Human Subjects' Protections

Summary: The conceptual, empirical, and educational projects described here aim to improve the protection of human participants in research, improve the system and processes of oversight, and to provide a conceptual framework to be used by IRBs, researchers, bioethicists, regulators, and others to analyze and address ethical issues in human subjects research.

Section: Ethics of Human Subjects Research

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Background: Clinical research ethics has been at the forefront of bioethics since its emergence as a field of inquiry. Despite an extensive literature on ethical principles governing clinical research, their application to particular studies, and oversight protections, theoretical and practical limitations attenuate the ethical analysis of issues in clinical research. For example, although several ethical requirements must be satisfied in order to make clinical research ethical, informed consent, which is neither sufficient to make clinical research ethical nor necessary in all clinical investigation, has been overemphasized as the key ethical requirement. Additionally, ethical norms and principles pertinent to patient care have been uncritically applied to clinical research without appreciating ethically significant differences between the pursuit of generalizable knowledge characteristic of clinical investigation and the personalized therapeutic attention characteristic of patient care. At the same time, ethical norms and guidance regarding

clinical research have been based on an assumption that research is exceptional, different in ethically important ways from other social activities. The basis for this assumption has not been critically examined. Third, the oversight mechanisms in place for clinical research are criticized for adding burden and delay without necessarily enhancing the protection of human participants, yet oversight mechanisms have not been critically evaluated or updated. Finally, ethical guidance has been promulgated without sufficient attention to the relevance of differences in the type of research, design, and methodology or the practical contexts in which studies are conducted.

The Department of Bioethics and NIH Intramural Research Activities

The Department of Bioethics as part of the NIH Clinical Center has close proximity to the design, review, and conduct of clinical investigation and therefore a unique opportunity to advance the understanding of the ethics of clinical research. Department staff serves as members, and bioethics fellows as observers, on NIH Intramural Institutional Review Boards (IRB). IRB membership provides access to cutting edge research, familiarity with scientific methodology, and the opportunity to reflect on complex ethical issues in research. Several department members also serve as members of Data Safety and Monitoring Committees. In addition, through the Department's Bioethics Consultation Service and participation in the Clinical Center's Ethics Committee, faculty and fellows grapple with challenging ethical dilemmas that arise in the conduct of clinical research, and with the development of policies related to research. Proximity to the enterprise of clinical research also facilitates collaboration with investigators who are interested in the ethics of clinical investigation.

The Department has had the opportunity to provide education to the research community at the NIH about the ethics of clinical research. We developed a 7-week-long course entitled "Ethical and Regulatory Aspects of Human Subjects Research" that covers many important topics related to the ethics of clinical research and includes as speakers experts in the field from both within and outside the NIH. Now in its 12th year, the course receives overwhelmingly favorable evaluations and continues to enroll hundreds of participants each year. Although originally developed to serve the educational needs of the NIH community, each year many participate from other institutions including the FDA, National Naval Medical Center, Walter Reed, as well as private IRBs and remote sites in other parts of the United States and the world, such as Peru, Sri Lanka, South Africa and other countries. Members of the department, in collaboration with colleagues from the University of Virginia, published an anthology of seminal articles on the ethics of clinical research based on the syllabus that was originally created for this course; the 2nd edition of this book is soon to be published by Johns Hopkins University Press. The Department has adapted a shorter, more intensive course from this curriculum which has been offered in many countries around the world (see Multinational Research description). In addition, an "advanced" research ethics workshop developed and offered at the annual meeting of PRIM&R for 8 consecutive years and continues to receive very favorable reviews.

Departmental Research Initiatives: The Department's conceptual and empirical work related to the ethics of clinical research over the last several years has focused primarily on the following areas:

- Philosophical analysis and application of an ethical framework for clinical research ethics;

- Risk and risk assessment
- Evaluation and improvement of oversight systems and protections.
- Recruitment, payment and undue inducement
- Research ethics consultation
- The ethics of various types of research (e.g. public health, chemoprevention, phase 0, dual use

Additional topics related to the ethics of research are summarized elsewhere in these materials. See especially summaries pertaining to Ethical Issues in Multinational Research, Ethical Issues in Research with Special Populations, Informed Consent, and Surrogate Decision Making.

