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Critical Issues Concerning Research Involving Decisionally Impaired Persons

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Critical Issues Concerning Research Involving Decisionally Impaired Persons

Abstract
This is a working paper prepared by staff to the Human Subjects Subcommittee of the National Bioethics Advisory Commission (NBAC). At the request of the subcommittee, the paper attempts to set out the critical issues facing the commissioners concerning the recruitment and participation in clinical research of those who are decisionally impaired.

Comments

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Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity

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CRITICAL ISSUES
CONCERNING RESEARCH
INVOLVING DECISIONALLY
IMPAIRED PERSONS

Introduction

This is a working paper prepared by staff to the Human Subjects Subcommittee of the National Bioethics Advisory Commission (NBAC). At the request of the subcommittee, the paper attempts to set out the critical issues facing the commissioners concerning the recruitment and participation in clinical research of those who are decisionally impaired. The critical issues considered in this working paper are as follows.

- Should the individual’s informed consent always be required for research participation?
- Should individuals be able to execute substantive advance research directives?
- Should the patient’s legally authorized representative be empowered to make research participation decisions, and on what basis should he or she decide?
- Should legally authorized surrogates be empowered to make research participation decisions, and on what basis should they decide?
- Should those who are decisionally impaired, and at high risk for decisional incapacity, be excluded from research?
- Should the patient who decides to participate in research be required to have appointed a legally authorized representative to make subsequent medical care decisions?
- Should those who are decisionally incapacitated be excluded from research?
- Should research involving the decisionally impaired or incapacitated be limited to that which is relevant to a medical problem from which the patient is suffering?
- Should investigators be required to notify individuals that they have been found to be decisionally incapacitated and that they are to be entered into a research project without their consent?
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- Should consent auditors ever be required?
- Should “reconsent” procedures ever be required?
- Should “wraparound” studies ever be required?
- Should placebo arms ever be prohibited?
- Should the NBAC promulgate new regulations concerning the participation in research of those who are decisionally impaired, or should it rather offer guidance for potential subjects, their physicians, clinical investigators, institutional review boards, and other policymaking bodies?

Should the individual’s informed consent always be required for research participation?

The Nuremberg Code is perhaps the most important touchstone of research ethics. The first sentence of the Code states that “[t]he voluntary consent of the human subject is absolutely essential.” As the field of medical ethics has grown, some distinguished commentators have continued to defend the view that no research is permissible without the subject’s informed consent. They point out that scientific progress is morally optional, while respect for human beings and their self-determination is not.

Yet research with children and other populations has continued and flourished in the half century since Nuremberg. These practices have been justified by seeking what many regard as the moral equivalent of subject consent, including parental permission and subject assent where feasible. A further justification is that significant benefits to many individuals would have to be foregone if the consent requirement were strictly interpreted, but few have found strict interpretation of the consent requirement to be morally obligatory. Various standards and procedures have been established to protect the well-being of subjects. It is also often noted that, since treatment of individuals for disease must continue, far more harm would be done through the widespread clinical use of modalities that had not been subjected to controlled study.²

Instead, conditions have been placed on research with those who cannot give their own consent. If research with children and others who lack decisionmaking capacity can be ethically acceptable, then presumably research with the decisionally impaired, who may have various levels of decisionmaking capacity, can also be done in a way that is ethically acceptable.³

Foremost among the conditions that may be imposed on research with those who are decisionally impaired or incapacitated is the gradually higher level of scrutiny that is accorded research proposals as the risk-benefit ratio becomes less favorable. Conditions may be imposed concerning not only acceptable levels of risk, but also through recruitment and selection of subjects, study design, consent processes, and independent monitoring.

Should individuals be able to execute substantive advance research directives?

