Informed Consent

Summary: Department faculty and collaborators have conducted a variety of conceptual and empirical ethics research projects relating to informed consent in the context of human subjects research.

Principal Investigator: Ezekiel Emanuel MD PhD
Christine Grady RN PhD
Reidar Lie MD PhD
Frank Miller PhD
Joseph Millum PhD
David Wendler PhD
Alan Wertheimer PhD

Collaborators:

Bioethics:
Danielle Bromwich PhD
James Flory BA
Emily Largent BS
David Shalowitz BA
William Smith Ba
Leanne Stunkel BS

NIH:
Jorge Tavel MD
Mary Smolskis RN
Mary Enama RN
Julie Ledgerwood DO
Ninet Sinaii PhD

Non-NIH:
Gabriella Bedarida MD PhD
Meredith Benson
Louise McCullough
Kenji Matsui, MD PhD
Mary McCabe RN
Shlomo Koyfman MD

Background: Informed consent is a fundamental norm of research ethics, initially articulated in the Nuremberg Code of 1947. Despite a vast literature on informed consent, there remain many unsettled issues. Surprisingly little systematic attention has been devoted to defining the contours of valid consent and specifying when tokens of consent should be considered invalid. Threats to the validity of consent concern both lack of adequate comprehension and insufficient voluntariness. Although everyone agrees that informed consent requires disclosure of specific

"elements" of consent, there is no agreement on what, if any, level of comprehension on the part of prospective subjects is required to constitute valid consent. One major issue in this regard is the "therapeutic misconception." A variety of evidence indicates that many patient-subjects in clinical research confuse study participation with routine medical care and fail to understand or appreciate how being a research subject differs from being a patient receiving medical attention. When do signs of the therapeutic misconception invalidate informed consent? In addition to a therapeutic misconception, empirical data suggest that research participants often fail to understand other critical aspects of research, such as randomization or the use of controls. Furthermore, some perceive that understanding is worse in disadvantaged individuals or communities. In addition, commentators sometimes claim that research participants are pressured, coerced, or unduly influenced to participate in studies. Without question it is unethical to physically compel or coerce people by threatening harm to participate in research (as in the Nazi concentration camp experiments); however, concerns are often raised about "coercion" and "undue inducement" primarily relating to offers of payment as an incentive for research participation. It is unclear whether genuine offers are ever coercive and when inducements qualify as undue. A different set of unsettled issues relate to the ethics of research without consent (either from subjects or authorized surrogate decisionmakers) and to the ethics of research employing deception. In addition to these specific issues, the general theory of informed consent has received inadequate critical attention. Finally, although much valuable empirical research on informed consent to research has been undertaken, many important questions have not been adequately explored.

Departmental Research Initiatives: The department's conceptual research has raised critical questions about the ethical salience of the therapeutic misconception, arguing that whether or not it invalidates consent depends importantly on the personal risk-benefit profile of particular studies. More broadly, ongoing research is addressing the question of how subject comprehension relates to the validity of consent. Other conceptual investigations have challenged the concept of coercive offers and argued that programs that make health care coverage conditional on research participation, such as Medicare's "coverage with evidence development," are not coercive or contrary to valid consent when the intervention in question does not have adequate evidence demonstrating its "medical necessity."

Four members of the department (Largent, Miller, Emanuel, Wendler) joined together in developing a comprehensive approach to the ethics of research on experimental emergency treatments when consent is not possible from either subjects or surrogate decisionmakers. A "consent substitute" model was formulated and defended, which stipulates substantive and procedural safeguards that protect autonomy and well-being of participants while allowing valuable research to go forward. Another paper argued for the legitimacy of medical records research without consent.

The ethics of deception in research has been a long-standing project of the department. The development and rationale of the "authorized deception" approach as an alternative to the typical non-disclosure of the use of deception in the informed consent process is described in the project write-up on the placebo effect. Other recent work on deception included a systematic examination of the ethics of debriefing, a detailed interpretation of the passages of the U.S.

federal regulations that permit deceptive research, a chapter on deception in the Oxford Textbook on Clinical Research Ethics, and a brief report on methodologically unnecessary deception in acupuncture clinical trials.

