

Research Consent for Cognitively Impaired Adults

Recommendations for Institutional Review Boards and Investigators

Alzheimer's Association

Abstract: Adults with cognitive impairment are considered a vulnerable population. The conditions associated with cognitive impairment, such as dementia and delirium, cause great suffering to affected patients and their families. Improving clinical care for these conditions depends on research involving cognitively impaired participants. Cognitive impairment is at times associated with partial or full impairment of the capacity to consent to research. This both limits the ability of the individual to consent personally to research participation, and also increases pressure upon Institutional Review Boards (IRBs) and investigators to place additional safeguards for the appropriate participation of cognitively impaired individuals in research. While the ethical and legal principles permitting and safeguarding the participation of cognitively impaired persons in research are generally agreed upon, there are no specific methods that operationalize these principles in a language that can be used by IRBs and researchers to guide their day-to-day work in this area. This document contains recommendations that IRBs and investigators can use to operationalize the informed consent process for individuals with cognitive impairment. In situations in which IRBs might not have specific policies in this area, this guideline may also serve as the foundation for such policies. The recommendations discuss when to consider that cognitively impaired participants might be involved in a research project, the use of screening for cognitive impairment, the conduct of assessments evaluating capacity to consent to research, situations in

which proxies might consent for research participation in the place of cognitively impaired participants, how to go about identifying appropriate proxies, and how to deal with the loss of consent capacity in the course of a research project.

Key Words: cognitive impairment, dementia, consent for research

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Research involving adults with cognitive impairment is most often discussed in terms of vulnerable populations and the need for appropriate protections for potential subjects. The conditions that are associated with cognitive impairment cause great suffering to affected patients and their families. Improving clinical care for these conditions depends on research involving cognitively impaired participants, research in which patients and families frequently say they are eager to participate, even if it is only in the hopes of benefiting others similarly affected in the future.

The participation of cognitively impaired adults in research is intended to study conditions whose main manifestation is cognitive impairment, such as dementia or delirium, or individuals who are at high risk for being cognitively impaired, such as intensive care unit patients, brain-injured patients, or the very old. Cognitive impairment is at times associated with partial or full impairment of the capacity to consent to research. This fact poses two problems. On the one hand, it limits the ability of the individual to consent personally to research participation; on the other hand, it properly increases pressure upon Institutional Review Boards (IRBs) and investigators to protect human subjects in research by putting into place additional safeguards for the appropriate participation of cognitively impaired individuals in research.

The ethical and legal principles involved in permitting and safeguarding the participation of cognitively impaired persons in research have been articulated elsewhere.^{1,2} However, while the principles are generally agreed upon, there are no specific methods that operationalize these principles in a language that can be used by IRBs and researchers to guide their day-to-day work in this area. This fact was recognized by a meeting convened by the National Institutes of Mental Health on July 1, 2002 “Proxy and Surrogate Consent in

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This document has been reviewed and approved by the Alzheimer's Association National Board of Directors. It was drafted by the Medical and Scientific Advisory Board of the Greater Maryland Chapter, in collaboration with the Maryland Office of the Attorney General, and was reviewed and approved by the Alzheimer's Association Ethics Advisory Panel and Medical and Scientific Advisory Council.

Members of the Maryland Board were as follows: Constantine G. Lyketsos, MD, MHS (Chair), Jason Brandt, PhD, Paul Fishman, MD, PhD, Michael Gloth, MD, Vassilis Koliatsos, MD, David Loreck, MD, Marsden McGuire, MD, Peter V. Rabins, MD, MPH, Debra Wertheimer, MD. Jack Schwartz, JD and Anand Das, MPA represented the Maryland Office of the Attorney General. Greg Sachs, MD (Chair, Alzheimer's Association Ethics Advisory Panel), Marilyn Albert, PhD (Chair, Alzheimer's Association Medical and Scientific Advisory Council), Stephen McConnell, PhD, and William Thies, PhD represented the Alzheimer's Association National Office.

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Geriatric Neuropsychiatric Research: Informing the Debate,” and it has recently been reiterated in an important paper by Karlawish.²

The document that follows is an effort to fill this void. It is a guideline that IRBs and investigators can use to operationalize the informed consent process for individuals with cognitive impairment. In situations in which IRBs might not have specific policies in this area, this guideline may also serve as the foundation for such policies. The development of this document was spurred by the National Institutes of Mental Health meeting mentioned above. It was developed by the Medical and Scientific Advisory Board (the Board) of the Greater Maryland Chapter of the Alzheimer's Association.