Some persons whose decisionmaking capacity is currently intact may be able to anticipate a period of incapacity, perhaps extending for the rest of their lives. Various neurodegenerative diseases have this kind of course, including Alzheimer’s. By the time an individual’s disease has progressed to a stage that is of research interest, he or she may no longer be capable of granting an informed consent. In theory, the individual may make both substantive and procedural arrangements, while capable, to enable study participation after a loss of decisionmaking capacity. An outstanding issue is whether such arrangements are acceptable approximations of the gold standard of ethical research enrollment, the subject’s contemporaneous informed consent.⁴

A substantive advance research directive would specify a research project or projects that an individual would be prepared to enter, should he or she lose capacity. These advance directives would be roughly equivalent to living wills for standard treatment. States would presumably need to pass legislation recognizing such devices. One question is whether federal regulations should recognize research advance directives and take them into account in rules concerning subjects who may lose their decisionmaking capacity before they can enter or complete a study.

The idea of an “advance directive for research” appears to be consistent with our society’s dominant philosophical beliefs about control over one’s body and with other practices. Some argue that, just as individuals may donate their remains to medical schools and laboratories, so they should be permitted to commit themselves to a research project as living subjects while they still have the ability to do so. This argument seems to gain strength when the anticipated research participation holds some prospect of benefit to the incapacitated subject.⁵

1 Rebecca Dresser, “Research Involving Persons with Mental Disabilities: A Review of Policy Issues and Proposals,” contract paper for National Bioethics Advisory Commission, 1997, p. 5. Relevant portions of this paper will hereafter be cited in footnotes as Dresser, followed by the manuscript page number.
2 Dresser, p. 6.
3 Dresser, p. 8.
4 Dresser, pp. 41–51.
5 Dresser, pp. 51, passim.
But potentially beneficial research for those who are incapacitated is the exceptional case; few studies offer even a remote chance of benefit. Many contend that it is exploitive to permit people, hoping desperately for a return to lucidity and health, to make such a commitment, often well in advance of the actual research intervention. They note that one's views about continued medical procedures may change as one's illness progresses, perhaps without the opportunity to review a research living will once it has been executed. Further, how can it be decided when the experimental involvement should cease, especially in studies that did not offer benefit to the subject in the first place?

If the idea of an advance directive for research is nevertheless attractive because of its consistency with our other values, such as the protection and promotion of patient autonomy and the advancement of medical knowledge, some conditions could be placed on its use. For instance, research advance directives might only be valid when the research presents some prospect of patient benefit, and strict time limits could be imposed that require active renewal of the living will. Another option is to require the appointment of a legally authorized representative to make a decision about stopping participation in the study, as a condition of validity of the advance directive for research.

There is another objection to research advance directives that is rather different from those mentioned above and that many find decisive. The incapacitated patient may be aware of being subjected to various experimental procedures, but be unable to understand their significance or appreciate that they had been consented to in advance. A person with waxing and waning awareness, often highly medicated and perhaps physically restrained, could experience study procedures as quite disturbing, and even as a kind of torture. To minimize this possibility, careful protections would need to be constructed, including perhaps the advance appointment of an alternative decision maker who could stop study participation at the least sign of subject distress.

Should the patient’s legally authorized representative be empowered to make research participation decisions, and on what basis should he or she decide?

In anticipation of a period of incapacity, many individuals have appointed others to make treatment decisions on their behalf. The authority to appoint such representatives, who are often called health care agents, has been recognized in the laws of many states, technically known as the “durable power of attorney” (DPA). In general, the health care agent is obligated to make medical decisions that are in accord with the patient’s previously expressed wishes, or, if those wishes are unknown to the agent, consistent with the patient’s expressed values. Failing that, the health care agent should make decisions that advance the patient’s medical best interests.6

Many have advocated extending this legal authority to enable the representative to make research participation decisions. There are several situations in which such an arrangement has practical appeal. Often individuals “fail” standard therapy but are incapable of deciding about trying to take advantage of a medication or device still under study. Or a person may not have anticipated becoming ill and, suddenly incapacitated, may have had no time to consider whether some experimental treatment might be preferable to a standard therapy. Or an individual may become decisionally incapacitated in the course of medical care without having considered the next step in his or her treatment. Finally, some may find donating their body to a research project to be a highly desirable and satisfying way to exit, but, rather than leave this to chance, wish a representative to identify a worthwhile scientific effort taking place at the time of death.