Recognizing that the literature on informed consent in research was limited by lack of attention to the way in which consent functions in other domains of human endeavor, Miller and Wertheimer edited a book on the theory and practice of consent-- *The Ethics of Consent: Theory and Practice*--, with contributions by a distinguished group of philosophers, lawyers, political theorists, and bioethicists. In addition to seven chapters on an array of theoretical issues, the book included discussion of consent to sexual relations, contracts, sale of body parts, political obligation, consent to medical treatment, and consent to clinical research. The editors, together and separately, wrote 3 chapters, including a theoretical chapter challenging the prevailing understanding of valid consent as autonomous authorization. A fair transaction model of consent was proposed as a more theoretically sound and practically reasonable approach. This approach is developed at more length in Wertheimer's recent book.

Members of the Department have contributed significantly to the literature and discussion about coercion, undue inducement or influence, and payment. Previous work by the department focused on important empirical and conceptual questions related to payment to research participants. In their empirical work, Grady, Dickert, and Emanuel established the prevalence of payment across a variety of institutions and types of research as well as a dearth of institutional guidance. In their conceptual work, Grady and Dickert described several possible models for establishing appropriate payment to research participants and defended the "wage payment model." Emanuel evaluated the concept of undue influence, arguing that it does not apply to most appropriately IRB reviewed studies that avoid excessive risk. Emanuel and Hawkins also explicated the concept of coercion in research distinguishing it from other ethical concerns. Dr. Wertheimer is widely recognized as an expert on coercion and exploitation. His contributions to clarifying coercion in the context of research have been invaluable. Responding to the widely held view that payment to research subjects can constitute a "coercive offer," Wertheimer and Miller argued that this view is mistaken. Building on Wertheimer's earlier work on coercion, they argue that coercion requires a threat, hence, arguments citing the possible coerciveness of payment can be set aside. In his paper and recent book, Wertheimer described the conditions under which payment might pose an undue inducement. He argues that this is possible if, and only if, the payment distorts a prospective subject's ability to weigh the risks and benefits of research participation. Although members of the department continue to have some healthy and robust disagreements on coercion and undue inducement, they generally argue that worries about coercion and undue inducement have been overdone and that incentives generally do not constitute a barrier to valid informed consent.

Ongoing debate exists about what people need to understand in order to give valid consent to research. Wendler and Grady argue that in addition to understanding the possible risks, benefits, and alternatives, research participants ought to understand that they will be contributing to a project designed to gather knowledge to benefit others, that the investigator's goal is to gather knowledge, and how participation in research differs from what they would experience if they did not participate.

Empirical research

Members of the Department previously conducted several empirical studies looking at the quality of informed consent (Pace et al. 2005, Pace et al. 2005), and the practices of investigators regarding consent (Sabik et al. 2005) as well as examining the process of ongoing consent and the meaning of a signature on a consent document. (Wendler, Rackoff). This body of research demonstrated, as others have, that comprehension of study information is quite variable, and that certain aspects of research- for example randomization- are particularly difficult for participants to undersand.

Recently, in collaboration with bioethics fellows and other collaborators, Grady and Wendler completed a study of the assent and parental permission process for adolescents participating in a wide range of clinical research studies at the NIH and at Seattle Children's Hospital. In addition to examining the assent/permission process, this study looked at teen's experience with research, how parents and adolescents understand and trade off risks and benefits, and how they make decisions about research participation. Data is being analyzed and manuscripts prepared.