The Board is a group of clinicians, researchers, and basic scientists in the Baltimore area from two major academic institutions, the Johns Hopkins University, and the University of Maryland at Baltimore, and from other local hospitals and healthcare organizations. Several disciplines are represented, including psychiatry, psychology, geriatric medicine, neuroscience, and medical ethics. In developing the document, the Board worked closely with the Office of the Attorney General of the State of Maryland and with the IRBs at Johns Hopkins, the University of Maryland, and the National Institutes of Health Clinical Center, all of which largely practice what is recommended in this guideline. Feedback was provided from a wide range of experts and clinicians locally and nationally.

The Board hopes that this document will serve as a basis for development of widely accepted specific practices regarding the involvement of cognitively impaired persons in research. Although this document may be imperfect, it is a good start that fills a critical gap in this area and may be used as a basis for further debate and refinement.

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Research Consent for Cognitively Impaired Adults

Recommendations for Institutional Review Boards (IRBs) and Investigators

1. OVERVIEW

Individuals with cognitive impairment are considered a vulnerable population. In this document, the term “cognitive impairment” refers to dementia, delirium, or more focal cognitive syndromes as defined in the DSM-IV.¹ Hence, research involving these individuals requires special care in design, review, and actual conduct. The purpose of these recommendations is to assist investigators and IRBs in identifying key considerations for research involving cognitively impaired persons. Several basic points should be kept in mind.

- 1) Cognitive impairment is *not* always associated with the lack of capacity for informed consent to research.² Exclusion from research of otherwise eligible persons with cognitive impairment for that reason alone, whether or not they lack the capacity to consent to research, is discriminatory and violates the ethical principle of justice.
- 2) Individuals who cannot themselves consent to participate in research due to cognitive impairment may be enrolled in research projects if the following three conditions are all met:
 - a. The research offers a reasonable prospect of a direct health-related benefit³ to the individual; if there is *no* reasonable prospect of a direct health-related benefit to the individual, then the research must pose no more than a minor increment above minimal risk, as determined by the IRB, and is likely to yield generalizable knowledge about the participant's disorder or condition.
 - b. Informed consent for research is provided by someone who, under state or federal law, has the legal authority to make such decisions for the patient.⁴ If other persons having close relationships with the individual with cognitive impairment are readily available, it is ethically appropriate for them to be consulted and to provide surrogate consent regarding the research participation.

¹American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. Washington, DC: American Psychiatric Association, 1994.

²Capacity to consent to research is defined as the ability to comprehend a research protocol, the meaning of personal participation in this protocol, including risks and benefits, as well as the ability to make and communicate a choice about participation. See also Section 3.2.

³A health-related benefit might include a quality of life improvement.

⁴In federal regulations related to research, this person is designated the “legally authorized representative.”

- c. And the individual with cognitive impairment assents if capable to participation, or does not dissent.
- 3) Enrollment into research of a cognitively impaired individual who is unable to give consent generally should not occur if the research presents greater than a minor increment over minimal risk and *does not* offer a reasonable prospect of a health-related benefit directly resulting from the research procedures. Investigators and IRBs should pay close attention to identifying and minimizing the risks of the research that are not justified by potential benefits to the participants. For example, a clinical trial that compares two medications may include multiple blood draws that are not clearly indicated for the benefit of the participant but are clearly indicated for assuring that the research gathers generalizable knowledge. The greater the risks of research procedures that are not justified by potential benefits to the participants, the more ethically challenging it is to enroll a noncapable participant in the research. In general, an IRB should assure that risks that are not justified by potential benefits to the subjects are no more than a minor increment over minimal risk, and that they are justified by the importance of the knowledge to be gained from the research. When assessing whether a risk is minimal (or a minor increment above minimal), the IRB should use the definitions supplied in the Common Rule.⁵ One exception to this general rule may be made if:
- the condition causing cognitive impairment is the object of study, so that the research could not otherwise be carried out without the involvement of individuals unable to consent; *and*
 - the individual has given a research advance directive that authorizes a proxy to provide consent for enrollment in research of this kind.