In one important sense, the power to appoint a “research agent” is an expression of the patient’s self-determination, for which all sorts of provisions are currently made in the delivery of health care. If individuals are empowered to identify those whom they wish to speak for them in making decisions about recognized medical interventions, then why not extend this authority to emerging medical alternatives?

One important difference between reliance on health care agents in the standard treatment setting and in the research setting is that recognizing the authority to decide about someone else’s care seems to be more easily justifiable when there is good reason to believe that the intervention will be in that person’s interest. Experimental procedures or maneuvers are not undertaken with the primary goal of subject benefit, but rather are intended to help advance knowledge about the problem motivating the study. Allowing other persons to decide about making someone an experimental subject, even when the individual in question has authorized them to do so, is a qualitative departure from ordinary DPA arrangements. Such decisions may entail considerable risks with little likelihood of substantial benefit.

Though great deference is given to individual self-determination in our political system, there does seem to be a legitimate societal interest when a private arrangement may present significant harm to the individual initiating it, in the absence of a reasonable prospect of offsetting advantages. Weighing against this societal interest is the possibility that greater medical knowledge may accrue to society in permitting these arrangements to go forward in spite of their risks. In some cases, the rejection of those who would make themselves

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6 Dresser, pp. 29–36.
available for research through an agent could significantly hamper studies of the condition that led to the person’s current incapacity.

A balance might be struck by limiting the conditions under which the health care agent’s authority would be valid. For instance, studies that present no prospect of direct benefit to the subject, but entail significant risk, could be ineligible for enrollment via a DPA. Studies that entail minimal risk could be regarded as consistent with a patient’s best medical interests and therefore permissible, even though they do not advance those interests.

Alternatively, a representative’s decision could be subject to review to establish that it is consistent with what is known about the patient’s wishes. But (short of intervention by a court of law), it is not at all clear how such a challenge could be warranted, especially if the patient leaves no written statement about his or her attitudes toward research. How should other responsible parties, like researchers and IRBs, assess whether the patient’s representative, in enrolling the patient in research, is truly acting in accordance with the patient’s wishes and values? Unlike treatment DPAs, one test that would have very limited applicability is the best interests of the patient. Since studies are not designed to satisfy individual subjects’ medical interests (though that may be a happy by-product of a study), to say that a study is in a person’s best interests, especially when that person no longer has capacity, is often going to be far-fetched. For many, this limitation on objective review of a representative’s decisions is important enough to reject procedural arrangements.

In partial amelioration of this problem, at least from the standpoint of potential harms to subjects, a warning to representatives might be appropriate in some cases. For example, legally authorized representatives could be informed of the possibility that the research would add to the patient’s risk of harm or discomfort. Were such information made part of the process, the difference between the expected course with and without research should be clearer to the lay person representing the decisionally incapacitated person.

Procedural advance directives, like DPAs, offer at least two advantages over substantive research advance directives. The first is that they are far more flexible than statements about preferred or permissible interventions. The second advantage, and one especially pertinent to patients who suffer from some degree of decisional impairment, is that it may be much easier to designate a representative whom one trusts than to assess the relative risks and benefits of a research study. Thus, it may be argued, if one wishes to grant patients the right to research participation when they no longer have decisionmaking capacity, then the approach that is most reliable concerning their expressed choice is probably the procedural one. However, it must be granted that there is little evidence for this argument, however intuitively plausible it may seem.

One objection to research DPAs is also an objection to research advance directives and, indeed, to any study participation by the decisionally impaired: that the disoriented patient-subject may feel imprisoned and forced to undergo procedures without understanding, even though they have been authorized by the legally authorized representative. This could be a terrifying, nightmarish experience for a decisionally impaired person. Although a procedural advance directive may reduce this risk, it remains a serious concern and may require more than one protective mechanism for the impaired subject.

Should legally authorized surrogates be empowered to make research participation decisions, and on what basis should they decide?

Usually people who lose decisionmaking capacity have not created an advance directive. Sometimes members of their family or other caretakers are identified as suitable surrogates in granting permission to enter them into research. But these arrangements have, at best, an uncertain legal standing. Regulations could recognize state legislation that established in the law what is now a matter of common practice by granting “natural” surrogates (such as family members or close friends) a specific role in the research recruitment process for decisionally impaired persons.

