

NIH HRPP SOP 14E v1

**HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL &
IMPLEMENTATION**

OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

SOP Number: 14E

**SOP Title: RESEARCH INVOLVING ADULTS WHO ARE OR MAY BE UNABLE TO
CONSENT**

**Distribution: Scientific Directors; Clinical Directors; Clinical Investigators, IRB
Chairs, IRB Administrators, Protocol Navigators**

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SOP 14E RESEARCH INVOLVING ADULTS WHO ARE OR MAY BE UNABLE TO CONSENT

14E.1 PURPOSE

This SOP discusses requirements for non-emergency research involving adults who are or may be unable to provide informed consent.

14E.2 POLICY

This SOP sets forth additional protections required by the NIH's Human Research Protection Program (HRPP) for NIH investigators conducting research at the NIH Clinical Center (CC) and non-CC NIH sites (i.e., NIDA Baltimore, NIDDK Arizona, NIEHS North Carolina, NIA Baltimore) and for NIH IRBs reviewing research involving these vulnerable subjects.

This policy is consistent with the requirements set forth at Medical Administrative Series (MAS) 87-4(rev) 19 May, 2011, "Research Involving Adults Who Are or May Be Unable to Consent" (see List of Links for link to this MAS policy.)

14E.3 BACKGROUND

Adults are presumed capable of giving informed consent. When questions arise regarding an adult's ability to provide initial or on-going consent, further evaluation is warranted. Federal regulations allow surrogate consent by legally authorized representatives (LAR) (45 CFR 46.116). Adults who are unable to provide initial or on-going consent may participate in research only when the IRB has approved the research for adults who cannot consent, and an LAR provides permission (unless the IRB waives the requirement for informed consent). Assent (i.e., affirmative agreement) should be obtained from research participants who are capable of providing it, if required or recommended by the IRB. Their objections (dissent) should be respected.

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14E.4 DEFINITIONS

- A. **Durable Power of Attorney (DPA) for Health Care:** A DPA for health care is an advance directive in which individuals appoint an agent to make health care decisions for them in the event that they become incapable of doing so, (see Research Advance Directives in Section 14E5.4 below).
- B. **Legally Authorized Representative (LAR)** (or surrogate decision-maker): means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participation in the procedure(s) involved in the research (see, e.g., DHHS regulations at 45 CFR 46.102(c) and FDA regulations at 21 CFR 50.3(l)). (Examples of LARs and surrogates [see definition below] include those having medical decision-making authority pursuant to a durable power of attorney or court appointment, such as a guardian.)
- C. **Living Will:** An advance directive in which individuals specify which medical interventions they would want instituted, continued, withheld, or withdrawn in the event that they are in a persistent vegetative state or diagnosed with a terminal illness and are incapable of making these decisions.
- D. **NIH Ability to Consent Assessment Team (ACAT):** is a Clinical Center group trained to conduct assessments of whether an individual at the Clinical Center has the capacity to provide consent (see Section 14E.8, below) and includes members qualified in psychiatry, bioethics and other disciplines.
- E. **NIH Advance Directive for Health Care and Medical Research Participation** (NIH Form 200): This Clinical Center form combines the essential components of a living will and a durable power of attorney for health care and research participation. Unlike a living will, this form is not restricted to individuals who are terminal or in a persistent vegetative state. This form is designed for use only at the Clinical Center. It may, however, provide guidance as to a person's preferences when they leave the Clinical Center.

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14E.5 PRINCIPAL INVESTIGATOR RESPONSIBILITIES**14E.5.1 STATEMENT OF INVOLVEMENT OF SUBJECTS UNABLE TO GIVE CONSENT**

All research protocols shall state whether adults who are unable to provide initial informed consent are excluded or are eligible to enroll, and the conditions, if any, in which adults who lose the ability to provide on-going consent subsequent to giving initial consent, may continue to participate.

14E.5.2 SUBMISSIONS FOR REVIEW

When protocols involving adults who are or may be unable to consent are submitted for initial review by an NIH IRB, the NIH Intramural Clinical Initial Protocol Application and Supplement G will be completed. If the PI did not originally anticipate inclusion of adults who are or may be unable to consent and later wants to include such subjects, the PI must amend the protocol using the Intramural Clinical Protocol Amendment Application and Supplement G. These initial or amendment reviews may be expedited if otherwise appropriate (see SOP 7A “Requirements for Expedited Review of Research by NIH Institutional Review Boards”).

