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"The voluntary consent of the human subject is absolutely essential." This, the first sentence of the Nuremberg Code, signals the centrality of the consent requirement in research involving human subjects. Before the Nuremberg Code was written in 1947 as a response to the atrocities committed in the name of science by Nazi physician-researchers, statements of medical and other professional organizations apparently made no mention of the necessity of consent. Ironically, the only nations known to have promulgated regulations that established a requirement for consent to research were Prussia and Germany. Subsequently, the tendency to focus on informed consent has been reinforced by public outcry over the inadequacy of consent in certain U.S. judicial landmark cases, such as Willowbrook, [the] Jewish Chronic Disease Hospital, [sociologist Laud Humphreys'] Tea Room Trade, and Tuskegee. Indeed, the issue of informed consent has so dominated recent discussion of the ethics of research that one might be led to think erroneously that other ethical issues (e.g., research design, selection of subjects) are either less important or more satisfactorily resolved

GROUNDING OF INFORMED CONSENT

Philosophical basis. The philosophical foundations of the requirement for informed consent may be found in several lines of reasoning. Based upon the Hippocratic admonition "to help, or at least, to do no harm," one can justify seeking consent for the benefit of the patient; to do so provides a mechanism for ascertaining what the patient would consider a benefit. Allowing the individual to decide what he or she considers beneficial is consistent with the perspective affirmed in U.S. public policy that competent persons are generally the best protectors of their own well-being. However, a focus solely on patient benefit would allow physicians and scientists not to seek consent when they judge that doing so might harm patients or subjects. Thus this justification alone does not suffice to establish a requirement to seek consent.

The requirement can also be justified on grounds of social benefit: The practice of seeking consent may contribute to producing the "greatest good for the greatest

number" by forestalling suspicion about research, thus ensuring a subject population and increasing the efficiency of the research enterprise. Again, however, the justification fails to stand alone, since it can also be used to justify not seeking consent; the social good might be better served by avoiding the inefficient and frequently time-consuming consent process. Some commentators express that, carried to its extreme, the social-benefit argument might support the use of unwilling subjects, as in Nazi Germany; such a position would necessarily rest on a very limited vision of the relevant social consequences.

The firmest grounding for the requirement to seek consent is the ethical principle "respect for persons," which according to the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (hereafter, U.S. National Commission) "incorporates at least two basic ethical convictions: First, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy and thus in need of protection are entitled to such protection." [...] In a legal context, Justice Benjamin Cardozo in 1914 stated that "every human being of adult years and sound mind has a right to determine what shall be done with his own body." To return to the Kantian terms that will be used often in this article, this principle ensures that the research subject will be treated as an end and not merely as a means to another's end. Thus the purpose of the consent requirement is not to minimize risk but to give persons the right to choose.

Religious basis. Several fundamental tenets of the Judaeo-Christian tradition also provide grounding for the requirement to seek consent. This tradition affirms that each human life is a gift from God and is of infinite and immeasurable worth (the "sanctity of life"). The infinite worth of the individual requires that persons treat each other with respect and not interfere in each other's lives without consent. The consent requirement can also be grounded explicitly in the notion of covenant. Seeking consent is an affirmation of the basic faithfulness or care required by the fundamental covenantal nature of human existence.

Legal basis. The legal grounding for the requirement for consent to research is based on the outcome of litigation of disputes arising almost exclusively in the context of medical practice. There is virtually no case law on the basis of which legal standards for consent to research, as distin-

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guished from practice, might be defined (there is one Canadian case, *Halushka v. University of Saskatchewan*). The law defines, in general, the circumstances under which a patient, or by extension, a subject, may recover damages for having been wronged or harmed as a consequence of failure to negotiate adequate consent.

