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Guidance on Human Subjects Research
with Decisionally Impaired Adults

Introduction

Human subjects research involving persons who have impaired decision-making capacity is an important endeavor for advancing the treatment of such persons. Cognitive disorders result in significant morbidity and carefully designed, ethically conducted studies related to the etiology, pathogenesis, symptom management, and treatments of these disorders are an important part of Oregon Health & Science University's mission. The purpose of this document is to provide guidance regarding how human subjects research at Oregon Health & Science University (OHSU) must be conducted with decisionally impaired (DI) adults. Specific research protections for children are already articulated in 45CFR46, Subpart D, and this guidance does not apply to subjects already protected by those standards. This document articulates standards for authorized representatives for research participation (ARRs), and describes the responsibilities of investigators conducting research with DI populations. The OHSU Institutional Review Board (IRB) is responsible for assessing the scientific merit and the potential benefits and risks of all human subjects research and will review protocols involving DI adults with these guidelines in mind. OHSU investigators proposing to include DI adults are responsible for providing the IRB with information outlined in this document and for the ethical conduct of research.

Throughout this document, limited decision-making capacity or decisional impairment will be used to refer to adults who may have one or more of four types of limitations as defined by the National Bioethics Advisory Commission (NBAC). These include:

1. **Fluctuating decisional impairment** - e.g. schizophrenia, bipolar disorders, depressive disorders, and delirium;
2. **Progressive decisional impairment** - e.g. persons for whom decision-making deficits can be predicted due to the course of their disease or the nature of their treatment. Although these individuals may be decisionally capable in the early stages of the disease progression, such as in Alzheimer's disease or other forms of dementia, they have prospective incapacity;
3. **Limited decisional impairment** - e.g. persons with limited capacity but who are still able to object or assent to research, as in the case of stroke, more advanced Alzheimer's disease, or developmental disability resulting in cognitive impairment; and
4. **Complete decisional impairment** - e.g. persons who have lost the ability to make decisions that involve significant reflection, as in the later stages of Alzheimer's disease or unconsciousness due to trauma.

The mere presence of a cognitive impairment should not lead to a presumption that a person is incapable of decision-making and providing informed consent to participate in research. Yet in some cases the decision-making capacity necessary to give a valid informed consent is impaired. The use of surrogate consent may be an appropriate alternative to support the subject's research participation.

Even with this in mind, researchers working with decisionally impaired adults must always seek subject assent when the DI subject is sentient and able to express assent or dissent. The following guidance describes how to obtain valid informed consent from a surrogate decision maker for an adult subject who is cognitively impaired and lacks decisional capacity.

Guidance for Human Subjects Research Involving Decisionally Impaired Adults

Guidance 1: Defining Risks and Benefits

The investigator and IRB must carefully consider the definition of minimal risk for the proposed subject population. As defined in 45 CFR 46.102(i), minimal risk means that the probability and magnitude of harm(s) or discomfort(s) anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life, during the performance of routine care, or during the course of routine physical or psychological examinations. Because the risks encountered in the daily life or during the course of routine care or physical or psychological examination may be different for a DI individual, it is appropriate to index the risk of a particular research project for the DI population being studied. Indexing risk may mean that harms that would be considered minimal risk for subjects with no decisional impairment may be more than minimal for a DI subject, perhaps due to the distress, confusion, or disruption that may be caused. Conversely, risks that are considered more than minimal for a subject with no decisional impairment may be considered minimal for a DI person, perhaps due to the routine medical, social, or environmental risks that are commonplace in that person's life.

The investigator and IRB must also consider potential benefits of the research with DI adults in light of the potential risks. Potential research benefits may be direct (having therapeutic value or likely to ameliorate a subject's current condition), psychosocial (having intrinsic or altruistic value to the subject because of the benefit to science or society), or kinship (having intrinsic or altruistic value to the subject because of the benefit in addressing a condition of a subject's relative). Secondary benefits due to increased attention and/or social interaction that may occur as a result of research participation may also be considered.

When reviewing protocols involving DI subjects, the OHSU IRB will involve individuals (who may be voting members of the IRB or internal or external ad hoc consultants) familiar with the nature of cognitive disorders and concerns related to the population being studied. Due to the complexities involved with the approval of protocols involving DI subjects, only some minimal risk studies will qualify for expedited review (as detailed in 45 CFR 46.110).

Guidance 2: Defining and Assessing Capacity

Whenever investigators propose to engage in research with DI subjects, the investigators shall include in the IRB application a protocol-specific plan for the assessment of the decision-making capacity of the subjects. This may provide for assessment of capacity at various points in the recruitment and consent process, depending on the circumstances and the subject population.