14E.5.3 ELIGIBILITY FOR ENROLLMENT

When adults who are or may be unable to consent are eligible for enrollment and/or continued participation, the protocol will describe:

- A. The justification for their inclusion.
- B. How and by whom their ability to provide initial and/or on-going consent will be assessed.
- C. That an LAR will be selected and evaluated for his/her ability to provide informed consent for research based on the requirements of Attachment 1 and 2 of this SOP.
- D. That the permission of the LAR will be obtained if required by this policy.

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- E. The risks of the research and prospects of direct benefit (if any) for adults unable to consent.
- F. The procedures for obtaining assent, and the procedures for respecting dissent, and
- G. Any additional safeguards that will be used (e.g., consent monitoring).

14E.5.4 RESEARCH ADVANCE DIRECTIVES AT THE CLINICAL CENTER (CC)

Investigators conducting research in the NIH CC shall encourage adults who are at risk of losing the ability to consent to complete an advance directive for health care and medical research participation as consistent with CC Medical Administrative Policy 92-7 (rev) "Advance Directives" (see List of Links for link to this MAS policy).

14E.6 NIH IRB RESPONSIBILITIES**14E.6.1 REVIEW REQUIREMENTS**

When reviewing research protocols involving adults covered under this SOP, the NIH IRB will:

- A. Ensure there is a compelling justification for including adults who cannot consent (e.g., the research question cannot be answered by enrolling only adults who can consent; participation offers the potential for important clinical benefit).
- B. Ensure that the procedures for evaluating an adult's ability to provide initial and on-going consent are appropriate.
- C. Stipulate that the consent of an appropriate LAR will be obtained as appropriate and consistent with this policy, including as outlined in Attachments 1 and 2.
- D. Document the risks and prospects of direct benefit (if any) for adults unable to consent.

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- E. Ensure that the procedures for obtaining assent and respecting dissent are appropriate, and
- F. Determine whether any additional safeguards will be used (e.g., consent monitoring).

14E.6.2 NIH IRB DETERMINATION OF ALLOWABLE CATEGORIES OF RESEARCH

NIH IRBs may approve research in the following categories only:

- A. ***Research not involving greater than minimal risk.*** Minimal risk means that 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.
- B. ***Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.*** Inclusion of adults who cannot consent may be approved in this category only when an NIH IRB determines that the prospect of benefit to the subjects justifies the risks and burdens to them and the risk-benefit profile of the research is at least as favorable for the subjects as the risk-benefit profile of available alternatives.
- C. ***Research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects.*** An NIH IRB must approve this category of research, and the PI must comply with the requirements set forth in Attachment 2 to this SOP.
- D. ***Research involving more than a minor increase over minimal risk and no prospect of direct benefit to individual subjects.***
 - 1. In order to approve this research, an NIH IRB must fulfill the other requirements of this SOP and determine and document that the knowledge to be obtained:
 - i. is of vital importance

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- ii. cannot reasonably be obtained by studying adults who can consent, and
 - iii. cannot be obtained in a way that poses less risk.
2. Additional NIH review and approval: After an NIH IRB approves this research, additional review shall be conducted by the NIH Deputy Director for Intramural Research (DDIR) who will convene a panel of independent Federal employee experts. The DDIR can approve research in this category only if the panel finds that the knowledge to be obtained is of:
- i. vital importance
 - ii. cannot reasonably be obtained by studying adults who can consent, and
 - iii. cannot be obtained in a way that poses less risk.

14E.6.3 NIH IRB MINUTES/RECORDS

The NIH IRB shall document its determinations regarding its review of the elements considered in 14E.6.1 and the risk category in 14E.6.2, in addition to other requirements (see SOP 4 “Human Research Protection Program (HRPP) Documentation and Records”).

14E.7. THE SURROGATE DECISION-MAKER

This section of the SOP applies *after* the IRB has approved the research for any category of risk and, for research involving more than a minor increase over minimal risk and no prospect of direct benefit to the subjects, *after* the DDIR has also approved the research following review of an independent panel of experts.