An obvious objection to such arrangements is that, unlike a representative appointed by the patient in advance, the surrogate’s standing as a substitute decision maker may arise only from the law. To many the moral basis for the surrogate’s authority appears inadequate, especially in the research context, because he or she has not been selected by the potential subject. According to many bioethicists, surrogates are supposed to act on the patient’s behalf in accordance with their “substituted judgement.” But there is no guarantee that even a close relative is aware of the patient’s preferences or values with respect to standard medical treatments, let alone research participation, or even that the surrogate will act on those preferences or values if they are known. A surrogate may only be able to decide based on the patient’s medical best interests. A “medical best interests” standard will not apply to studies that offer no prospect of direct benefit to the subject.

However questionable the legal basis of this process, a large number of research subjects have been recruited through identification of a surrogate and restrictions on these measures would constitute a severe blow to a great deal of research on diseases that involve cognitive disabilities. And many studies do hold out the prospect of direct benefit, including the use of new drugs and medical monitoring. One option would be to recognize in regulation the role of surrogates in research that involves only procedures that are potentially beneficial to the subject, or that entail no more than minimum risk.
Should those who are decisionally impaired and at high risk for decisional incapacity be excluded from research?

In the final analysis, both substantive and procedural advance directives for research are at best problematic. The underlying difficulty is that, unlike the usual medical circumstances for which these legal devices have been designed, in a research context the individual is giving himself or herself over, in advance, to an enterprise that is likely to be of benefit only to the society at large, through the advancement of medical knowledge.

Considering the inherent limitations of measures intended to enable the incapacitated research subject to continue to have a voice in his or her treatment, it may be argued that those who are at greatest risk of decisional incapacity should simply be excluded from research. Were the assessment of risk for loss of decisional capacity required prior to enrollment in a study, the remaining subjects would be those who are less likely to require the application of substantive or procedural advance directives, though these devices might still be a condition of study participation.

There are several objections to a rule-out procedure based on the prospect of a potential subject’s losing decision-making capacity. First, although the prospect of decisional incapacity is often clear, especially in progressive diseases or when a patient is going to be heavily medicated, in many cases the loss of capacity is not so predictable. Second, however one weighs the importance of advancing medical knowledge, prohibiting research on those most likely to lose capacity would create a significant obstacle to the study of some diseases in their most debilitating stages. Third, some research may be concerned with determining at what dosage a drug impairs cognitive function, an issue that could be of great importance to preventing future patients from losing their decisionmaking ability. Fourth, the proposed exclusion would not avoid instances of uncertainty about the meaning of a substantive advance directive or the propriety of a decision made by representative empowered through a procedural advance directive.

Nonetheless, the idea that ethical problems raised by incapacity should be avoided if possible has intuitive force. One approach could be to require that a research project begin by enrolling those least likely to lose their decisionmaking ability during the study period, and that the selection of at-risk subjects be justified by the particular goals of the study. A different approach would look again to the risk-benefit ratio, excluding prospective subjects from certain studies depending on their likely ability to make future decisions, as well as the anticipated level of risk.

Should the patient who decides to participate in research be required to have appointed a legally authorized representative to make subsequent medical care decisions?

Apart from decisions having to do specifically with continuing study participation, medical decisions must often be made while a patient is enrolled in research. To avoid confusion about who is authorized to make medical care decisions if the subject loses capacity, investigators might be required to ensure that all subjects have a legally authorized representative. In some jurisdictions this may require that the subject appoint a health care agent prior to enrollment in a study.

From the researcher’s standpoint, it also seems prudent to ensure that a patient with a decisional impairment not be left without a representative to make health care decisions; such a representative could help the study team avoid problems if treatment issues arise. However, there may be confusion about the limits of the representative’s authority, since it may not extend to issues having to do with the research itself. For example, conceivably the patient’s medical care representative could decide that continued participation in a current research project is incompatible with the patient’s medical well-being and could have the power to remove the patient from the study, but lack the power to enroll the patient in a different research project.

Should those who are decisionally incapacitated be excluded from research?