The IRB does not prescribe standardized measures for PIs to use when assessing a prospective subject's capacity. However, such persons may be assessed based upon their abilities to understand the following concepts:

- Nature of the research and the information relevant to his/her participation;

- Consequences of participation for the subject's own situation, especially concerning the subject's health condition;
- The difference between research and clinical care (avoiding therapeutic misconception);
- Available alternatives to participation and their consequences;
- Potential risks involved in the study;
- Procedures to follow if he/she experience discomfort or wishes to withdraw; and
- The voluntary nature of participation.

The capacity to understand all of these concepts may not be necessary in order to self-consent to participate in a particular research protocol. However, greater capacity will be required for higher-risk protocols, as determined by the IRB. Cognitive testing may be required by the IRB to inform capacity assessment, but will not always be required.

Whenever possible, investigators will obtain valid informed consent directly from the subject, but must always seek assent directly from the subject. When appropriate, the consent process may be altered to allow for non-verbal or other alternative consent methods. Proposed alterations to the consent process must be submitted for IRB approval. Investigators who wish to obtain consent from an Authorized Research Representative (ARR) must submit an application to the IRB that details a protocol-specific plan for assessing the decision-making capacity of subjects and a plan for determining the appropriate ARR (See Guidance 3).

If the investigator determines that the subject lacks decision-making capacity, the investigator shall inform the subject of the investigator's intent to seek consent from an ARR and shall document this discussion in the research file. As a part of this discussion, investigators should also remind subjects that their wishes will always be respected and that involvement of an ARR is to serve as a protection of their interests. If the subject is unconscious, the investigator shall document that condition in the research file and discussion regarding intent to seek ARR consent is waived. If the subject expresses resistance or dissent to participation or to the use of ARR consent, the subject shall be excluded from the research study.

In cases of fluctuating or progressive decisional impairment, a subject's capacity to consent may change throughout the study. In these cases, the plan for assessing capacity should include repeat assessments at appropriate intervals. When a subject regains capacity to consent, the subject shall have the opportunity to provide informed consent for his or her own continued participation. Likewise, when a subject loses capacity, consent for the subject's continued participation shall be obtained from an ARR. When it is anticipated that subjects may lose capacity to consent during the course of the research, the IRB recommends involving an individual at the beginning of the study who may later serve as an ARR.

For studies determined to involve more than minimal risk the IRB may require that a clinician not associated with the research protocol but who has expertise in that research area evaluate the subject's level of decision-making capacity. Other safeguards may also be required by the IRB, such as independent consent monitors and medically responsible clinicians (see Guidance 5). In this case, the IRB will confer with the investigator and study team early in the review process.

Guidance 3: Standards for Authorized Representative for Research

The IRB will make study-specific, risk-based decisions to allow subjects with mild to moderate decisional impairment to enter studies with subject assent and Authorized Representative for Research (ARR) consent. In some cases, it may be permissible to obtain consent for subjects through the person with medical decision-making ability or a facility administrator.

Persons who may serve as an ARR for a DI adult must meet the following standards:

- A.** The subject may designate an ARR when the subject has adequate decision-making capacity to do so, or an ARR may be identified by the investigator in the same manner that he or she would determine a decision maker for health care treatment. The following list of possible ARRs is not proscriptive; nonetheless, the examples are listed in order of preference. However, if two or more possible ARRs disagree about a potential DI subject's values or wishes, the investigator may not enroll or continue research with that subject unless the dispute is resolved to the satisfaction of the investigator and the multiple ARRs.
- A legal guardian or surrogate of the patient who is appointed by an advance directive to make health care decisions;
 - The patient's spouse;
 - An adult designated by the other listed in this subsection who can be located, so long as no person listed in the subsection objects to the designation;
 - A majority of the adult children of the patient who can be located;
 - Either parent of the patient;
 - A majority of the adult siblings of the patient who can be located with reasonable effort;
 - Any adult friend or relative;
 - The attending physician in consultation with the Patient Advocate.

The OHSU Research Integrity Office has chosen to use ARR to refer to a surrogate decision maker to avoid the suggestion that authority to consent or refuse consent to research participation for DI persons must be court determined. However, if a DI adult does have a Legally Authorized Representative (LAR) or other court-appointed legal guardian, this person is acknowledged to have decision-making ability for research participation, as well as for health care treatment. A LAR may be the subject's agent as designated by an advance health care directive per ORS § 127 or the court-appointed guardian of the subject. If the LAR is unable to fulfill the responsibilities of a decision maker in research (see the following responsibilities), he or she may designate someone else (friend or relative) to serve as a proxy. If the LAR and the ARR are two different people, the LAR takes precedence. Any person designated as a surrogate decision maker for research must meet the standards for ARRs set forth in paragraphs B through E below.

A friend with no blood or legal relationship to the subject may serve as the subject's ARR when designated as such by the non-impaired subject, or if no relative or LAR is available, provided that he/she meets the standards for ARRs set forth in this guidance.

