Tip Sheet 26: Reviewing Research Involving Adult Participants with Diminished Functional Abilities Related to Capacity to Consent

Related Accreditation Elements: II.4.A. and II.4.B.

The Department of Health and Human Services (DHHS) regulations do not provide specific requirements for research involving individuals with diminished functional abilities or who lack the capacity to consent. However, several provisions might be relevant and should be considered by IRBs reviewing research for which DHHS regulations are applicable. Section 111 calls for "additional safeguards" for research involving "mentally disabled persons." Section 102 provides a broad definition of "legally authorized representative" (LAR), and sections 16 and 17 outline precise requirements for the consent process, including when consent is provided by an LAR.

The Department of Veterans Affairs (VA) and Department of Defense (DoD) have requirements pertaining to research involving participants with diminished functional abilities. VHA Handbook 1200.05 provides requirements for research involving persons who lack decision-making capacity especially regarding the assessment of prospective participants' ability to consent to enroll in a study. For research subject to DoD regulations, IRB members should consult DoD Instruction 3216.02, which gives criteria for approving research involving participants requiring consent by an LAR.

Internationally, the ICH GCP (E6) guideline defines those individuals who are incapable of giving consent as vulnerable, and outlines procedures for the consent process, including when consent is provided by a legally acceptable representative of the participant. In particular, ICH-GCP (E6) offers criteria for determining when research involving participants requiring consent by legally acceptable representatives may be approved.

The recommendations in this Tip Sheet should be applied in the legal jurisdiction in which researchers will conduct the research. IRBs and researchers should familiarize themselves with any regulations regarding research involving adult participants with diminished functional abilities or no capacity to consent that are applicable to their institution, and consult legal counsel when necessary.

Recommended Content:

I. Application of these recommendations

I.A. Capacity to consent

Prospective adult participants in most research studies are capable of consenting to enroll and participate. However, conducting research involving adult participants who cannot consent to enroll because of a physical or psychological condition is vital to expanding knowledge that ultimately improves the lives of many individuals.

Whether a prospective research participant has the capacity to consent is a *legal* distinction; capacity to consent is defined as the ability to provide *legally effective* consent to enroll in a research study. Researchers and IRB members must familiarize themselves with any applicable legal requirements regarding the determination of competence to consent to enroll in a research study.

This Tip Sheet first discusses research involving adult participants who have the legal capacity to consent but who also have diminished functional abilities (section II.B), and then discusses research involving adult participants with no capacity to consent (part IV). The purpose of this Tip Sheet is to encourage such research by clarifying the ethical issues organizations, IRBs, and researchers should consider when prospective adult participants have the legal capacity to provide consent but also have diminished functional abilities or when prospective adult participants cannot provide legally effective consent.

I.B. Identifying research involving adult participants with diminished functional abilities or no capacity to consent

Research involving participants with diminished functional abilities should only be approved when it cannot reasonably be conducted without their participation. Their participation in research should never be justified based simply on their availability or the convenience for the researcher. **When reviewing research involving participants with diminished functional abilities, the convened IRB or reviewer using the expedited procedure should consider whether the population targeted for recruitment represents the population with the least degree of impairment to functional abilities compatible with the aims of the study.**

While many types of personal capabilities and skills generally fall under the label “functional abilities,” this Tip Sheet refers primarily to cognitive functions (such as attention, comprehension, Memory, and intellect), communication abilities, and other abilities that affect prospective participants’ ability to make and express decisions regarding participation in research. This Tip Sheet is not intended to address research involving participants who have impairments to functional abilities that will not affect their capacity to consent.

Functional abilities exist along a continuum, and prospective adult participants can have greater or lesser ability because of various physical and psychological conditions. The extent and nature of impairment will vary based on the nature of the condition and on factors specific to individual participants. However, **prospective adult participants with impairments to functional abilities are presumed to be capable of providing consent to enroll and participate in a research study unless there is substantial evidence that they are not capable.** Researchers and IRB members **should not** consider the mere presence of a condition that leads to diminished functional abilities as indicative of a lack of capacity to consent.

