

Cognitively Impaired Subjects

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Ethical questions regarding the use of human subjects in research are not new, but the special circumstances concerning potential subjects who are cognitively impaired have received less attention. Various conditions and disorders including Alzheimer disease, cerebrovascular disease, schizophrenia, and irreversible coma can cause mental impairment that diminishes or eliminates a person's capacity to understand and consent to participation in research. Cognitive impairment renders persons incompetent to make their own decisions to participate in research if it eliminates the person's ability to understand, make choices about, or communicate a decision regarding particular research. Investigation into certain areas such as dementing syndromes, however, by their very nature require the involvement of impaired subjects. Special protections to safeguard the welfare and rights of cognitively impaired subjects must be applied because these subjects are particularly vulnerable, especially since they are often institutionalized.

The axioms that consent must be obtained and that it must be informed and voluntary are often referred to collectively as the doctrine of informed consent. Because the informed consent process protects the rights of patients and human dignity, it is an essential means of ensuring the ethical integrity of human subject research. Based on the principles of privacy and autonomy, an individual has a right of bodily self-determination. In the research context, where the intervention is not intended solely to benefit the potential subject, it is especially important that consent be voluntary and based on full disclosure of the purposes, risks, and benefits of the research. The elements of informed consent for research involving human subjects, as defined by the Department of Health and Human Services' *Regulations for Protection of Human Subjects* (45 CFR Sec. 46.116), are listed in the Appendix.

Research on incompetent patients must meet a number of requirements common to all human subject research before consent may be sought. First and foremost, adequate protection of the rights and welfare of the subject must be provided, including appropriate

methods for obtaining and documenting informed consent. The risks and benefits to the subject must be evaluated, risks must be minimized, and the information sought must be both unobtainable by other means and beneficial to society. Finally, the study design and hypotheses must be scientifically sound (1-3).

Researchers whose protocols meet these requirements may still find the process of obtaining informed consent problematic when medical research involves cognitively impaired patients (4). In the later stages of, for example, Alzheimer disease, affected individuals have a progressive loss of cognitive ability and may require institutionalization. Issues relating to competence and voluntariness are particularly important with regard to research involving impaired populations. These issues will be addressed in this position paper, and a proposal will be made that a national review body make final determinations on research protocols involving cognitively impaired individuals not otherwise permissible under the guidelines set forth here.

Although medical research is always intended to benefit society, it may or may not offer potential benefit to the individual subject. Consequently, research involving human subjects may be divided into two categories: nontherapeutic and therapeutic experimentation (5). Nontherapeutic experimentation provides no direct benefit to research subjects. A study in which blood serum from persons with a particular disease is examined in an attempt to identify or characterize disease markers is an example of nontherapeutic experimentation. Therapeutic research, on the other hand, may directly benefit the individuals who receive the experimental agent or procedure. Randomized clinical trials of drugs are examples of this type of research. When appropriate, each category of experimentation will be considered separately.

In the absence of specific federal regulations governing cognitively impaired individuals as research subjects, the American College of Physicians believes that the positions set forth here will allow progress in research without violating society's obligation to uphold the rights and protect the welfare of potential experimental subjects. As Hans Jonas has noted, society would ultimately be diminished more by a loss of these rights and values than by a slowing of scientific inquiry. In his words: "Let us . . . remember that a slower process in the conquest of disease would not threaten society, grievous as it is to those who have to deplore that their particular disease be not yet conquered, but that society would indeed be threatened by the erosion of those moral values whose loss, probably

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caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having" (6).

Position 1

Consent to participate in research can, at times, be obtained in advance from the subject, before he or she becomes incompetent. In such instances, researchers should develop and use a mechanism that allows a competent subject to consent in advance to a research protocol and designate a proxy to supervise the subject's later participation in the research project after he or she becomes incompetent. The proxy's role is to protect the subject and under certain circumstances withdraw the subject from participation in the research project.