The legal bases for the consent requirement—which also shed light on the ethical dimensions of consent—are twofold. First, failure to obtain proper consent was traditionally treated as a battery action. Closely related to the principles of respect for persons and self-determination, the law of battery makes it wrong *a priori* to touch, treat, or do research upon a person without the person's consent. Whether or not harm befalls the patient/subject is irrelevant: It is the unconsented-to touching that is wrong.

The modern trend in malpractice litigation is to treat cases based upon failure to obtain proper consent as negligence rather than battery actions. The negligence doctrine combines elements of patient benefit and self-determination. To bring a negligence action, a patient/subject must prove that the physician had a duty toward the patient; that the duty was breached; that damage occurred to the patient; and that the damage was caused by the breach. In contrast to battery actions, negligence actions remove as a basis for the requirement for consent the simple notion that unconsented-to touching is a wrong. Rather, such touching is wrong (actionable) only if it is negligent and results in harm; otherwise, the patient/subject cannot recover damages. Under both battery and negligence doctrines, consent is invalid if any information is withheld that might be considered material to the decision to give consent.

FUNCTIONS OF INFORMED CONSENT

Jay Katz and Alexander Capron identified the following functions of informed consent: To promote individual autonomy; encourage rational decision making; avoid fraud and duress; involve the public; encourage self-scrutiny by the physician-investigator; and reduce the civil and/or criminal liability of the investigator and his or her institution.

In general, the negotiations for informed consent are designed to safeguard the rights and welfare of the subject, while documentation that the negotiations have been conducted properly safeguards the investigator and institution. The net effect of the documentation may, in fact, be harmful to the interests of the subject. Retaining a signed consent form tends to give the advantage to the investigator in any adversary proceeding. Moreover, the availability of such documents in institutional records may lead to violations of privacy and confidentiality. Consequently, federal regulations permit waivers of the requirements for consent forms when the principal threat to the subject would be a breach of confidentiality and "the only record

linking the subject and the research would be the consent document."

Those who are interested in making operational the requirement for consent have a tendency to focus nearly all of their attention on the consent form. Federal regulations prescribe what information must be included in and excluded from these forms. This seems to reflect an assumption that the consent form is an appropriate instrumentality through which researchers might fulfill their obligation not to treat persons merely as means. Most commentators on informed consent disagree, however, seeing consent as a continuing process rather than an event symbolized by the signing of a form; for example, Robert Levine characterizes informed consent as a discussion or negotiation, while Katz envisions consent as a searching conversation.

Whether or not negotiations for informed consent to research should be conducted according to different standards than consent to practice is controversial. Alvan Feinstein observes that it is the custom to adhere to a double standard: "An act that receives no special concern when performed as part of clinical practice may become a major ethical or legal issue if done as part of a formally designed investigation." In his view there is less need for formality in the negotiations for informed consent to a relationship where the interests of research and practice are conjoined—for example, as in research conducted by a physician-investigator who has the aim of demonstrating the safety and/or efficacy of a nonvalidated therapeutic maneuver—than when the only purpose of the investigator-subject relationship is to perform research. Capron, on the other hand, asserts: "Higher requirements for informed consent should be imposed in therapy than in investigation, particularly when an element of honest experimentation is joined with therapy." Levine concludes that patients are entitled to the same degree of thoroughness of negotiations for informed consent as are subjects of research. However, patients may be offered the opportunity to delegate some (but not all) decision-making authority to a physician, while subjects should rarely be offered this option. The most important distinction is that the prospective subject should be informed that in research, in contrast with practice, the subject will be at least in part a means and perhaps primarily a means to an end identified by someone else []

INFORMED CONSENT: CONDITIONS AND EXCEPTIONS

According to the Nuremberg Code, to consent to participate in research one must (1) be "so situated as to be able to exercise free power of choice"; (2) have the "legal capacity" to give consent; (3) have "sufficient . . . comprehen-

sion" to make an "enlightened" decision; and (4) have "sufficient knowledge" on which to decide. Recent discussion emphasizes the knowledge or information component of consent—hence the term "informed consent." Nuremberg's focus on freedom of choice rather than on the quantity or quality of information transmitted is represented by its use of the term "voluntary consent," not "informed consent" [. . .] Most commentators agree that compromise of any one of the four conditions specified by the Nuremberg Code jeopardizes the ethical acceptability of the consent