2. AT-RISK POPULATIONS

When applying for IRB approval, all investigators should consider the risk of clinically significant cognitive impairment among potential participants eligible for their study. An investigator who is trying to determine whether the study population is at risk for incapacity related to cognitive impairment might ask a clinician experienced in the care of this population (if the investigator is not), “In this population of patients, do you typically look to a family member or someone else to make clinical decisions for or along with the patient, because of impairments in the patient’s cognition?”

IRBs should include in their application forms a “check-off box” in the section on “vulnerable populations” where investigators are asked to address this issue. The issue should also be addressed in the special section of the protocol as well

using the format of this guideline. Certain populations that are a target of clinical investigation have been reported in the literature to have high rates of cognitive impairment. By way of example, these include patients with Alzheimer disease and related disorders, brain disease, patients with certain psychiatric conditions, hospitalized patients with congestive heart failure, patients with AIDS, acutely ill emergency room patients, intensive care patients, nursing home residents, assisted living residents, and individuals of very advanced age.

3. ASSESSMENT

3.1. Screening of At-Risk Populations for Cognitive Impairment

When research involves individuals at risk for clinically significant cognitive impairment, investigators should consider whether to specify a screening procedure in their protocols and, if they decide *not* to do so, they must justify this decision to the IRB. In general, screening for cognitive impairment reduces participant burden, as it allows investigators to identify individuals who have significant cognitive impairment and who may be unable to consent to the research, thus allowing better targeting of in-depth capacity assessments. Further, screening enhances the quality of the research project as it allows investigators to identify individuals who might be poorly compliant because of cognitive impairment. Screening for cognitive impairment should not be confused with screening for incapacity to consent to research. Whether or not to use a screening procedure in a given research study, and what the procedure and its “cutoffs” should be, is up to the investigator to develop with the approval of the IRB. Screening should not be confused with capacity assessment (see Section 3.2).

3.2. Assessing Capacity for Consent to a Specific Research Project

The protocol should describe, to the IRB’s satisfaction, how the investigator would conduct a capacity assessment and the nature of the assessment (ie, whether a formal assessment instrument will be used). This should include discussion of how consent to conduct the capacity assessment will be obtained. The rigor of the capacity assessment process should relate to the risks presented by the research. For minimal risk research, informal capacity assessment by qualified members of the research team, as defined by the IRB, would ordinarily suffice. For higher risk research, consideration might be given to the use of an independent (ie, not part of the research team), qualified professional, or the use of a capacity assessment instrument, to assess formally the potential subject’s capacity to consent.

At a minimum, the investigator, or IRB-approved designee, must review and discuss the research project, and the consent document, with the potential participant and decide whether he or she is able to

⁵The Common Rule refers to the Code of Federal Regulations governing Human Subjects research.

- (1) understand the nature of the research and of his or her participation;
- (2) appreciate the consequences of the participation, including personal consequences;
- (3) show the ability to consider alternatives, including the option not to participate; and
- (4) show the ability to make a reasoned choice.

This discussion should include oral and written descriptions of research, its significance, and the subject's options. Both for persons with dementia, because of health literacy concerns, and because persons with dementia may come from culturally and linguistically disadvantaged diverse backgrounds, the vocabulary and syntax should be simple and avoid medical jargon. In the consent document, the type font and size should be easily readable by older subjects. Key elements of the discussion (ie, purpose, procedures, risks, benefits, alternatives) should be presented sequentially, to help the potential subject understand and deal individually with each element.

4. ACTION IF CAPACITY IS IMPAIRED

4.1. Permission and Assent

If a potential participant is determined to lack capacity to consent to the specific research project, the investigator ordinarily must obtain permission from a proxy (see Section 4.2), with both actual capacity and legal authority to give it, and assent from the participant. Permission means the proxy's informed consent to the proposed participation. Assent is defined in Section 4.4. Permission or assent need not be obtained if an IRB, in accordance with ethical and regulatory standards for minimal risk research, has waived the requirement, for example, in chart review studies.