Rationale

In the early stages of some diseases, many patients may be competent to consent to particular research; later in the disease, however, the patient may become incompetent. Many research studies can be carried out in either the early or later stages of disease. Respect for autonomy requires that consent obtained directly from subjects at the time of the study be preferred to any alternative methods for recruiting subjects. Thus, when it is possible to answer the research question by studying competent patients, only competent subjects should be studied.

If competent persons cannot be the only subjects participating in the study, consent for the participation of incompetent subjects may be obtained in advance from the subject, while the subject is still competent. This is encouraged because, traditionally, researchers have not had contact with potential subjects before their cognitive impairment. An advance directive mechanism analogous to a durable power of attorney for health care presently used in treatment decision making and governed by state laws (7), which would allow for the designation of a proxy to carry out the intent of the directive, should be developed and used to allow subjects to consent to research to be done after they have become incompetent. As always, the purpose, methods, risks, and potential benefits of the future research would have to be disclosed. The Institutional Review Board (IRB) would be responsible for monitoring the status of such a document under state law.

There are, however, important differences between advance directives for experimental intervention and those used to guide nonexperimental therapy and supportive care. In nonexperimental care, advance directives are generally used by patients to indicate their intent to refuse procedures (for example, life-sustaining treatment) which they believe will be contrary to their interests. Respect for autonomy creates a strong presumption for adherence to instructions for nonintervention. In contrast, advance directives for research purposes would authorize interventions that do not benefit the subject in the case of nontherapeutic re-

search, or that may not benefit the subject in the case of therapeutic research. Such directives may be abrogated if it is later determined that the proposed research would unduly threaten the subject's welfare.

Advance directives would require that consent be obtained well before research is conducted. It is possible, therefore, that progress in the field would necessitate changes in the methods originally consented to by the subject by the time the research is to be done. Likewise, changes in the subject's physical condition may mean that the subject's participation would cause substantially more risk of harm or discomfort than was anticipated originally. To protect the subject's interests in such matters, a proxy appointed by the patient at the time consent is given must review the research protocol in its final form and decide whether the directive should be followed.

Because proxies might not fully understand their role, researchers must make clear to them the proper standards for decision making. The proxy would determine whether any proposed changes in the research procedure constitute an increased risk to which the subject had not already consented. Some changes, however, may be considered minor and within the scope of the original consent. Examples of minor changes might include drawing additional blood samples, or adding a noninvasive test such as a CT scan or an EEG. Changes whose only effect is to reduce risk should also be considered acceptable.

The proxy should also determine whether the subject's condition has changed such that the research constitutes a risk to his or her welfare greater than that covered by the original consent. If risk is increased unexpectedly because of a change in medical condition (as might happen, for example, if comorbid conditions arise after the subject executes the advance directive), the proxy should refuse participation by the subject on the grounds that his or her original consent does not apply to the present circumstances. The proxy should also withdraw the subject if he or she believes that participation will cause the subject substantial distress (for example, if the subject becomes uncooperative).

Position 2

In cases where there is no advance directive (and therefore no proxy designated by the subject), a legally authorized representative should act as the surrogate decision maker for an incompetent potential subject. Researchers must inform surrogates of the proper standards for decision making.

The surrogate should not consent to research that he or she believes the patient would have refused if competent. With the guidance of the individual's attending physician, surrogate decision makers should, in all other cases, act in the incompetent individual's best interest. As such, surrogates should not consent to nontherapeutic research that presents more than a minimal risk of harm or discomfort.

When there is no advance directive, surrogates may consent to therapeutic research if participation is in

the incompetent person's best interest, that is, if the net additional risk caused by participation is small, and there is scientific evidence that participation is reasonably likely to offer benefits over standard treatment or no treatment, if none exists.