I. Philosophical Analysis of the Ethics of Research and Application of an Ethical Framework for Clinical Research Ethics

The department continues to engage in philosophical analysis of research ethics and of the principles that make clinical research ethical. Several initiatives have also built on the framework initially proposed by members of the Department in 2000 (What makes clinical research ethical? Emanuel et al. *JAMA 2000*).
Wertheimer and Miller recently co-authored a paper on paternalism in research ethics. This paper argues that the current system of regulating human subjects' research with competent adults places a variety of restrictions on permissible research beyond the requirement of obtaining informed consent, making it fundamentally paternalistic. This argument urges society to explain when paternalism is justifiable and when it is not, and suggests that contrary to the usual rhetoric of bioethics, paternalism can be justified.

Books and Other Materials

Several books have been published by members of the department on issues related to research ethics. Three Department books utilized the framework referred to above. Two newer books challenge previous assumptions about the ethics of clinical research.
One book, developed by Department members in collaboration with faculty from the University of Virginia, is an anthology of classic papers in research ethics published by Johns Hopkins Press. A second extensively revised edition is expected in 2011. In this book, each paper was edited and is preceded by scholarly introductions to different sections. The book has received excellent reviews and is used in numerous courses, including our own NIH research ethics course and the research ethics course at Johns Hopkins School of Public Health. Reviews include: "Many of the chapters easily deserve to be required reading... Most of the readings that have been chosen for the book can lay claim to being classics. They represent sophisticated thinking on various topics." -- *Bulletin of the World Health Organization* "This book is an excellent textbook for bioethics with wonderful framework, comprehensive approach, and many relevant articles…good for beginner as well as for expert on this field" *www.amazon.com*.

A second textbook, *The Oxford Textbook of Research Ethics*, published by Oxford University Press in 2008 is also organized according to the Department's framework and is intended to be a definitive and comprehensive textbook on research ethics. Contributors of each of the 73

chapters are known experts in the field from diverse institutions and locations. Reviews have been very positive, including:

> "…This book is a gem. The editors have admirably met their goal of producing a book that is comprehensive, that provides a systematic analysis, and that does so from a multicultural approach."--*New England Journal of Medicine*.
> "Reading the Oxford Textbook of Clinical Research Ethics is to take a grand tour of the evolution of clinical research ethics over the years... The book provides scholarly, well referenced analyses of different points of view on many of the challenging issues confronting clinical trial ethics."—*Lancet.*

A third book also published by Oxford University Press in 2007- *Ethical Issues in International Biomedical Research*- again is organized using the Department's framework. The book presents 21 actual cases that pose complex ethical challenges in international research, and each case is followed by two commentaries. Oxford describes this book as "…the definitive book on the ethics of research involving human subjects in developing countries…it covers the most controversial topics, including the ethics of placebo research in Africa, what benefits should be provided to the community after completion of a research trial, how to address conflicts between IRBs in developed and developing countries, and undue inducement of poor people in developing countries. Each case is accompanied by two expert commentaries, written by many of the worlds leading experts in bioethics as well as new voices with research experience in developing countries. No other volume has this scope. Students in bioethics, public and international health, and ethics will find this book particularly useful." The casebook has also received positive reviews including from the *Lancet*: "Provides a wealth of examples, debate, and dilemmas...[an] invaluable book."

Dr. Emanuel, working with several bioethics fellows in the Department, created a novel and unique educational pamphlet entitled *Research Ethics: How to Treat People who Participate in Research.* This pamphlet provides an introduction to the 7 principles delineated in the framework proposed by the Department, and was designed for use by high school students and undergraduates to learn about the ethics of clinical research. Several thousand copies of the pamphlet have already been distributed to several places around the country and internationally.

Dr. Alan Wertheimer's recent book entitled *Rethinking the Ethics of Clinical Research: Widening the Lens*, published by Oxford University Press in 2011, provides an in-depth philosophical analysis of what justifies subjecting research participants to risk in order to benefit others. Dr. Wertheimer challenges many of the assumptions and principles that guide the ethics of clinical research and argues that such assumptions are often hard to defend. He argues that because respect for autonomy has been central to understanding the ethics of research, many fail to recognize that the current regulatory structure for research is deeply paternalistic. He re-examines and challenges current thinking about the basis for informed consent and undue inducement, and turning to research in developing societies, considers claims of exploitation and of obligations to communities.