4.2. Identifying a Proxy

Persons with cognitive impairments often must rely on proxy decision-makers, usually a spouse, child, caregiver, or other trusted individual, for decisions of everyday life or medical care. Research participation is not an exception to this necessary and beneficial dependence on others. Where possible, permission should be sought from someone who, under state law, has the right to be the participant's legally authorized representative. While the exact order may vary from state to state, the following priority ranking is consistent with most state laws about proxy decision making for clinical care and might also be used in the research setting. If a potential proxy is not available at a given priority level, the investigator should seek to identify a proxy from the next level down:

- (1) legal guardian;
- (2) proxy (research agent) named in the participant's research-specific advance directive;
- (3) proxy (health care agent) named in an advance directive or durable power of attorney for health care;

- (4) family member or other surrogate identified by the state law on health care decisions. *Example:* In Maryland, spouse, adult children, parents, adult siblings, other relative, or friend.

4.3. Permission From the Proxy

Permission for participation in a research project should be consistent with the proxy's legally defined role and with the types of research consistent with surrogate consent as outlined in Section 1 of this document. *Example:* A guardian may give permission only if this is allowed by the court, either in the order appointing the guardian or a special order. *Example:* A healthcare surrogate may give permission if participation in the research offers a reasonable prospect of direct medical benefit, even if the research also includes procedures unrelated to potential benefits. Custom may also recognize proxy permission for participation in some research with no expected benefits.

Disagreements among proxies with equal priority should be resolved informally, whenever possible, and, if necessary, through more formal means as identified in law or policy. *Example:* In Maryland, disagreements among surrogates are to be referred to a facility's ethics committee.

The informed consent form should include instruction to the proxy to base his or her decisions on the participant's expressed wishes or, in the absence of expressed wishes, what the participant would have desired in light of his or her prognosis, values, and beliefs. If the participant's wishes are unknown and cannot be inferred, the decision should be based on the participant's best interests. The instructions should also include a statement that the proxy should consider how much the subject would have granted the proxy leeway or freedom to choose for the subject.

4.4. Assent From the Participant

If the participant is capable of providing affirmative agreement to participate, the participant should be informed in the presence of the proxy that he or she is about to be enrolled in a research study. The procedures, risks, benefits, and alternatives involved should be explained in a simple fashion. The participant should then be asked if he or she agrees to be in the research, and the response should be recorded.

If the participant is incapable of providing affirmative agreement to participate, then assent (or dissent) should be judged behaviorally based on cooperativeness with study procedures (eg, does he or she refuse to have blood drawn, take pills, or lie still for an imaging study?). Dissent for any study-related procedure should be respected, and consistent dissent may be a basis for removal from the research study.

If at any time after the participant is enrolled in the study through proxy permission, the participant regains the capacity

to provide informed consent, the investigator must obtain the participant's informed consent for continued participation in the research.

5. CAPACITY IMPAIRMENT IN THE COURSE OF RESEARCH

5.1. Risk of Loss of Capacity

If at the time of enrollment a participant who has the capacity to consent is known to be at risk for loss of that capacity due to cognitive impairment, the investigator must, to the IRB's satisfaction:

- (1) show a plan for reassessment of cognitive capacity and capacity to consent if there is a clinically significant change in cognitive function that could reasonably change the subject's current status as either capable or not capable;
- (2) offer the participant the opportunity to appoint a proxy (research agent, see Section 4.2) to make ongoing consent decisions regarding the research project should the participant's capacity to consent become impaired during the course of the project; and
- (3) when applicable, ask the participant to give guidance to her or his proxy about the conditions under which she or he would and would not want to participate in the present and future protocols, in the event of loss of capacity.

5.2. Apparent Loss of Capacity

If a participant who gave consent personally appears to lose capacity during the study, the investigator must:

- (1) formally assess the participant's capacity to consent (see Section 3.2); and
- (2) if capacity is impaired, obtain permission for further research participation from a proxy (see Section 4.2).

5.3. Intermittent Capacity

In cases of intermittent capacity, periodic reevaluations are indicated. The proxy need not be called on as long as, in the judgment of the investigator, all decisions can be safely and appropriately delayed until the participant's decisional capacity returns.

6. DOCUMENTATION

Proper documentation of the process above must be kept in the participant's study records. Reassessment of consent and assent and associated documentation should occur on a regular basis during the course of the study, using a time schedule set by the investigator with the IRB's approval. Documentation is to include assessment of cognitive capacity, assessment of capacity to consent, proxy identification and permission (if applicable), and assent.

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