A comprehensive analysis of empirical literature on interventions to improve informed consent conducted by Flory and Emanuel (2004) identified few strategies that statistically improved understanding. Some of the interventions reviewed, however, such as shorter consent forms and test-feedback, had not been subjected to rigorous well designed evaluations. In response, the Department developed several intervention studies to evaluate the impact of improved consent documents on understanding and satisfaction. Through eliminating repetition, using active voice and simpler concepts, and providing information about risks in tables, we have been able to reduce consent forms to about a third of their original length. In recent years, we have been able to successfully conduct randomized studies of consent documents with various populations participating in different kinds of clinical trials. In each case, the study cohort is randomized to either the standard consent form or a simpler, more concise consent form and their comprehension of study information and satisfaction with the process is measured. A pilot study, conducted with collaborators in the NIH intramural research program testing vaccines for influenza, was done to evaluate the feasibility of conducting a randomized consent study and to satisfy the IRB that a shorter form did not put subjects at risk. (Emanuel and Grady 2008). Subsequently, we have conducted larger randomized consent trials with a cohort of healthy volunteers in Vaccine Research trials at the NIH, with a cohort of healthy volunteers in a bioequivalence study at the Pfizer Clinical Research Unit, and with an international cohort of HIV infected individuals participating in a treatment study in many countries (the START study). The hypothesis for these consent studies is that comprehension will be similar between the 2 groups, but that satisfaction will be higher with a simpler consent form. In the Pfizer and VRC cohorts, the first hypothesis was confirmed, but not the second- i.e. satisfaction was not statistically different between the groups. Of note, we found that in the Pfizer cohort, comprehension was higher in those who said their primary motivation for participation was financial, suggesting that financial motivations do not necessarily obscure risks or other study details. (Stunkel et al. 2010). The START study will allow us to evaluate consent in different languages and across different settings in participants who have the illness being studied.

Based on previous work analyzing consent forms for phase 1 oncology research and work simplifying consent documents, Grady and Emanuel worked with collaborators to develop a template for phase 1 consent forms. (Koyfman et al. 2009). The template is available in English and Spanish and has been adopted by at least one university that we aware of (Wayne State University) for their phase 1 oncology studies.

In a study in Japan we evaluated participant understanding and participation rates of two different approaches to obtaining informed consent, using 2,192 research subjects in a genetic cohort study (Matsui et al. 2007). One group received the routine approach consisting of written materials and an oral explanation. The other group received a more intense approach consisting of educational lectures and group meetings. The study showed complex relationships between self perceived understanding and reading of the background material among the two groups, raising questions about the value of the informed consent forms. Further information about this study is included in the write-up on multinational research.

In keeping with the Department's interests in international research ethics, several projects related to informed consent in the developing world are in progress or planned. One project compared understanding of study information in 2 cohorts participating in a malaria vaccine study in the US and in Mali (Ellis et al. 2010). Grady and others working with bioethics fellows have undertaken a systematic review and comparison of empirical studies evaluating informed consent in both developed and developing countries. This review shows that understanding is quite variable across the world and not clearly different or worse in the developing world. Research participants everywhere seem to have difficulty understanding certain issues, especially those related to randomization and random assignment. Data suggest, however, that participants in the developing world are generally less likely to say that they can choose not to participate or to believe that they have other choices unaffected by their research decision. Joe Millum, in collaboration with others in the Department, has begun a project to collect and discuss examples of strategies used by researchers in the developing world that are designed to enhance individual choice when making decisions about research participation.

We surveyed participants of a longitudinal HIV treatment study after they had participated for more than a year to evaluate how well they retained information relevant to their on-going participation. (Smith et al. 2010). We found that individuals did not feel sufficiently informed about crucial aspects of the study, such as their right to withdraw, and that many respondents felt that they did not have an opportunity to ask questions. These data provide empirical support for claims that clinical research should include a process of on-going consent. Further information about this study is in the summary regarding the Ethics of Research with Special Populations.

Impact of Research:

A review of Miller and Wertheimer's book *The Ethics of Consent* was published in *JAMA* 2010;303(24):2531-2532 and opened with the statement: "This is the most important book on consent in at least 20 years…"

There has been considerable interest in our randomized studies on informed consent. For example, participation in the consent study was optional for sites involved in the START international HIV study, and more than 85% of sites opted to participate. Grady was asked by the Secretary's Advisory Committee on Human Research Protections (SACHRP) to give a presentation on the methods, results, and implications of the randomized consent studies. As mentioned above, the phase 1 template has been adopted and is required by at least one university that we aware of (Wayne State University) for their phase 1 oncology studies.

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