14E.7.1 WHO CAN BE A SURROGATE DECISION-MAKER?

A legally authorized representative (LAR) may be able provide legally effective informed consent on behalf of a subject who is unable to consent to participation in a research protocol. Examples of LARs include when a

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competent person assigns an agent to make decisions on the person's behalf should he/she become incompetent (such as a durable power of attorney), those named by a court order (such as legal guardians), those authorized by state statute, or by the NIH Clinical Center policy, which applies only within the Clinical Center (See Section 14.7.3 below) Some subjects may not have the ability to understand a research consent, but the individual may retain the ability to designate a durable power of attorney.

14E.7.2. HOW IS AN APPROPRIATE SURROGATE DECISION-MAKER SELECTED?

The following steps are required for the selection of a surrogate decision-maker:

1. The PI must evaluate what information and individuals exist pertaining to the appointment of a surrogate decision-maker, including whether there is applicable state law, or CC policy, and/or whether the subject has the ability to designate a surrogate decision-maker at that time.
 - a. If a subject has a court appointed guardian from a state that allows it¹ or a DPA², that guardian or DPA is the subject's LAR and may authorize the individual's research participation if the requirements in Attachment 1 and 2 are followed.
 - b. If a subject does not have a court appointed guardian or a DPA and has the ability to designate a DPA, but not the ability to consent to the research, the subject may assign a DPA and the assigned DPA may authorize the individual's research participation provided the requirements in Attachment 1 and 2 are followed.
 - c. If no guardian or DPA exists, and the subject is unable to appoint a DPA, to determine who is the LAR, rely as a guide on applicable state law³ or, at the CC, CC policy (found at 14.7.3). The requirements of Attachment 1 and 2 must be followed.

¹ A guardian may only consent to enroll a subject in research if allowed by their appointing state to do so. The Office of General Counsel should be consulted on questions regarding the specific authority of guardians.

² Consult with the Office of the General Counsel regarding the authorities provided in a non-CC Durable Power of Attorney.

³ For questions about applicable law, consult the Office of the General Counsel.

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2. Certain types of LARs may only provide informed consent for certain risk levels of research. See Attachment 1 and 2 for the decision tree for determining the type of LAR appropriate to each risk level of research. After identification of a potential LAR, NIH requires that an assessment be done regarding the appropriateness of the LAR to consent to research. This assessment process varies, depending on the mechanism used to designate surrogate, the level of risk of the research and the location of the research. Attachment 1 and 2 describe the requirements for who can assess the LAR's ability to consent to research, based on the location and level of risk of the research. The assessment includes answering the following questions:
 - a. Does the surrogate understand that the protocol involves research?
 - b. Does the surrogate understand the risks, potential benefits, (if any), and alternatives to the study?
 - c. Does the surrogate have information to show that participation in the study is consistent with the subject's preferences and values?

14E.7.3 NIH CLINICAL CENTER POLICY ON SELECTION OF A SURROGATE

If a subject at the Clinical Center does not have a court appointed guardian or a DPA, and has the ability to designate a surrogate decision-maker, but not the ability to consent to the research, the subject may assign a DPA and the assigned DPA may authorize the individual's research participation provided the evaluation requirements in Attachment 1 and 2 are followed.

If a subject at the Clinical Center does not have a court appointed guardian or a DPA, and does not have the ability to designate a surrogate decision-maker, a person at the highest level on the following list may serve as surrogate for the subject but *only* for participation in research that the NIH IRB has approved as not greater than minimal risk OR that has a prospect of direct benefit (see 14E.6.2.A. and B. above):

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1. spouse or domestic partner⁴
2. adult child
3. parent
4. sibling
5. other close relative

14E.8 NIH CC CONSULTATIVE RESOURCES

Consultation to assess whether an individual at the Clinical Center has the capacity to provide consent or is able to assign a surrogate, as well as assessment of the appropriateness of a surrogate, may be obtained by contacting the NIH Ability to Consent Assessment Team (ACAT) (301-496-9675 or 301-496-2429) or the Department of Bioethics (301) 496-2429 for CC or non-CC sites.