When the participant recruitment plan includes individuals who are likely to have severe impairment to their functional abilities, the capacity of such prospective participants to consent to enroll in the study in question should be assessed on an individual basis prior to their enrollment. At initial review, IRB members might consider whether appropriate procedures for assessing prospective participants' capacity to consent to enroll in the study, if necessary, have been described in the protocol. Researchers should seek the consent of participants who are determined to be capable of providing it.

The IRB application should include questions asking researchers whether they plan to enroll adult participants who have a condition known to cause diminished functional abilities that affect capacity to consent. Researchers and IRB members should consider the recommendations provided in this Tip Sheet when the participant recruitment plan includes individuals who have a condition of a type and severity likely to lead to impairment to functional abilities to the extent that it might affect capacity to consent. These include, but are not limited to:

1. Acute medical conditions,
2. Psychiatric disorders,
3. Neurologic disorders,
4. Developmental disorders, and
5. Behavioral disorders.

If researchers or IRB members are uncertain as to whether a given condition might be associated with diminished functional abilities, they should consult a health professional who regularly interacts with individuals with the relevant condition.

Finally, IRB members and researchers should be aware that some conditions might cause functional abilities to fluctuate over time, or to decrease gradually over the course of the study. When the participant recruitment plan includes individuals likely to experience fluctuating functional abilities or functional abilities that will decrease over time, IRB members might consider whether provisions should be included for the event that participants' capacity to consent changes over the course of the study, including whether:

1. procedures have been described for reevaluating participants' capacity to consent over the course of the study;

2. such participants are asked to designate an individual to serve as an LAR, if necessary;
3. individuals identified as potential LARs are involved in the consent process;
4. such participants are asked to document their wishes regarding participation in the study.

Additionally, for studies involving adult participants likely to experience fluctuating functional abilities, IRB members might consider whether:

1. the consent process plans to avoid, if feasible, periods during which prospective participants are likely to experience greater than normal impairment to functional abilities (for example, due to changes in participants' medication schedules, acute intoxication, or episodic increases in the severity of the symptoms associated with their conditions);
2. procedures are described for obtaining the consent of any participant who is initially judged incapable of providing consent, but regains the capacity to consent.

I.C. Composition of the IRB

Any IRB that regularly reviews research involving adult participants who may have diminished functional abilities should include, as a permanent member, at least one member who is knowledgeable about the conditions that cause, and their effects on, diminished functional abilities. In the event that an IRB is asked to review research involving participants who have a condition known to cause diminished functional abilities and that IRB does not regularly review research involving such participants, the IRB should identify an expert to serve as an ad hoc consultant. The expert reviewer should be present at the meeting of the convened IRB when research involving adult participants who have the relevant condition is reviewed and present his or her review either orally or in writing, except when the research does not involve interaction with the participants (e.g., use of existing data in a study).

II. Review of research involving participants with diminished functional abilities

II.A. Evaluating risk in research involving adult participants with diminished functional abilities

When the convened IRB reviews research involving participants with diminished functional abilities, it must determine that the risks to participants are reasonable in relation to the importance of the knowledge that may reasonably be expected to result (See 45 CFR 46.111)

Research, unlike medical treatment, is intended to generate new or generalizable knowledge. Subjecting unimpaired participants to risks associated with IRB-approved research is ethically permissible when the participants decide that doing so is in their interests or in line with their values and provide consent. However, some participants with conditions leading to diminished functional abilities might be less likely to understand the purpose or voluntary nature of research, or to anticipate reasons against their participation than participants with unimpaired functional abilities.[1] This can make it difficult for them to determine whether participation in a given study is in line with their interests and values. For this reason, it might be ethically appropriate to limit risks to such participants

to a level below that which is permissible for unimpaired participants, or to include additional protections for such participants.