Dr. David Wendler's book *The Ethics of Pediatric Research* was published by Oxford University Press in 2010. Further description of this book is included in the summary on the Ethics of Research with Special Populations.

Another recent book edited by Drs. Wertheimer and Miller -- *The Ethics of Consent* (Oxford U. Press 2010*)*— includes consideration of consent in clinical research, but goes well beyond research to examine consent in other social contexts. Further description of this book is included in the summary on Consent.

The framework developed by the Department has had a major impact on research ethics. It is used in many courses of research ethics and cited frequently (more than 450 times as of Nov. 2010) in the literature. The framework has been adopted by numerous IRBs and at least three countries — Kenya, Nigeria, and Sri Lanka — have explicitly adopted the seven principle framework in their revised national regulations regarding clinical research. The 2004 Kenyan "Guidelines for Ethical Conduct of Biomedical Research Involving Human Subjects in Kenya," for example, has a section entitled "A systematic and coherent framework for determining whether clinical research is ethical" which lists our seven principles and virtually quotes verbatim the explanation of each one.

The work of Drs. Miller and Wertheimer has challenged settled notions of research ethics and pushed people to rethink their justifications and reasons. One commentator wrote: "One of the reasons I wrote that commentary is because important arguments in bioethics are often not picked up and discussed by others: sometimes the literature seems fragmented in way that is less common in philosophy. I should also say that I admire the way that both of you *(Wertheimer and Miller)* are pushing ahead our understanding of research ethics and causing many to revisit foundational ideas that up until recently were taken as givens. Coercion and payment for research participation are bandied around in a fairly loose way in research ethics, so your paper struck me as significant and one that should be responded to."

The NIH Office of Communications developed a public website < http://clinicalresearch.nih.gov/ethics_guides.html> about clinical research utilizing the seven principle framework to educate the public about the ethics of clinical research.

II. Risk/Benefit Evaluation

To be ethical, clinical research should offer an appropriate balance of risks and potential benefits. In addition, regulations require additional protections from risks for special populations, many of whom cannot make these evaluations themselves. To help to ensure that this protection is realized in practice, the Department has been working on developing a systematic approach to evaluating the risks of clinical research. The goal of this work is to develop an approach that helps to ensure research participants receive the protection they need without inadvertently blocking appropriate research needed to improve health and well-being.

Previous work by the Department found that the evaluation of research risks is inconsistent, ad hoc and too often mistaken (Wendler 2005). Based on this work, we called for development of systematic methods for evaluating the risks of clinical research (Wendler, Varma 2006). Over the past several years, the Department has been working to develop such a method with the goal of ensuring that research participants receive appropriate protection. This research involved extensive work with focus groups and outside consultants, culminating in a 2 day workshop with 40 international experts on risk, clinical research and research review. The result is development of the first ever systematic method for evaluating research risks (Rid, Emanuel, and Wendler 2010). This approach attempts to minimize the influence of cognitive biases on risk evaluation by systematically comparing the risks of research interventions to the risks of appropriate comparator activities. The potential harms posed by research interventions are categorized into seven levels of severity, from negligible to catastrophic, allowing pair-wise comparison of magnitudes to magnitude and likelihoods to likelihoods.

Evaluation of research risks should be based on empirical data regarding the potential harms of the interventions in question. Unfortunately, there are few systematic data available for making these evaluations. To address this concern, we proposed the development of a Research Risk Repository which would be a publicly available database on the risks posed by common research interventions. This repository would allow IRBs, investigators and funders to base their risk evaluations on the relevant data. To facilitate development of this approach, we systematically collected and published the best existing data on 17 common research interventions (Rid, Wendler, *in press*).

The federal regulations for pediatric research, like many guidelines around the world, focus on 'direct' benefits. On this approach, the risks to which individuals who cannot consent are exposed can be compensated by direct benefits, but not by indirect benefits. Unfortunately, there has been little examination of this crucial concept. The most systematic analysis comes from Nancy King, who defines a direct benefit as one that is the result of the intervention being tested in the study in question. Our analysis suggests King's account is unnecessarily restrictive and could inadvertently block important and appropriate research. Based on this analysis we argue for a new account of direct benefits as benefits that result from the interventions necessary to answer the scientific question posed by the protocol (Friedman and Wendler, *in press*).