Free power of choice. The Nuremberg Code proscribes "any element of force, fraud, deceit, duress, overreaching, or other ulterior forms of constraint or coercion" in obtaining consent. Any flagrant coercion—for instance, when competent, comprehending persons are forced to submit to research against their expressed will—clearly renders consent invalid. There may be more subtle or indirect "constraints" or "coercions" when prospective subjects are highly dependent, impoverished, or "junior or subordinate members of a hierarchical group." Some argue that consent obtained from such persons violates the intent of the Nuremberg Code. This argument has been posed most sharply with respect to prisoners and other institutionalized populations, since institutionalization often involves both dependency and impoverishment (Biomedical research involving prisoners as subjects has become quite rare since 1976 when the U.S. National Commission recommended very stringent standards for its justification.) Some argue that consent to participate in research is not valid when it is given (1) to procure financial reward in situations offering few alternatives for remuneration; (2) to seek release from an institution either by evidencing "good behavior" or by ameliorating the condition for which one was confined; or (3) to please physicians or authorities on whom one's continued welfare depends.

Cornel West argues, however, that such indirect forms of constraint do not constitute coercion in a strict sense and thus do not render consent involuntary. Coercion, says West, consists in a threat to render one's circumstances worse if one does not do something. Hence, a threat to withdraw basic necessities of existence, or in some other way to render a prison inmate's situation worse if he or she declines to participate in research, would constitute coercion and render consent invalid. Similarly, to condition release from prison upon participation would constitute coercion, since it would make the inmate's situation worse by removing normal alternatives for seeking release. But the provision of better living conditions in exchange for participation in research does not constitute a threat to make conditions worse; rather, it is an enticement to make conditions better. While enticement and bribery can invalidate consent by undermining the rational grounds for choice,

they do not undermine the voluntariness of the choice. Similarly, a desire to "get well" or to favorably influence institutional authorities is not an "ulterior" constraint in the strict sense of the Nuremberg Code, though it may be a very real psychological constraint.

Other commentators, however, are less concerned with a sharp distinction between coercion and other forms of constraint or undue influence. Even outside such total institutions as prisons there are many situations in which junior or subordinate members of hierarchical groups may be exploited or manipulated. Such persons may assume that their willingness to consent to research may be rewarded by preferential treatment or that their refusals could provoke retaliation by those in positions of authority in the system. Whether or not such assumptions are justified, it is the assumptions themselves that make such persons susceptible to manipulation. Examples of such persons are medical or nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical firms, and members of the military services. Other persons whose dependency status can be exploited include residents of nursing homes, people receiving welfare benefits, patients in emergency rooms, and those with incurable diseases [. . .]

While most regulations and ethical codes proscribe undue material inducements, there is no consensus on what this means. Some commentators argue that in most cases in which competent adults are recruited to serve as subjects in research that presents only slight increases above minimal risk, the role of the research subject is similar to that of an employee. Consequently, the amounts of cash payments or other material inducements can be determined by ordinary market factors. Others protest that because participation in research entails "selling one's body" as opposed to "selling one's labor" the role of the research subject might be considered more akin to prostitution than to any other type of employment. According to this view, research subjects should not be paid at all; rather they should be motivated by altruism.

Attempts to regulate the amounts of permissible material inducements are inevitably problematic. Setting the rates at a low level results in inequitable distribution of the burdens of participation among those who have no opportunities to earn more money for each unit of their time. Higher rates may overwhelm the capacity of the impoverished to decline participation.