Rationale

When persons are incompetent to make the choice to participate in research and have not completed an advance directive, decisions regarding participation in research should be made for them by a surrogate decision maker authorized by applicable law, in concert with the person's attending physician. Although state laws do not address surrogate consent for research, in the treatment decision making context, legally effective consent from someone other than the patient must come from a person (who could be a family member) appointed by the court to be the patient's legal guardian unless state law provides otherwise. A number of states have provided otherwise through statutes and court decisions. Some states (including Arkansas, Georgia, Idaho, Louisiana, Maine, Maryland, Mississippi, Missouri, North Carolina, and Utah) have statutes that authorize particular family members to consent to medical treatment for adults who cannot speak for themselves (8, 9). Eleven states (Arkansas, Connecticut, Florida, Iowa, Louisiana, New Mexico, North Carolina, Oregon, Texas, Utah, and Virginia) have statutes authorizing certain family members to exercise the right of specified patients (most require the patient to be terminally ill) to have life-sustaining treatment withheld or withdrawn (8). Courts in some states have held that family members of incapacitated adult patients can consent to certain medical care on their behalf, or have authority to withhold or withdraw life-sustaining treatment without recourse to the courts regarding the decision, under certain circumstances (8, 9).

Because incompetent subjects cannot give consent themselves, authorized surrogate decision makers should consent to participation on the subjects' behalf only when the involvement of the incompetent person is essential to the conduct of the research. This means not only that it must be impossible to substitute competent subjects, but also that the matter being investigated should be related to the subject's incompetence. Unless the issue being studied is associated with cognitive impairment, others who are not cognitively impaired could serve as subjects and the incompetent subject's participation may not be essential to the research.

Regarding standards to be used by surrogate decision makers in the research setting, the American College of Physicians believes that substituted judgments (that is, judgments as to whether the incompetent individual would consent to research if competent) should only be used in narrowly defined circumstances, as described below. Otherwise, the surrogate's proper role is to act in the best interest of the incompetent individual. Because surrogates may not fully understand their role (10), researchers must inform

them of the standards for decision making described in this position paper.

Substituted judgments as to participation in research are likely to be highly speculative, as most incompetent people for whom the decision is being made were never presented with such a choice in the past and are unlikely to have formulated and expressed any opinions on the matter (11). When subjects had never given specific prior consent to their participation in research, surrogates should consent to research only when they believe it is in the incompetent person's best interest. Even if participation is in the person's best interest, however, consent should not be given if it is believed that the patient would not have agreed to participate.

Because nontherapeutic research offers no potential benefits, surrogates should not consent to nontherapeutic research for incompetent subjects who left no advance directive when the risk of harm is more than minimal. Federal regulations define "minimal risk" as risks "not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (12).

A surrogate may properly consent to therapeutic research when there is no advance directive if a careful weighing of the risks and benefits shows that foregoing standard treatment (or no treatment, if none exists) to participate is in the incompetent person's best interest. Because the potential benefits of experimental or innovative therapy are to a substantial degree still speculative, exposing subjects to substantially greater levels of risk than those associated with standard treatment (or with no treatment, if none exists) would not be in the subject's best interest. Thus, surrogates should only authorize therapeutic research if the net additional risks of participation (including the risk of foregoing standard treatment, if any exists) are not substantially greater than the risks of standard treatment (or of no treatment, if none exists). In addition, the surrogate should not conclude that participation is in the incompetent subject's best interest unless there is scientific evidence to indicate that the proposed treatment is reasonably likely to provide substantially greater benefit than standard treatment (or than no treatment, if none exists).

Before asking surrogates for consent, researchers should disclose to surrogates all information that is material to a decision about participation in the research. Surrogates must be told when the proposed research intervention is not clearly therapeutic or not clearly the therapy of choice and that, although it is hoped the patient will benefit, another purpose of the research is to advance medical science. The surrogate should be instructed to consent only if he or she believes the incompetent individual would not have refused and that participation is in the person's best interest. Because participation in research may not be clearly in the subject's best interest, the surrogate may appropriately refuse even highly promising research.

Position 3

Special protections are necessary for chronically institutionalized subjects. An Institutional Review Board should determine whether changes in daily routine might unduly influence or distress such subjects. In addition, the IRB should consider asking a committee composed mostly of representative residents of, for example, a nursing home, to review proposed research projects to be conducted at the facility. The resident committee would make a nonbinding recommendation to bar or allow the research and would be allowed to present their rationale to the full board.