We are currently working on several manuscripts which involve refinement and further development of the systematic approach to evaluating research risks. This work has 3 goals: further develop method to address exceptional cases, make method applicable to all cases, and develop processes for implementing the method. We are also working on a framework that IRBs can use to evaluate the risks and potential benefits of clinical research. The goal of this work is to provide a coherent framework that incorporates the Departments work and the work of others on understanding and evaluating research risks and benefits. This work will be combined with a project evaluating which risks of research should be considered in IRB review.

III. Evaluation and improvement of oversight systems

Emanuel and Grady (2006) characterized our understanding of clinical research oversight since World War II by outlining four distinct paradigms. The first paradigm, characterized as one of researcher paternalism, was one in which few checks and balances were built into the system of clinical research because research was conducted by physicians who were trusted to be committed to the safety and welfare of their patients. Now famous scandals and abuses that received a great deal of attention shifted this paradigm to one emphasizing protection of participants, especially the vulnerable, from the risks and burdens of research. In the 1980s and 1990s, largely spurred by AIDS activism, the paradigm shifted again to emphasize individual autonomy in accepting risks, and demanding access to the benefits of research. A fourth paradigm, emphasizing the ethical importance of community partnership, has since evolved along with an increase in international research and genetics research.

Members of the Department, in collaboration with the Consortium on Clinical Research Ethics, had previously published a paper delineating problems with the current system of IRBs and calling for reform (Emanuel et al. *Annals of Internal Medicine* 2004). During this review period, Grady in collaboration with Lura Abbott in the NIH Office of Human Subjects Research conducted a systematic review of empirical studies evaluating IRBs (Abbott and Grady, *in press*). The review identified more than 40 published studies conducted over the last several decades that have repeatedly shown that IRBs are inconsistent in their interpretation of the federal regulations, and widely variable in their decisions and the time it takes to review a proposed study. Although the identified studies represent a range of methodologies and sample sizes, important information about the function of IRBs can be gleaned from these data. Yet, significantly, no study attempted to measure the effectiveness of IRBs or their impact on the protection of human subjects. Although others have called for data on the effectiveness of IRBs, identifying the appropriate metrics is challenging and will require consensus on the goal of IRBs and appropriate indicators of quality review. Grady (2010) published a commentary identifying the urgency of this issue and calling for innovative ideas for measuring IRB effectiveness.

Controversy persists in the research community about for-profit IRBs. Emanuel engaged in a point-counter-point discussion with Lemmens and Elliot about the benefits and problems with for-profit IRBs, arguing that for-profit or non-profit status is not necessarily an indicator of anything relevant to IRB functioning, and that we should measure quality directly. Furthermore, the purported conflict of interest of for-profit IRBs is not unique — academic IRBs also have a conflict of interest.

Dr. Joseph Millum, in collaboration with the Director of the Office of Human Research Protections (OHRP), described important ways the research review can be streamlined under the current regulatory framework. They describe their goal as both informing and reassuring the research community about current mechanisms that are often underutilized. (Millum and Menikoff 2010)

Over the last several years, a debate has ensued regarding the appropriate distinction for purposes of oversight between quality improvement activities and research with human subjects. In 2007, Dr. Peter Pronovost of Johns Hopkins University was reprimanded by OHRP for not obtaining the consent of hospitalized patients while evaluating the implementation of a check list for central line care in intensive care units in Michigan hospitals. Dr. Pronovost had previously

shown that use of the checklist led to fewer deaths from infections. The OHRP's action led to a flurry of commentary and debate about under what circumstances, if any, quality improvement activities should be considered different than human subjects research and therefore not subject to the federal regulations. Emanuel and Miller, in a commentary in the *NEJM*, argued that OHRP erroneously focused on consent, which should not have been required, but they concluded that Dr. Pronovost's project was research and should have been reviewed in an expedited fashion by the IRB chair. Around the same time, a report–*Health Care Quality Improvement: Ethical and Regulatory Issues*–was published by a Hastings Center Task Force commissioned to examine the ethics of quality improvement. The report was summarized in an article by Joanne Lynne in the *Annals of Internal Medicine*. A commentary in *Annals* written by Grady (2007) discussed the Hastings center recommendations and identified where more work was needed. Grady also participated in 2008 in a jointly sponsored meeting by the Institute of Medicine and the American Board of Internal Medicine Foundation on Quality Improvement Oversight to further explore this issue, and was invited to present on oversight of quality improvement activities to the Secretary's Advisory Committee on Human Research Protections (2008).