Competence and comprehension. The Nuremberg Code requires both "legal capacity" to consent (often called "competence") and "sufficient understanding" to reach an "enlightened" decision. Definitions of competence often include elements of comprehension, for example, to evaluate relevant information, to understand the consequences of action, and to reach a decision for rational reasons. [. . .]

Assessments of incompetence. The various standards employed for assessing competence are variations of four basic themes

1. Reasonable outcome of choice. This is a highly paternalistic standard in that the individual's right to self-determination is respected only if he or she makes the "right" choice—that is, one that accords with what the competency reviewer either considers reasonable or presumes a reasonable person might make.
2. Factual comprehension. The individual is required to understand, or at least be able to understand, the information divulged during the consent negotiation.
3. Choice based on rational reasons. Individuals must demonstrate a capacity for rational manipulation of information. They may, for example, be required to show that they not only understand the risks and benefits but also have weighed them in relation to their personal situations.
4. Appreciation of the nature of the situation. Individuals must demonstrate not only comprehension of the consent information but also the ability to use the information in a rational manner. Furthermore, they must appreciate the fact that they are being invited to become research subjects and what that implies.

While there is disagreement as to the grounds for assessing incompetence, most commentators agree that such assessments are limited in several ways. First, a judgment of incompetence may apply only to certain areas of decision making, for example, to one's legal but not to one's personal affairs. Second, confinement to a mental institution is not in itself equivalent to a determination of incompetence. Third, some who are legally competent are functionally incompetent, while some who are legally incompetent are functionally competent.

The Nuremberg Code does not permit the use of subjects lacking legal capacity or comprehension. Most subsequent codes and discussions allow their use with certain restrictions: for example, that mentally competent adults are not suitable subjects, that the veto of a legally incompetent but minimally comprehending subject is binding, and that consent or permission of the legal guardian must be obtained.

According to the U.S. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (hereafter, U.S. President's Commission), "decisionmaking capacity requires, to a greater or lesser degree: (1) possession of a set of values and goals; (2) the ability to communicate and understand information;

and (3) the ability to reason and deliberate about one's choices." Moreover, individuals may have sufficient capacity to make some decisions but not others. In the words of the U.S. President's Commission:

Since the assessment [of capacity] must balance possibly competing considerations of well-being and self-determination, [one should] take into account the potential consequences of the patient's decision. When the consequences for well-being are substantial, there is a greater need to be certain that the patient possesses the necessary level of capacity. . . . Thus a particular patient may be capable of deciding about a relatively inconsequential medication, but not about the amputation of a gangrenous limb [. . .]

Disclosure of information. The Nuremberg Code requires that the subject be told "the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come." These requirements have been modified by subsequent codes and regulations. U.S. federal regulations require (1) a statement of the purpose of the research and a description of its procedures; (2) a description of foreseeable risks and discomforts; (3) a description of benefits; (4) disclosure of appropriate alternatives, if any; (5) a statement of the extent of confidentiality; (6) an explanation of the availability of medical treatment for injury and compensation for disability; (7) an explanation of whom to contact for answers to questions; and (8) a statement that participation is voluntary and that neither refusal to participate nor withdrawal at any time will result in a loss of benefits to which the subject is otherwise entitled. The regulations further specify six additional elements of information to be provided when appropriate: (1) additional risks to the subject or to the fetus if the subject becomes pregnant; (2) circumstances in which a subject's participation may be terminated without his or her consent; (3) additional costs to the subject that may result from participation; (4) the consequences of a subject's decision to withdraw and procedures for orderly termination of participation; (5) a commitment to divulge significant new findings developed during the research that may relate to the subject's continued willingness to participate; and (6) the approximate number of subjects in the study. Finally, the regulations forbid requirements that subjects waive any of their legal rights as well as releases of the investigator, sponsor, or institution from liability for negligence.