Rationale

There must be adequate procedural safeguards to protect individual rights. Federal regulations have resulted in the creation of IRBs to protect experimental subjects in institutions that conduct research on human subjects using federal funds. An IRB reviews all human subject research proposed to be conducted at its institution or affiliate and must bar any research it believes would adversely affect the rights or welfare of subjects. It is also charged with overseeing the consent process and periodically reviewing ongoing research (1). The American College of Physicians believes that chronically institutionalized subjects need protection beyond that specified by current regulations.

Patients in a chronic institutional setting may be unduly influenced to consent to research by subtle pressures created or exacerbated by their environment. The relationship of physician-investigator to patient is an inherently unequal one, with most patients relying on health care professionals for medical information. These effects are amplified for many elderly patients in chronic institutions whose physical, mental, and social resources may be sharply limited. These patients live in an environment where most personal decision making is delegated, often permanently, and they may be extremely dependent on caregivers. They may be influenced by tacit fears that refusal of research would be interpreted as an act of disobedience, or that refusal might prejudice their care in some way. They may be more susceptible to positive inducements to give consent, such as a change in living quarters, than less frail patients. Surrogates concerned about the welfare of institutionalized patients may also be influenced by similar fears or beliefs.

Institutional Review Boards currently are required to ensure that "appropriate additional safeguards have been included in the study" in cases where "some or all of the subjects are likely to be vulnerable to coercion or undue influence" (13). The American College of Physicians believes that stricter scrutiny of issues relating to coercion and undue influence should be required when subjects are institutionalized. Review boards should be instructed to investigate in detail and make written findings about how subjects are approached and offered the opportunity to participate in a study, how the proposed research or its effects would alter the daily routine and lifestyle of subjects, and

whether any procedure would constitute coercion or undue influence. Whether coercion is present will often depend on the specific circumstances of the residents. For example, the offer of a move to a floor with more nursing care might unduly influence very frail, but not healthier, residents. Institutional Review Boards should prohibit research involving changes it finds might have a coercive effect.

Special procedures are also necessary to protect the welfare of chronically institutionalized subjects. Methods that might seem minimally intrusive to IRB members, and which might be perceived as innocuous by less frail patients, might be very distressing or disorienting to residents of chronic care facilities. Input on such matters from, for example, nursing home residents would allow IRBs to assess more accurately the impact of research on resident welfare. Boards reviewing research on chronically institutionalized populations should consider consulting a standing committee composed of, and chosen by, residents of the institution (11). The committee would review the proposed research and recommend either that the IRB bar or allow the research. Committee findings in oral or written form would also be allowed to be presented to the full board.

Position 4

A national review body should be created to evaluate and make a final determination on research protocols involving incompetent persons that may not otherwise be allowed under the guidelines set forth here, such as nontherapeutic research which poses more than a minimal risk of harm or discomfort to cognitively impaired subjects. An Ethical Advisory Board with broadened authority could accomplish this, or review by the Department of Health and Human Services, in consultation with a multidisciplinary panel of experts, can be modeled on federal regulations which provide additional protections for children involved as subjects in research.

Rationale

Under the federal regulations, two methods for reviewing specified research not otherwise approvable under the regulations are set forth. Provision is made for the conduct or funding of research involving children not otherwise approvable if the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. Funding of research involving children may also be approved if the Secretary of DHHS, after consultation with a panel of experts in pertinent disciplines (for example, science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either "that the research . . . [in fact satisfies conditions previously stated in the regulations] or the following: The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affect-

ing the health or welfare of children; the research will be conducted in accordance with sound ethical principles; adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians . . ." (14).

Likewise, such a procedure, providing an additional level of review as a "National IRB," could exist for the protection of cognitively impaired persons involved as subjects in research when participation in the research project would otherwise have to be denied under the guidelines set forth in this paper. Such a procedure could be used, for example, to review important nontherapeutic research which entails more than a minimal risk of harm or discomfort to cognitively impaired subjects. The usual informed consent requirements, and not the "assent" and "permission" standards, however, would apply where adult subjects are involved.