Designation of an ARR may occur by court-appointment, subject consent or assent, or other means. In any case, the investigator should document the name, address, and contact information of the ARR, as well as the date of designation and relationship to the subject. If the designated ARR becomes unavailable (due to death, relocation, or other circumstances), the

subject (if possible) should designate a new ARR. If this is not possible, the researcher should identify a new ARR by following the standards of this guidance and exercising due diligence to contact the appropriate family members (e.g., next of kin) or others (e.g., emergency contacts), while recognizing that other processes may be necessary in emergency or urgent situations. ARR determination and designation should be documented in the subject's research record or other official research documentation.

When an ARR is making a decision to enroll a DI adult into a research study, the ARR's decision must reflect the subject's prior values insofar as they are known or can be determined. In meeting this standard, the following may be considered: prospective authorization (e.g. an advance directive for research participation) related to a specific study or category of research; statements made by the subject when he/she had no decisional impairment about categories of research or about risks related to research; previous research participation by the subject; and testimony from others who are well acquainted with the subject and likely to be familiar with his/her values including relatives, friends, or health care providers. The greater the risks posed by the research protocol under consideration, the more stringent will be the requirement for prospective authorization and the more specific (to a study or category of research) the subject's prospective authorization must be to entitle the ARR to permit enrollment. If the subject's values are not known, the ARR should act in the subject's best interest given the anticipated risks and benefits of participation in the research.

- B.** An ARR must be willing and able to monitor the subject's recruitment, enrollment, participation, and termination/withdrawal from the research. This should not be interpreted as a requirement for ARRs to be physically present during all phases or procedures in a particular protocol. For example, in cases where the physical presence of the ARR during research interventions could potentially affect the outcomes, the PI has the discretion to exclude the ARR from that portion of the research. This intent must be clearly stated in the research consent/authorization form. The ARR's presence during the consent process may be required by the IRB depending on the nature of the study and level of risk to the subject. If a subject with cognitive impairment can participate in the informed consent process when it is presented in simple language or alternate formats, the ARR should act as a witness during this process.
- C.** An ARR must clearly understand the distinction between therapy and research and any therapeutic misconception must be addressed. Investigators are responsible for ensuring and documenting this understanding.
- D.** An ARR may not be part of the research team.
- E.** An ARR must comply with all applicable Oregon and federal law.

Guidance 4: Information for Subjects

Once a subject has been determined to have decisional impairment and an ARR has been identified, an investigator shall obtain the assent of any DI adult capable of giving assent prior to involving the individual in research. An investigator may not involve an individual in any research procedure if the individual dissents. Unless the subject is unconscious, prior to participation in research, an investigator shall inform the subject of the following, in a manner appropriate to the subject's capacity for understanding:

- A. The fact that he/she is being asked to participate in research;
- B. That he/she has been determined to lack capacity to self-consent to research participation;
- C. The name of the ARR who has been identified, and that he or she has granted permission for the subject's participation in the research and will monitor the subject's research participation;
- D. Information about the purpose, design, procedures, risks and benefits, and potential personal impacts of the research study; and
- E. That the subject may choose freely to undergo these procedures or may withdraw from participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Guidance 5: Research with More than Minimal Risk and No Known/Doubtful Direct Benefit

The National Commission for the Protection of Human Subjects recommended that a minor increase over minimal risk may be permitted in research involving those institutionalized as mentally disabled, but only where the research is designed to evaluate an intervention of foreseeable benefit to their care. The National Institutes of Health recognizes the potential value of research involving greater than minimal risk with no or doubtful benefit to the subject, but requires local IRBs to scrutinize and monitor such protocols according to the potential risks posed to the subject. Risk determinations will be reviewed by the IRB on a case-by-case basis and indexed to the subject population. Greater risks require more intense oversight.

Research in this category may require additional safeguards. For instance, in some circumstances the IRB may require independent capacity assessment (evaluation by a clinician outside the research team); independent consent monitors (oversight of the consent process by IRB staff), and/or the use of medically responsible clinicians (independent providers involved in the subject's medical care to contribute oversight). Prior to instituting such requirements, the IRB will obtain assistance from expert consultants in this type of research and will confer with the investigator and the study team. PI's and staff who perform research with DI subjects and are concerned about the possibility of the latter requirements are encouraged to consult with IRB staff early in the protocol design for assistance and advice.

Authority and Resources

National Institutes of Health, "[Research Involving Individuals with Questionable Capacity to Consent: Points to Consider](#)" (November 2009)

National Bioethics Advisory Commission (NBAC), "[Research Involving Persons with Mental Disorders That May Affect Decision-Making Capacity](#)" (December 1998)

OHRP Guidance: [Informed Consent FAQs](#)