Certain unique considerations should occur when assessing the risks of participation in research by individuals with diminished functional abilities. IRB members should consider whether participants who have diminished functional abilities might be especially sensitive to levels of discomfort typically associated with minimal risk. For example, participants with some conditions might react more severely to pain associated with routine medical procedures than participants who are unimpaired.[2] They might also be particularly susceptible to certain types of social harm, such as harm resulting from stigmatization associated with their condition. In assessing risk, the convened IRB should consider whether any components of research involve risks that are greater for participants with diminished functional abilities than they would be for participants with unimpaired functional abilities. At continuing review, IRB members should consider whether existing protections and procedures for minimizing risks are adequate.

II.B. Points to consider when approving research involving adult participants with diminished functional abilities who can consent

In some studies involving adult participants with diminished functional abilities the participant recruitment plan might require that all participants are capable of providing consent, and exclude prospective participants who are not capable. These studies might still include participants who have a condition of a type and severity likely to lead to substantial impairments to their functional abilities to the extent that their capacity to consent must be assessed during the consent process. In addition to the criteria described in the standard procedures for review of research by the convened IRB, IRB members might consider whether studies involving greater than minimal risk to participants who have the legal capacity to consent but who also have diminished functional abilities should meet criteria such as the following:[3]

1. any experimental intervention has previously been tested on animals other than humans and on humans with unimpaired functional abilities (when either or both of these are appropriate);
2. any knowledge likely to be gained through the study will improve the understanding of the condition or disease or behavior affecting the participant population;
3. IRB members have considered whether any of the following should be included, based on the extent and nature of likely risks to participants:
    a. a written description of procedures for minimizing risk,
    b. documentation of the importance of knowledge to be obtained by answering the research question,
    c. appointment of one or more independent monitors to assist with various aspects of the study. [4] This might include:
        i. a participant advocate, such as a member of the target population or family member thereof, or an employee of an organization that advocates for the target population;

ii. an individual with expert knowledge of the relevant psychological or physical condition who will monitor the consent of participants;
iii. a health care professional to serve as a consultant to participants; or
iv. a safety and data monitoring committee.

d. a list of resources and referrals offered to participants to assist them in coping with any foreseeable harm;
e. a written rationale for the inclusion of participants with diminished functional abilities, submitted for review by the convened IRB;
f. procedures for obtaining the re-consent of participants when cognitive functional abilities fluctuate;
g. continuing review conducted more frequently than annually; and
h. a description of procedures for withdrawing participants or terminating the study, if necessary.

II.C. Financial compensation

In some instances it is appropriate for researchers to offer remuneration to participants with diminished functional abilities to compensate them for their time or for costs incurred through participation. When remuneration is to be offered to any individual other than the participant, the convened IRB should review and approve the amount offered and the mechanism by which it is to be distributed. For remuneration intended to displace costs associated with participation, researchers should be able to justify the amount and explain why recipients are likely to incur the costs for which they are compensated. For remuneration intended to compensate the participant for his or her time, researchers should only deliver monetary payments to the participant or to an individual who regularly manages the participant's finances, if he or she does not manage expenses on his or her own behalf.

III. Review of procedures for evaluating capacity to consent

Researchers and IRB members should familiarize themselves with the applicable laws regarding the legal determination of competence to consent to participate in research. However, when the participant recruitment plan includes individuals with a condition of a type and severity likely to cause impairment to functional abilities to an extent that participants are rendered incapable to consent, researchers should describe procedures for evaluating prospective participants' capacity to consent in the study and the provisions for enrolling them in the study to ensure that the study is ethically justifiable.

When assessing prospective participants' capacity to consent to enroll in a study, the relevant criteria concern their ability to understand information relevant to participation *in the particular study in question* and to make a decision about participation in *that study*, based on their considered values and interests. Assessments should not seek merely to give general accounts of prospective participants' ability to consent to participate in research.

Various approaches to assessing prospective participants' capacity to consent to enroll in a study are appropriate, depending on the nature of the research. **The assessment methodology should increase in rigor as the degree of risk associated with participation and extent of likely impairment to prospective participants' functional abilities increase.** One or more individuals with relevant expertise should be identified to evaluate prospective participants' capacity to consent and make an objective determination regarding the capacity to consent of each participant. In most instances, this will be a member of the research team, but for studies involving a high degree of risk to participants it might be necessary to engage an independent evaluator. Methods to assist with evaluators' determinations include:

1. conducting clinical interviews with prospective participants and asking them to describe aspects of the study;
2. using standard psychological and neuropsychological screening tests; and
3. utilizing a formal instrument for assessing capacity to consent in clinical research.

