

**Guidance and Procedures Number: 24**

**Title: Special Subject Populations: Cognitively Impaired**

**Date of Last Revision: July 5, 2007**

## I. Introduction

The primary ethical concern in research involving cognitively impaired individuals is that their disorders may compromise their capacity to understand the nature of their participation and their ability to make an informed decision about participation. The [Belmont Report](#) principle of *respect for persons* “incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection.”<sup>1</sup>

Cognitive impairments, such as those resulting from psychiatric disorders or other serious illnesses, deeply affect not only patients but their families and communities. In discussing the protection of research subjects who have a questionable capacity to consent, UCLA IRBs make determinations based on the ethical responsibility to respect their autonomy, the nature of shared decision making by potential subjects with their family and friends and its relationship to informed consent, and ensuring appropriate and continued informed consent to participate in research.

This guidance sets out considerations, requirements and procedures pertaining to scenarios such as the following: (1) A project involves a population from which investigators would need to identify individuals lacking the capacity to provide consent so that those individuals would be properly excluded; (2) A project is specifically designed to involve individuals who might have cognitive impairments and might lack the capacity to provide consent; and (3) A subject's capacity to consent changes or fluctuates during the course of participation.

## II. Definitions<sup>2</sup>

**Capacity (to consent to research):** The ability of an individual to understand the choices presented, to appreciate the implications of choosing one alternative or another, and to make and communicate a decision (*e.g.*, to participate in a particular study).

**Cognitively Impaired:** Having either a psychiatric disorder (*e.g.*, psychosis, neurosis, personality or behavior disorder, or dementia) or a developmental disorder (*e.g.*, mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain,

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<sup>1</sup> National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, [The Belmont Report](#), U.S. Government Printing Office, Washington, D.C. 1979.

<sup>2</sup> OHRP (formerly OPRR), [Human Research Subjects: Institutional Review Board Guidebook](#), US Government Printing Office, Washington D.C., 1993, Chapter 6, Section D.

terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.

**Competence:** Technically, a legal term, used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice.

**Legally Authorized Representative:** An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research [45 CFR 46.102(c) and 21 CFR 50.3(l)].

**Voluntary:** Free of coercion, duress, or undue inducement. Used in the research context to refer to a subject's decision to participate (or to continue to participate) in a research activity.

### III. Considerations and Requirements Related to Cognitive Impairment

#### A. General Requirements

Federal regulations related to the protection of human subjects require that (1) an institution give consideration to including one or more persons on the IRB who are knowledgeable about and experienced in working with vulnerable subject populations;<sup>3</sup> and, (2) an IRB ensure that a study involving vulnerable subjects include additional safeguards to protect the rights and welfare of vulnerable subjects.<sup>4</sup>

#### B. Recruitment

1. The recruitment process for any study must uphold the Belmont Report principle of justice and therefore may not lead to the systematic selection of subjects simply because of their easy availability, their compromised position, or because of social, racial, sexual, economic or cultural biases institutionalized in society. Where possible, the IRB strongly suggests that studies first recruit from non-institutionalized populations even though it may be more convenient to work with such populations (such as nursing home residents).
2. It is often difficult for potential subjects who are **not** cognitively impaired to understand the differences between research and standard practice. It is therefore essential that particular attention be paid to distinguishing between standard clinical practice and research options during the recruitment and informed consent processes.

#### C. Process for Determining Decision-Making Capacity

1. Individuals with cognitive impairments may or may not have the capacity to consent to participate in research. If the disorder has affected their reasoning, they may not be able to process information about the research, or they may be subject to actual or perceived duress. The capacity to consent to participate will depend on both the individual and the complexity of the research.