One way to avoid the practical and philosophical problems with justifying research with those who are no longer able to consent would be to exclude such individuals from being part of research. A wholesale exclusion from research of those who lack decisionmaking ability would square with the letter of the Nuremberg Code, but would not be consistent with research practices even in the decades since the code was written. In general, it is thought that ethical research with human subjects who cannot give informed consent can be and has been conducted, especially if some form of advance directive or surrogate decision making arrangement is in place. Several subsequent ethics guidelines (including those of the Helsinki declarations of the World Medical Association and the Council for International Organizations of Medical Science) have endorsed research with those unable to consent under certain conditions. Recent scholarship indicates that even the Nuremberg Code itself was not intended to refer to clinical research with those who are ill, but to research with normal subjects.
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Furthermore, though it is controversial, the recently authorized exception to informed consent requirements for certain emergency research is a greater departure from the Code’s voluntary consent requirement than any contemplated herein concerning research with those who are decisionally incapacitated. A primary consideration in the creation of the narrow exception to the federal rules was the need for improvements in the care of emergent, life-threatening conditions. A similar argument can be mounted on behalf of the improved treatment of those who are or are at risk for a loss of decisionmaking ability.

Should research involving the decisionally impaired or incapacitated be limited to that which is relevant to a medical problem from which the patient is suffering?

Some “vulnerable” or “special” populations are currently accorded a particular protection in the regulations to ensure that they are not unfairly burdened with involvement in research simply because they are easily available. Thus, prison research is to be limited to conditions that especially affect that population. Considering that the decisionally impaired are often not only institutionalized but may also be unable to speak for themselves, their position bears earmarks of special vulnerability. One important justification for involving those with decisional impairments in research is the need for progress in the treatment of certain diseases. In order to thwart the temptation to engage them in research simply because they are more available than others, it may be appropriate to restrict research involving decisionally impaired persons to that which is relevant to conditions responsible for the impairment itself. A less restrictive rule would limit research to that which is relevant to conditions that tend to afflict those who are decisionally impaired.

Should investigators be required to notify individuals that they have been found to be decisionally incapacitated and that they are to be entered into a research project without their consent?

To be found decisionally incapable and then enrolled in research according to alternative decisionmaking arrangements is to have certain of one’s rights curtailed, however justifiable the curtailment research may be. Some argue that whenever an individual is found to be decisionally incapable, the individual should be put on notice of this finding, especially when it could have important consequences for the individual’s medical treatment, as in the case of enrollment as a subject.\(^7\)

Such an notification process will often be an empty ritual. Worse, a requirement that implies a duty to so inform those who are in an advanced stage of dementia prior to research involvement could well contribute to undermining health professionals’ respect for the regulatory system. Nevertheless, to be unaware that one has been found decisionally incapable is to be deprived of the opportunity to seek review and perhaps of the right to judicial intervention. The implications of such a determination, including the loss of control over one’s own person, are among the most serious one can imagine for a liberal, democratic society.

Rather than require that all individuals who have been found to be decisionally incapacitated be informed of that finding prior to their enrollment in a study, such a rule may be limited to those potential subjects who show any signs of consciousness. The notification would also enable the patient to assent to his or her research role, by no means a trivial recognition of individual dignity.

Should consent auditors ever be required?

The consent auditor is one device that has frequently been suggested as an additional procedural protection in the recruitment of research subjects who may be decisionally impaired. The consent auditor, who is not a member of the study team but perhaps a member of the IRB or an institutional ethicist, witnesses the consent process and then either certifies the consent as valid, or informs the principal investigator that an individual is not able to give valid consent.\(^8\)

The consent auditor may be adopted as an alternative or as a complement to the blanket notification requirement discussed above. Rather than requiring researchers to engage in what will often be an empty ritual, consent auditors could be required for potential subjects who have conditions associated with a decisional impairment. A system of audited consent will require a substantial investment by research institutions. The requirement may be limited to studies that have certain characteristics, such as those that involve greater than minimal risk and/or those that do not hold out the prospect of direct benefit to the subject.

Should “reconsent” procedures ever be required?