⁴ Domestic partner is a relationship between two individuals who: (1) are at least 18 years old, (2) are not related to each other by blood or marriage within four degrees of consanguinity under civil law rule, (3) are not married or in a civil union or domestic partnership with any others, and (4) have agreed to be and continue to be in a relationship of mutual interdependence in which each individual contributes to the maintenance and support of the other individual and the relationship, even if both individuals are not required to contribute equally to the relationship.

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LIST OF LINKS

- A. MAS 87-4(rev) “Research Involving Adults Who Are or May Be Unable to Consent”: <http://cc-internal.cc.nih.gov/policies/PDF/M87-4.pdf>
- B. MAS 92-7 (rev) “Advance Directives”: <http://cc-internal.cc.nih.gov/policies/PDF/M92-7.pdf>

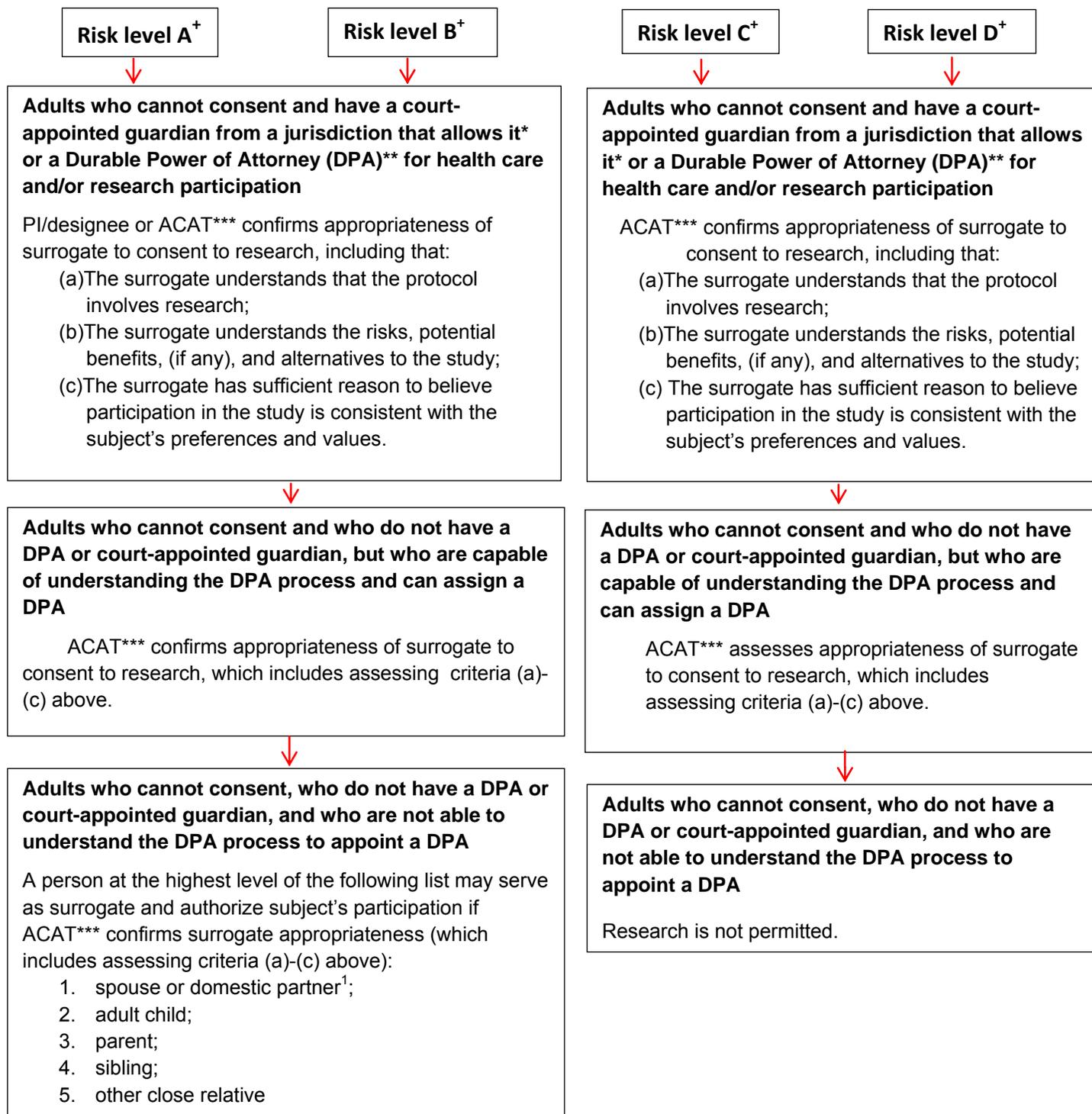
LIST OF ATTACHMENTS

Attachment 1: Decision tree for assessment of surrogate in the Clinical Center based on research risk level.