While these requirements have the force of law, they are by no means exhaustive of possible standards for disclosure. To them one might add the following: A clear invi-

tation to participate in research, distinguishing maneuvers required for research purposes from those necessary for therapy; an explanation of why that particular person is included (selected); a suggestion that the prospective subject might wish to discuss the research with another person; and an identification of the source of funding for the research. [. . .] In short, there is no universal agreement on standards for disclosure of information or on what it takes for a person to have "sufficient knowledge" to give "informed" consent.

Those who agree on the need for disclosure of information in a particular category—the risks, for example—often disagree on the nature of the information that must be made known. The Nuremberg Code requires explication of hazards "reasonably" to be expected. Does this include a very slight chance of a substantial harm, or a substantial chance of a very slight harm? Neither the quality nor the probability of the risks to be divulged has been clearly determined legally.

Disagreements over particulars arise in part from disagreements about underlying standards: Is disclosure to be determined by (1) general medical practice or opinion; (2) the requirements of a "reasonable person"; or (3) the idiosyncratic judgment of the individual? While the legal trend may be shifting from the first to the second, it may be argued that only the third, the "subjective standard," is truly compatible with the requirement of respect for the autonomy of the individual person.

Yet even those who adopt the subjective standard disagree as to its implications. Freedman holds that the idiosyncratic judgment of the individual is overriding, to the point that the prospective subject can choose to have less information than a "reasonable" person might require. Veatch, however, argues that anyone refusing to accept as much information as would be expected of a "reasonable person" should not be accepted as a subject.

In the context of medical practice, two exceptions to the requirement for informed consent are recognized—"emergency exception" and "therapeutic privilege." The former, which permits the doctor to proceed without delay to administer urgently required therapy in emergencies, is included in a limited form in the regulations of the U.S. Food and Drug Administration; in some "life-threatening" emergencies in which informed consent is "infeasible," physician-investigators are authorized to employ investigational drugs and devices. There is continuing controversy over whether the emergency exception can be invoked to justify "deferred consent," that is, postponement of soliciting the consent of the subject or permission of the next-of-kin for up to several days after the subject has been enrolled

in a research protocol in an emergency. The therapeutic-privilege exception to the informed-consent rule permits the doctor to withhold information when, in his or her judgment, disclosure would be detrimental to the patient's interests or well-being. Most commentators agree that invoking the doctrine of therapeutic privilege to assure a subject's cooperation in a research project is almost never appropriate; it gives the investigator entirely too much license to serve vested interests by withholding information that might be material to a prospective subject's decision. U.S. federal regulations do not explicitly endorse the use of the therapeutic-privilege exception in research, although some authors have suggested that they could be interpreted as an implicit endorsement.

The success of some research activities is contingent upon withholding from the subjects information about their purposes or procedures or, in some cases, by deliberate deception (providing false information). U.S. federal regulations permit "waivers and alterations" of consent requirements if there is no more than minimal risk; if the waiver or alteration will not adversely affect subjects' rights or welfare; if without the waiver or alteration the research "could not practicably be carried out"; and if the subjects will be debriefed (given a full and accurate explanation afterward) when appropriate. [. . .] Various proposals have been made to minimize the need for and harmful effects of deceptive practices: Subjects might be invited to consent to incomplete disclosure with a promise of full disclosure at the termination of the research; subjects might be told as much as possible and asked to consent for specified limits of time and risk; or approval of the plans to withhold information from or to deceive subjects might be sought from "surrogate" populations that resemble the actual intended subject populations in relevant respects.

CONCLUSIONS

The use of a person as a research subject can be justified only if that person, or one authorized to speak on his or her behalf, consents to such use. The legal and ethical requirement for consent is grounded in fundamental tenets of the Judaeo-Christian religious tradition as well as in basic ethical principles that create the universal obligation to treat persons as ends and not merely as means to another's end. The consent requirement also reflects the perspective that competent persons are generally the best protectors of their own well-being. Most major disagreements over the form and substance of the consent requirements derive from conflicting interpretations of one or more of the basic principles [. . .]