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<sup>3</sup> 45 CFR 46.107(a) and 21 CFR 56.107(a)

<sup>4</sup> 45 CFR 46.111(b) and 21 CFR 56.111(b)

2. Potential subjects who may have a questionable capacity to consent should undergo an evaluative test to determine understanding of the consent form and process.
  - a. In order to provide consent for participation, a subject should be alert, able to communicate and be able to explain, at a minimum, (1) what participation entails, (2) significant risks and benefits, (3) what to do if they experience distress or discomfort, and (4) how to withdraw from the study.
3. Informed consent is an ongoing process of communication rather than just being a form or a discrete point in time. Competence may fluctuate as a function of the natural course of a subject's condition, response to treatment, effects of medication, general physical health and other factors. Determinations of capacity to provide continuing consent should be made routinely when such capacity is questionable.
4. When potential subjects do not have the capacity to provide consent or lose the capacity to provide continuing informed consent, they must be excluded from the research unless the research is IRB-approved for inclusion of subjects either without any prospective informed consent or with the informed consent of a legally authorized representative (see Sections D and E below).
  - a. When a study includes subjects who do not have the capacity to consent, it may be necessary or appropriate to use an assent process to communicate details of the research to subjects.
    - i. Whether an assent process is appropriate depends on factors including, but not limited to, subjects' ability to communicate as well as the level of risk and/or sensitivity of the research procedures.
    - ii. An assent process would use language and methods that are understandable to subjects, and allow subjects an opportunity to provide affirmative agreement to participation.
    - iii. An assent process may be appropriate for all subjects involved in a study or only for particular subjects.

#### **D. Participation in Research Without Prospective Informed Consent**

1. Except for FDA-regulated research, the IRB may waive or alter the requirement to obtain informed consent for research that poses no more than minimal risk to subjects and meets other criteria for such waiver or alteration. For further information, see [HRPP Guidance & Procedure #29: Informed Consent Process and Documentation](#).
2. In narrowly-defined circumstances in emergency settings, Federal regulations and California law allow for the inclusion of a subject in research without the prospective informed consent of either the subject or a legally authorized

representative. Such research must be designed, reviewed and conducted in accordance with [HRPP Guidance & Procedure # 35: IRB Approved Research in an Emergency Setting](#).

## E. Participation in Research With the Consent of a Legally Authorized Representative

1. When potential participants lack the capacity to provide consent, state law determines the situations in which the consent of a legally authorized person may be sought. The proposed research and the involvement of subjects based on consent provided by legally authorized representatives must meet the following conditions of California Health & Safety Code, Section 24178:
  - a. The research must relate to the cognitive impairment, lack of capacity, or serious or life-threatening diseases and conditions of research participants.<sup>5</sup>
  - b. Consent by legally authorized representatives is not allowed on behalf of persons on an inpatient psychiatric ward, inpatients of a mental health facility or persons on psychiatric hold.<sup>6</sup>
2. Section 24178 of the California Health & Safety Code specifies the individuals authorized to give surrogate or proxy informed consent. The law distinguishes between emergency room and non-emergency room research and describes specific surrogate trees for each type of research. The OPRS document [Guidelines and Procedures for Proxy/Surrogate Informed Consent](#) describes the surrogate trees. Individuals authorized under state law are considered to meet DHHS and FDA definitions of “legally authorized representative.”
3. The consent of a legally authorized representative does not override any objection by the potential subject even though the potential subject lacks the capacity to provide consent.<sup>7</sup> **An incapacitated person may not be included in research over his or her dissent or resistance to participation.**
4. State law prohibits legally authorized representatives from receiving any financial compensation for providing consent.<sup>8</sup> This does not prohibit legally authorized representatives from receiving reimbursement for expenses related to participation in the research.

## F. Continuing Consent

1. As noted in C(3) above, subjects who are able to consent for entry into research may lose their capacity to consent during the course of research.
  - a. If the IRB has not approved the research for consent by legally authorized representatives, participation of subjects who lose capacity to consent must cease.

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<sup>5</sup> California Health & Safety Code §24178(b)

<sup>6</sup> California Health & Safety Code §24178(j)

<sup>7</sup> California Health & Safety Code §24178(c) and (e)

<sup>8</sup> California Health & Safety Code §24178(i)