Attachment 2: Tables for defining mechanisms of surrogate delegation for each of the four levels of research risk.

SOP 14E- Attachment 1 v.1 8-7-2013

ATTACHMENT 1: DECISION TREE FOR ASSESSMENT OF A SURROGATE DECISION-MAKER IN THE CLINICAL CENTER BASED ON RESEARCH RISK LEVEL⁺



*A guardian may only consent to enroll a subject in research if allowed by their appointing state to do so. The Office of General Counsel should be consulted on questions regarding the specific authority of guardians.

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[†]Level A: Research not involving > minimal risk, See SOP 14E.6.2.A

[†]Level B: Research involving > minimal risk but presenting the prospect of direct benefit to the individual subjects, See SOP 14E.6.2.B

[†]Level C: Research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects, See SOP 14E.6.2.C

[†]Level D: Research involving > a minor increase over minimal risk and no prospect of direct benefit to individual subjects, See SOP 14E.6.2.D

* * DPA means the individual holding the durable power of attorney for healthcare. Consult with the Office of the General Counsel regarding the authorities provided in a non-CC Durable Power of Attorney.

*** ACAT = NIH Ability to Consent Assessment Team

¹ Domestic partner is a relationship between two individuals who: (1) are at least 18 years old, (2) are not related to each other by blood or marriage within four degrees of consanguinity under civil law rule, (3) are not married or in a civil union or domestic partnership with any others, and (4) have agreed to be and continue to be in a relationship of mutual interdependence in which each individual contributes to the maintenance and support of the other individual and the relationship, even if both individuals are not required to contribute equally to the relationship.

ATTACHMENT 2: TABLES FOR EVALUATING LEGALLY AUTHORIZED REPRESENTATIVES (LAR) AND THE ROLE OF THE LAR FOR THE FOUR LEVELS OF RESEARCH RISK.

Instructions: These tables should be followed after IRB approval has occurred for the particular category of research risk. Research involving more than a minor increase over minimal risk and no prospect of direct benefit to individual subjects (Section 14E.6.2.D above) also requires review of an independent panel of experts and subsequent approval by the DDIR.

REQUIREMENTS FOR SURROGATES FOR RESEARCH NOT INVOLVING GREATER THAN MINIMAL RISK AND FOR RESEARCH INVOLVING GREATER THAN MINIMAL RISK BUT PRESENTING THE PROSPECT OF DIRECT BENEFIT TO THE INDIVIDUAL SUBJECTS (SOP 14E.6.2.A AND 14E.6.2.B)

(First preference is #1. If not possible, go to option #2. If #2 is not possible, go to option #3.)

Cognitively Impaired Adults and Circumstances Involving a Surrogate Decision-Maker	Requirements for Evaluation of Surrogate Decision-Maker to Consent to Research		The role of Surrogate at all sites
	Clinical Center	Non-Clinical Center Sites	
1. Adults who cannot consent and have a court-appointed guardian from a state that allows it ¹ or a DPA ² for healthcare and/or research participation	PI/designee or NIH Ability to Consent Team (ACAT) must assess appropriateness of surrogate to consent to research, including that: <ul style="list-style-type: none"> (a) Whether the surrogate understands that the protocol involves research; (b) Whether the surrogate understands the risks, potential benefits (if any), and alternatives to the study; and (c) Whether the surrogate has sufficient reason to believe participation in the study is consistent with the subject's preferences and values 	PI/designee must assess the appropriateness of the surrogate to consent to research, including the criteria a-c used at the Clinical Center	Surrogate may give permission for the research and sign the consent form for the protocol on behalf of the subject
2. Adults who cannot consent and who do not have a DPA or court-appointed guardian, but who are capable of understanding the DPA process and can assign a DPA	ACAT must assess the appropriateness of the surrogate to consent to research, including the criteria a – c above	An independent qualified professional approved by the Bioethics Dept. or the IRB must assess the appropriateness of the surrogate to consent to research, including the criteria a – c above	

¹ A guardian may only consent to enroll a subject in research if allowed by their appointing state to do so. The Office of General Counsel should be consulted on questions regarding the specific authority of guardians.