Examples of existing cognitive tests include the *Mini-mental State Evaluation* (MMSE) and the *Montreal Cognitive Assessment* (MoCa). Comprehensive capacity assessment instruments include the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) and the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC). When seeking to apply cognitive screening tests and competence assessments, researchers should consult scholarly reviews to ensure that the chosen test or instrument is effective and appropriate to the study. [5] Additionally, formal guidelines for conducting assessments include those given by VHA Handbook 1004.01 and the American Psychological Association *Guidelines for Assessing the Decision-Making Capacities of Potential Research Subjects with Cognitive Impairment*. Standard cognitive screens evaluate only the extent of impairment to prospective participants' cognitive abilities, whereas capacity assessments can be used to evaluate whether prospective participants are capable of exercising functional skills relevant to making a decision regarding participation in a study. **However, cognitive tests and competence assessment instruments alone cannot provide the basis of the evaluator's determination regarding a participant's capacity to consent, and should at most supplement or support the evaluator's expert judgment.**

IRB members should consider whether procedures for assessing capacity to consent provide reasonable assurances that the evaluator's judgments will be impartial when he or she is affiliated with the institution or research team, especially when participation is associated with greater than minimal risks. For some studies involving no greater than minimal risk, it might be appropriate to assess the decision-making ability of participants informally, without the use of a specified procedure. The effectiveness of procedures for assessing the capacity to consent of prospective participants should be considered at initial and continuing review.

When feasible, researchers should make efforts to support or enhance prospective participants' ability to consent. Some individuals who are not capable of consenting under routine consenting procedures might be capable when special measures are adopted. Such methods include:

1. designing a stepwise consent process, which involves a waiting period between each phase of the process: capacity assessment, initial presentation of information, and obtaining consent;
2. enhanced presentation of consent information during initial presentation and/or immediately prior to obtaining consent, including:
    a. repetition of information (especially misunderstood information),
    b. both oral and written presentation of information,
    c. multi-media presentation of information,
    d. interactive questioning, and
    e. written study summaries;
3. continuous dissemination of consent information throughout the course of the study; and
4. conducting the consent process in an environment in which the participant is comfortable.

IV. Review of research involving adult participants with no capacity to consent

IV.A. Points to consider when approving research involving adult participants with no capacity to consent

In addition to the criteria described in the standard procedures for review of research by the convened IRB, IRB members might consider whether studies involving greater than minimal risk to participants with no capacity to consent should meet criteria such as the following: [6]

1. any experimental intervention has previously been tested on animals other than humans and on humans with unimpaired functional abilities (when either or both of these are appropriate);
2. the risks to participants (including the risks of foregoing standard treatment) are not substantially greater than those associated with standard treatment (or no treatment, if none exists);
3. the knowledge likely to be gained through the study will improve the understanding of the condition, disease, or behavior affecting the participant population;
4. IRB members have considered whether any of the following should be included, based on the extent and nature of likely risks to participants:
    a. a written description of procedures for minimizing risk,
    b. documentation of the importance of knowledge to be obtained by answering the research question,
    c. appointment of one or more independent monitors to assist with various aspects of the study. [7] This might include:
        i. a participant advocate, such as a member of the target population or family member thereof, or an employee of an organization that advocates for the target population;
        ii. an individual with expert knowledge of the relevant psychological or physical condition who will monitor the consent of participants capable of providing it as well as the assent of participants incapable of consenting and the consent of their LARs;
        iii. a health care professional to serve as a consultant to participants and their LARs; or

iv. a safety and data monitoring committee.

d. a list of resources and referrals offered to participants to assist them in coping with any foreseeable harm;
e. a written rationale for the inclusion of participants with diminished functional abilities, submitted for review by the convened IRB;
f. procedures for obtaining the consent or re-consent of participants when cognitive functional abilities fluctuate;
g. continuing review conducted more frequently than annually; and
h. clearly outlined procedures for withdrawing participants or terminating the study, if necessary.