Another part of the federal regulations calls for the creation of a review body in the form of an Ethical Advisory Board (EAB) to review certain research. Ethical Advisory Boards are to be established by the Secretary of the Department of Health and Human Services to review research on fetuses and research on human in-vitro fertilization. The first EAB was chartered in 1977 but not renewed in 1980 when funding ran out (15). Currently, no EAB exists. Additionally, the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (1974 to 1978) had recommended that the class of research involving children later to be described in the federal regulations, should also be reviewed by the EAB (15). This recommendation for EAB oversight was not adopted; the regulations ultimately provided for a less formal advisory process in the form of "consultation with a panel of experts in pertinent disciplines." There should be an EAB with broadened authority or a panel of experts to review research on cognitively impaired persons that may not otherwise satisfy the guidelines set forth here. Although this proposal calls for an additional level of review, it is intended not to impede research, but to provide a forum for evaluating research that would otherwise not be permissible.

Appendix: General Requirements for Informed Consent from the Department of Health and Human Services' Regulations for Protection of Human Subjects

Except as provided elsewhere in this or other subparts, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understand-

able to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section [not included here], in seeking informed consent the following information shall be provided to each subject:

- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
- (2) A description of any reasonable foreseeable risks or discomforts to the subject;
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research;
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
- (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
- (8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

- (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable;
- (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
- (3) Any additional costs to the subject that may result from participation in the research;
- (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
- (5) A statement that significant new findings developed during the course of the research which may re-

late to the subject's willingness to continue participation will be provided to the subject; and
(6) The approximate number of subjects involved in the study (16).

Subsections (c) and (d) are not included because the requirements of this section are being cited as the necessary basic elements of informed consent; the American College of Physicians does not advocate allowing the waiver of informed consent even though this is permissible under sections (c) and (d) in certain circumstances.

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References

1. Department of Health and Human Services. *Regulations for Protection of Human Subjects*. 45 CFR Sec. 46.
2. The Nuremberg Code. In: Annas GJ, Glantz LH, Katz BF. *Informed Consent to Human Experimentation: The Subject's Dilemma*. Cambridge, Massachusetts: Ballinger Publishing Company; 1977.
3. World Medical Association. Declaration of Helsinki, rev. 1983. In: Areen J, King PA, Goldberg S, Capron AM, eds. *Law, Science, and Medicine*. New York: The Foundation Press, Inc.; 1984.
4. Ratzan RM. The experiment that wasn't: a case report in clinical geriatric research. *Gerontologist*. 1981;21:297-302.
5. Annas GJ, Glantz LH, Katz BF. *Informed Consent to Human Experimentation: The Subject's Dilemma*. Cambridge, Massachusetts: Ballinger Publishing Company; 1977.
6. Jonas H. Philosophical reflections on experimenting with human subjects. *Daedalus*. 1969;98:219-47.
7. For an overview of current statutes, see Society for the Right to Die. *Handbook of Living Will Laws*. New York: 1987.
8. Areen J. The legal status of consent obtained from families of adult patients to withhold or withdraw treatment. *JAMA*. 1987;258:229-35.
9. Fowler M. Appointing an agent to make medical treatment choices. *Columbia Law Review*. 1984;84:985-1031.
10. Warren JW, Sobal J, Tenney JH, et al. Informed consent by proxy: an issue in research with elderly patients. *N Engl J Med*. 1986;315:1124-8.
11. Annas GJ, Glantz LH. Rules for research in nursing homes [Editorial]. *N Engl J Med*. 1986;315:1157-8.
12. Department of Health and Human Services. *Regulations for Protection of Human Subjects*. 45 CFR Sec. 46.102(g).
13. Department of Health and Human Services. *Regulations for Protection of Human Subjects*. 45 CFR Sec. 46.111(b).
14. Department of Health and Human Services. *Regulations for Protection of Human Subjects*. 45 CFR Sec. 46.407.
15. Levine RJ. *Ethics and Regulation of Clinical Research*. Baltimore: Urban & Schwarzenberg; 1986.
16. Department of Health and Human Services. *Regulations for Protection of Human Subjects*. 45 CFR Sec. 46.116(a) and (b).