropriate for analyzing proxy contests.

To develop a more realistic approach to these questions, the authors employ a probabilistic version of a standard weighted voting model that explicitly incorporates two critical features of corporate voting: first, that shares are normally voted in large blocks rather than in single shares; and second, that independent third party proxy voting advisors play an important, and often pivotal, role in determining the outcome of corporate elections. In addition, the authors explicitly incorporate information about the size of different corporate constituencies and their voting preferences. Using their model, Professors Edelman and Thomas show experimentally

how the distribution of shares among various investor constituencies will affect the outcome of different types of voting contests.

Using this model, and these different sets of assumptions, the authors find that neither proxy contests, tender offers, nor combined proxy contests and tender offers will always lead to the desirable outcome for target company shareholders in any scenario. With each type of acquisition technique, bidders succeed in obtaining control of the target company in some value decreasing transactions, and are defeated in their acquisition efforts in some valuc increasing transactions. These results hold whether the authors permit existing defensive tactics or eliminate them.

Professors Edelman and Thomas conclude that in order to properly analyze the role of defensive tactics, courts must take into account the underlying shareholder ownership patterns. This requires them to engage in a fact sensitive analysis of whether defensive tactics are impeding or facilitating the maximization of shareholder value. When the authors examine the Delaware Chancery Court's decisions, the reasonableness analysis that the courts have employed to decide whether to overturn defensive tactics permits them to do so. The authors recommend that the courts continue to apply this type of analysis in the future with more direct consideration of the impact of the underlying ownership structure in determining whether the defenses are being used to maximize shareholder value.