IV. Subject Selection, recruitment, payment, and eligibility

The work of several members of the Department has focused on issues related to recruitment and the use of incentives, including payment, for research subjects. Conceptual work has served to clarify concepts of coercion in research and undue influence, and propose models for payment to research participants. Empirical work on payment has complemented this conceptual work. Further description is in the Research Summary on Informed Consent. A current empirical project conducted by Wertheimer, Miller, Grady and Largent, and in collaboration with colleagues at Public Responsibility in Medicine and Research (PRIM&R), involves a national survey of individuals derived from the PRIM&R database who are IRB members or otherwise involved in human subjects research. The survey was designed to collect information about attitudes and concerns regarding payment, coercion, and undue influence in research, as well as application to hypothetical scenarios. Data from 610 individuals across the country is currently being analyzed.

Research ethics norms and literature emphasize that research participation is voluntary and supererogatory. In a controversial and much cited paper, members of the Department (Shaefer, Wertheimer, and Emanuel) proposed a public goods argument for an obligation to participate in biomedical research. Acknowledging that biomedical research is a widely available public good, and that participation in research is a way to support this public good, they conclude that all citizens have a duty to participate unless they have a good reason not to.

Eligibility and exclusion criteria for research protocols are delineated based primarily on scientific appropriateness for inclusion in research and considerations of risk and potential benefit. Fairness in subject selection requires that individuals not be excluded from research studies unless there are scientific or risk-based grounds for their exclusion. Members of the department (Grady and Persad) working with an oncologist from the NCI (Little) argued that HIV infection should not be a categorical exclusion criteria for trials of cancer treatments.

Because HIV infected individuals are increasingly suffering from common and unique cancers, there is a need for evidence about how to treat their cancers. The scientific and ethical justification for including or excluding HIV infected individuals should be trial specific. Trial designs that deliberately look for differences based on HIV infection are also needed.

V. Research ethics consultation

Many ethical challenges arise in the conduct of clinical research even after a study has been reviewed and approved by an Institutional Review Board. Researchers struggle, for example, with whether certain a particular socioeconomic circumstance of a prospective participant is a reason for exclusion, how the needs of participants family members should be handled, when it is acceptable to take an individual out of a study. The CC Bioethics Consultation Service has received requests for consultation of this type from its inception. In other institutions, and especially since the NIH has required a mechanism to address ethical concerns in research at each of the institutions that receive a Clinical and Translational Science Award, ethics consultation is increasingly sought for issues related to clinical research. Because the CC Bioethics Consultation Service has substantial experience and a unique perspective, members of the Department are developing a book of research ethics consultation cases to be published by Oxford. More explanation of this book project and related papers on research ethics consultation is described in the summary on Ethics Consultation.

IV. Ethical considerations in different types of research

The research ethics literature has largely focused on the ethics of treatment trials, especially randomized controlled trials for efficacy and safety. Many diverse types of research raise unique challenges which are often unaddressed in the literature. For example, studies of cancer chemoprevention raise distinct challenges of balancing the seriousness of being at-risk of a certain cancer with that of being exposed to the risk of a chronic drug or intervention. Members of the department examined these issues and the implications of this balance for study design, subject selection, and the value of the research (Slutsman et al.). In another analysis, members of the Department (Wendler, Abdoler) examined the ethics of phase 0 studies in cancer. Proponents say that phase 0 exploratory trials are necessary for expediting the development of new treatments. Others raise concerns because these studies have no prospect of benefit and enroll individuals with advanced disease. Because there is no benefit, the authors suggest that there is less concern about a therapeutic misconception than in phase 1 trials, and because phase 0 studies are small and time-limited, the risks are less. They recommend careful evaluation of the value of the study, the rationale for subject selection, and the understanding of prospective participants.

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