IV.B. Points to consider when reviewing procedures for obtaining consent by LARs of adult participants who are not capable of consenting

In some U.S. states and other countries, applicable law will determine who may consent on behalf of a prospective research participant. IRB members and researchers must familiarize themselves with the applicable laws regarding consent to research by an individual other than the prospective participant, and consult legal counsel when uncertainty exists regarding legal requirements. Because the extent of diminished functional abilities can vary, IRB members and researchers should be aware that some participants deemed incapable of providing consent might be capable of appointing a LAR, and should be encouraged to appoint one if they have not done so already. [8] For each participant who is determined not to be capable of providing consent or appointing an LAR, IRB members should ensure that consent is sought, consistent with applicable law, from an LAR based on a hierarchy, such as the one suggested below: [9]

1. a person designated by the individual, while retaining the decisional capacity to do so, to make decisions for her/him regarding participation in research;
2. a person designated by the individual, while retaining the decisional capacity to do so, to make decisions for her/him regarding non-research health care decisions;
3. the individual's legal guardian with authority to make health care decisions for her or him;
4. the spouse, or if recognized by applicable law, the civil union partner or domestic partner;
5. an adult son or daughter;
6. a parent;
7. an adult brother or sister; or
8. an adult who has exhibited special care and concern for the prospective research participant.

In the event that two or more potential LARs of equal standing disagree regarding the decision to enroll a prospective participant in a study, that individual should not be enrolled. [10]

At initial review, the convened IRB should consider whether procedures have been outlined for screening LARs and informing them of their responsibilities, especially those pertaining to monitoring the assent and wellbeing of participants. **These procedures should increase in rigor as degree of risk and extent of likely impairments to participants' functional abilities increase.** Procedures should include a provision that if reasonable concern exists as to whether an LAR is capable or willing to execute his or her responsibilities, his or her consent is not sufficient to enroll the participant in the study. The effectiveness of procedures for screening and informing LARs should be considered at initial and continuing review.

If an individual who lacks the capacity to consent to enroll in a study has previously issued an advance directive (AD) regarding participation in research, his or her expressed wishes should be heeded. However, an AD should not function as a permanent or unlimited license for an individual's participation in a study. Consistent with applicable law, the participant's LAR should interpret his or her AD to determine if participation in a given study is accounted for, and should retain the right to refuse or terminate the participant's enrollment. No individual should be enrolled in a study when participation is against his or her wishes as expressed in an AD.

IV.C. Points to consider when reviewing procedures for obtaining assent from adult participants

Due to the nature of their physical or psychological conditions, some prospective participants will not be capable of assenting to their participation in research (for example, participants whose condition involves extended loss of consciousness). However, for any prospective participant incapable of providing consent, but capable of communicating his or her preferences regarding participation, researchers should make reasonable efforts to offer information regarding the procedures that he or she will undergo and ensure that his or her participation is willing. At initial review, the convened IRB should consider whether procedures for obtaining the assent of adult participants who cannot consent, if appropriate, have been outlined. **The content of these procedures will depend on the degree of risk and extent of likely impairments to participants' functional abilities and should increase in rigor as risk and functional abilities increase**.

Mere lack of objection by participants should not be interpreted as assent. Moreover, the dissent of a participant, whether communicated orally or otherwise, should always be respected. If a participant expresses dissent only to a component of a study and not to participation in the study as a whole, researchers might return at a later point and see whether the participant is willing to undergo the procedures involved in that component. However, if a participant dissents repeatedly to participation in a component of a study, he or she should be withdrawn from that component and, if necessary, from the study. If a dissenting participant cannot be withdrawn from a study or component of a study for medical or safety reasons, he or she should be kept on the study intervention under compassionate use or off-label use, if possible. The effectiveness of procedures for obtaining the assent of participants who cannot consent should be considered at initial and continuing review.