2. When such research qualifies for review under the Expedited process, the IRB Chair or designated reviewer may request additional review by the appropriate subject representative.
- B. The IRB shall ensure that the recruitment plan for a study takes into account the vulnerability of individuals with cognitive impairments.
  - C. The IRB shall ensure that appropriate procedures are in place to identify individuals who may have impaired capacity to provide consent. Procedures shall be appropriate to the anticipated subject population and the nature of the research.
    1. The IRB shall ensure that continuing evaluation of capacity to provide consent is routinely performed when appropriate to the anticipated subject population and the research.
  - D. The IRB shall ensure that subjects with impaired capacity to provide consent will be excluded unless the research qualifies to include such subjects by way of waiver or the consent of a legally authorized representative.
  - E. When investigators wish to involve subjects in research based on the consent of a legally authorized representative, the IRB shall ensure that appropriate scientific and ethical justifications are provided and that the process for identifying and obtaining consent from a legally authorized representative is compliant with applicable state law.
    1. If the research will take place outside California, the IRB will ensure that the investigator's plans demonstrate knowledge of local requirements regarding consent by a legally authorized representative. OPRS staff will confirm all such information, with the assistance of University Counsel as needed.
    2. The IRB will assess whether an assent process is necessary or appropriate according to Section III(C) above, and determine whether the requirement for assent extends to all subjects of the study. The IRB may determine that an assent process is not necessary or appropriate if, for example, the capacity of the subjects is so limited that they cannot reasonably be consulted.
  - F. In its initial review of research in which the capacity of individuals may change during the course of the research, the IRB will ensure that procedures are in place for stopping participation, obtaining the consent of a legally authorized representative, and/or obtaining the consent of the subject as appropriate to the circumstances.
    1. Informed consent documents shall contain descriptions of what will happen in the event of a change in capacity.

## **V. Investigators' Responsibilities**

- A. An IRB application should always include a complete description of the expected study population. When the research will either include individuals who might lack the capacity to consent or need to identify such individuals in order to exclude them, the investigator should describe processes and procedures designed to address the following general considerations as detailed in Section III above.

1. The recruitment and consent processes shall take into account the vulnerability of individuals with cognitive impairments.
  2. There shall be processes for evaluating and documenting individuals' capacity to provide consent, and to routinely do so over the course of research to ensure continuing consent from individuals whose capacity to consent may be questionable.
  3. The research shall either exclude individuals unable to provide consent or, with IRB approval, include individuals either under a waiver of consent or with the consent of a legally authorized representative.
  4. Research that will enroll subjects with the consent of a legally authorized representative shall include appropriate procedures for identifying legally authorized representatives, documenting their status and obtaining consent from them.
    - a. If the research will take place outside California, the investigator is responsible for researching local requirements regarding consent by a legally authorized representative.
    - b. The investigator shall follow IRB determinations regarding the necessity or appropriateness of obtaining assent from subjects.
  5. Investigators shall anticipate changes in capacity and describe in both the protocol and informed consent documents how such changes will be handled.
- B. For research involving the informed consent of legally authorized representatives, investigators must also include with their IRB applications a completed Form HS-1 Sub-Application for Requesting Proxy/Surrogate Consent.<sup>10</sup>

### **Regulations:**

45 CFR 46.102(c)  
45 CFR 46.107(a)  
45 CFR 46.109(e)  
45 CFR 46.111(b)  
21 CFR 50.3(l)  
21 CFR 56.107(a)  
21 CFR 56.109(f)  
21 CFR 56.111(b)  
California Health & Safety Code Section 24178

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<sup>10</sup> See <http://www.oprs.ucla.edu/human/forms/proxy>.

## References:

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, The Belmont Report - Ethical Principles and Guidelines for the Protection of Human Subjects of Research, April 18, 1979.

<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>

U.S. Office for Human Research Protections' (OHRP, formerly OPRR) *Protecting Human Research Subjects Guidebook* (1993). [http://www.hhs.gov/ohrp/irb/irb\\_guidebook.htm](http://www.hhs.gov/ohrp/irb/irb_guidebook.htm)

Carpenter, William Jr., Nina R. Schooler, John M. Kane, The Rationale and Ethics of Medication-Free Research in Schizophrenia, Archive of General Psychiatry, Vol. 54, May 1997, p. 405.

Rebecca Dresser, "Mentally Disabled Research Subjects: The Enduring Policy Issues", Journal of the American Medical Association, July 3, 1996, Vol. 276, No 1, p 71.

University of California Office of the President, *Guidance on Surrogate Consent for Research*, January 1, 2003. <http://www.ucop.edu/research/news/surrcon.pdf>