Studies with those who are decisionally impaired may take place over extended periods. One of the essential conditions of ethical research is continued voluntary participation, but those who are deeply involved with and dependent upon the health care system may not feel able to disenroll from a study. A
requirement for periodic “reconsenting” would help ensure that a patient’s continued involvement is truly voluntary by giving “permission” to leave the study. Such a requirement would also provide the occasion to reassess decisionmaking capacity, and it could trigger an advance directive or surrogate arrangement. Reconsent mechanisms conform with the spirit of informed consent as a process rather than a single event, and with the view of human research participants as collaborators rather than as passive subjects.\(^9\)

Reconsenting is, however, another labor-intensive measure that would add to the cost and complexity of the human research system. Yet a number of long-term studies already include such a procedure. A reconsent requirement could be attached to certain studies depending on their length and the condition of the individuals to be included, such as those with progressive neurological disorders.

### Should “wraparound” studies ever be required?

With or without a decisional impairment, many who are ill and candidates for a research study can suffer from the “therapeutic misconception,” the notion that the research maneuvers or procedures might be of personal benefit even though that possibility has clearly been ruled out in the consent process. One way to deal with the therapeutic misconception is to incorporate a non-research or “wraparound” phase into the project, one that provides the subject with some beneficial intervention independent of the study itself.

A serious problem with a wraparound phase is that it may shift the balance in the opposite and equally problematic direction of the therapeutic misconception, by providing an inappropriate incentive to study participation in order to derive the benefits of a recognized therapeutic strategy without payment. On the other hand, wraparounds could be suitable follow-ups to certain kinds of research that involve the provocation of symptoms.

### Should placebo arms ever be prohibited?

Many decisional impairments are associated with psychiatric disorders that can be managed symptomatically with neuroleptic medication. When a known risk of placebo is the return of symptoms, it may be argued that it is unethical to include a placebo arm. Thus, some contend that new drug investigations should be controlled by measures against standard therapy, in spite of the methodological shortcomings of such designs.

A basis for excluding placebo arms in particular studies could be an individualized assessment that concludes that certain patients would be at high risk for relapse if their current therapeutic regimen was discontinued, that a “drug holiday” is not contemplated for this patient apart from enrollment in a study, and that standard therapy is generally considered effective if not ideal. However, any change in human subjects regulations concerning permissible research design should presumably accommodate other federal requirements for drug approval.

When drug-free research is conducted (whether as part of a “blinded” placebo-controlled study or otherwise), it is important to follow patient-subjects who are at risk for relapse. Presumably, under current regulations for “vulnerable” subjects, IRBs should take such arrangements into account when evaluating research proposals. One regulatory option is to require investigators to explain how they propose to monitor subjects for symptom relapse in studies with a drug-free component that enroll decisionally impaired individuals with a history of psychiatric disorders.

### Should the National Bioethics Advisory Commission promulgate new regulations concerning the participation in research of those who are decisionally impaired, or should it rather offer guidance for potential subjects, their physicians, clinical investigators, institutional review boards, and other policymaking bodies?

The desirability of governmental regulation depends not only on the importance of the policy enunciated or the practices addressed, but also on the rules’ ultimate efficacy. Presumably, the least formal measures taken by governmental entities are the preferred ones, so long as those measures are consistent with achieving the important societal goals that have been identified. Many who are familiar with the current federal regulations concerning human subjects research complain that they are already unjustifiably complex and bureaucratic. Some of those engaged in research on conditions related to decisional impairment are fearful that further regulation affecting these populations will unnecessarily retard scientific progress and stigmatize individuals who may be suitable subjects.

But many others note that, in spite of the imperfections of the current regulations, the period since their enactment has been largely free of the sorts of large-scale controversies that helped give rise to them. It may also urged that the issues discussed in this working paper illustrate some of the shortcomings of the common rule. The commission will need to determine whether issues concerning the decisionally impaired in research are of such a magnitude that new regulations are required, or whether some or all of the reforms it may determine are indicated could be advanced through another mechanism, such as a statement of recommendations for relevant parties.

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\(^9\) There are related suggestions. See Dresser, pp. 26–27.