V. Review of research involving adult participants with diminished functional abilities or no capacity to consent by the expedited procedure

Research involving adult participants with diminished functional abilities or no capacity to consent may be reviewed by the expedited procedure consistent with DHHS or other legally applicable regulatory criteria. The IRB chair might consider whether review by the expedited procedure should be conducted by the IRB member with expert knowledge of the relevant condition, or, when no IRB member is an expert, consulting an expert to supplement the review as conducted by an IRB member. Review of modifications and continuing review should use the same procedures as initial review.

VI. Re-reviewing research when an enrolled adult participant unexpectedly loses the capacity to consent

In the event that a participant unexpectedly experiences a substantial impairment to his or her functional abilities that is not foreseeably temporary, researchers should notify the IRB. In such cases the IRB should determine whether it is necessary to re-evaluate the participant's capacity to consent to determine whether the participant who has lost the capacity to consent is permitted to remain in the study. Re-review of research should use the same procedures as initial review.

If the participant is determined to be incapable of consenting and is not likely to regain the capacity to consent in the near future, but the convened IRB determines that his or her ongoing participation is reasonable, researchers should obtain his or her assent to continue enrollment (when feasible) and the consent of an LAR, as soon as possible.

If researchers or IRB members determine that it is necessary to withdraw the participant from the study, or from a component thereof, but the participant cannot be withdrawn for medical or safety reasons, he or she should be kept on the study intervention under compassionate use or off-label use, when possible.

Definitions

Diminished functional abilities: *Substantial* impairment of cognitive functions (such as attention, comprehension, memory, and intellect), communication abilities, or other abilities that affect capacity to make and express a decision regarding participation in a study.

Capacity to consent: The ability to provide legally effective consent to enroll in a research study.

Minimal Risk: Defined, based on DHHS regulations, as studies for which, "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

Assent: A positive indication of willingness to participate in a study.

Dissent: Any expression of unwillingness to participate in a study or component of a study, including refusal to undergo a procedure involved in the study.

Notes

[1] See, for example, Kaup et al. (2011). "Decisional capacity and consent for schizophrenia research." *IRB*; 33 (4): 1-9; Misra, S. and Ganzini, L. (2004). "Capacity to consent to research among patients with bipolar disorder." *Journal of Affective Disorder*; 80 (2-3): 115-123; and Fisher et al. (2006). "Capacity of persons with mental retardation to consent to participate in randomized clinical trials." *American Journal of Psychiatry*; 163 (10): 1813-1820.

[2] See Dresser, Rebecca. (1999). "Research involving persons with mental disabilities: a review of policy issues and proposals." Washington: National Bioethics Advisory Commission.

[3]Whether any of these criteria should be applied to a given study is at the discretion of the convened IRB, and will depend on the nature and degree of risks to participants, importance of the knowledge that can be reasonably expected to result from the study, and on sound research design.

[4]The precise responsibilities of independent monitors should be clearly outlined in the research plan.

[5]On cognitive screening tests, see Cullen et al. (2007). "A review of screening tests for cognitive impairment." *Journal of Neurology, Neurosurgery & Psychiatry*, 78: 790-9. On capacity assessment instruments, see Dunn et al. (2006). "Assessing decisional capacity for clinical research or treatment: a review of instruments." *American Journal of Psychiatry*, 163: 1323-34; and Jeste et al. (2007). "A new brief instrument for assessing decisional capacity for clinical research." *Archives of General Psychiatry*, 64(8): 966-74.

[6]Whether any of these criteria should be applied to a given study is at the discretion of the convened IRB, and will depend on the nature and degree of risks to participants, importance of the knowledge that can be reasonably expected to result from the study, and on sound research design.

[7]The precise responsibilities of independent monitors should be clearly outlined in the research plan.

[8]See, for example, Kim, S.Y.H. et al. (2011). "Preservation of the capacity to appoint a proxy: decision maker: implications for dementia research." *Archives of General Psychiatry*, (69) 12; 214-20.

[9]"SIIIDR Recommendation Previously Approved by SACHRP." (2009). Washington: U.S. Department of Health and Human Services.

[10]Except when applicable law specifies a procedure for resolving the disagreement that allows for the individual's participation.