² DPA means the individual holding the durable power of attorney for healthcare. Consult with the Office of the General Counsel regarding the authorities provided in a non-CC Durable Power of Attorney.

<p>3. Adults who cannot consent, who do not have a DPA or court-appointed guardian, and who are not able to understand the DPA process to appoint a DPA:</p> <ul style="list-style-type: none"> • At the Clinical Center: A person at the highest level of the following: 1) spouse or domestic partner³, 2) adult child, 3) parent, 4) sibling, 5) other close relative • Sites other than the CC: Refer to state law.⁴ 	<p>ACAT must assess the appropriateness of the surrogate to consent to research, including the criteria a – c above</p>	<p>An independent qualified professional approved by the Bioethics Dept. or the IRB must assess the appropriateness of the surrogate to consent to research, including the criteria a – c above</p>	
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³ Domestic partner is a relationship between two individuals who: (1) are at least 18 years old, (2) are not related to each other by blood or marriage within four degrees of consanguinity under civil law rule, (3) are not married or in a civil union or domestic partnership with any others, and (4) have agreed to be and continue to be in a relationship of mutual interdependence in which each individual contributes to the maintenance and support of the other individual and the relationship, even if both individuals are not required to contribute equally to the relationship.

⁴ For questions about applicable law, consult the Office of the General Counsel.

RESEARCH INVOLVING A MINOR INCREASE OVER MINIMAL RISK AND NO PROSPECT OF DIRECT BENEFIT TO INDIVIDUAL SUBJECTS AND RESEARCH INVOLVING MORE THAN A MINOR INCREASE OVER MINIMAL RISK AND NO PROSPECT OF DIRECT BENEFIT TO INDIVIDUAL SUBJECTS (SOP 14E.6.2.C AND 14E.6.2.D).

(First preference is #1. If not possible, go to option #2. If #2 is not possible, go to option #3.)

Cognitively Impaired Adults and Circumstances Involving a Surrogate Decision-Maker	Clinical Center Requirements for Evaluation of Surrogate To Consent to Research	Non-Clinical Center Sites Requirements for Evaluation of Surrogate To Consent to Research	Role of Surrogate at all sites
1. Adults who cannot consent and have a court-appointed guardian from a state that allows it ¹ or a DPA ² for healthcare and/or research participation	ACAT** must evaluate the appropriateness of the surrogate to consent to research, including: (a) Whether the surrogate understand that the protocol involves research; (b) Whether the surrogate understand the risks, potential benefits (if any), and alternatives to the study; (c) Whether the surrogate has sufficient reason to believe that participation in the study is consistent with the subject’s preferences and values	An independent qualified professional approved by the IRB or Bioethics Department must evaluate the appropriateness of the surrogate to consent to research, including the criteria a-c used at the Clinical Center	Surrogate may give permission for the research and sign the consent form for the protocol on behalf of the subject
2. Adults who cannot consent and who do not have a DPA or court-appointed guardian, but who are capable of understanding the DPA process and can assign a DPA	ACAT must assess the appropriateness of the surrogate to consent to research, including the criteria a – c above	An independent qualified professional approved by the Bioethics Dept or the IRB must assess the appropriateness of the surrogate to consent to research including the criteria a – c above	Surrogate may give permission for the research and sign the consent form for the protocol on behalf of the subject
3. Adults who cannot consent, who do not have a DPA or court-appointed guardian, and who are not able to understand the DPA process to appoint a DPA	Surrogate consent not permitted for research	Surrogate consent not permitted for research	Surrogate consent not permitted for research

¹ A guardian may only consent to enroll a subject in research if allowed by their appointing state to do so. The Office of General Counsel should be consulted on questions regarding the specific authority of guardians.

² DPA means the individual holding the durable power of attorney for healthcare. Consult with the Office of the General Counsel regarding the authorities provided in a non-CC Durable Power of Attorney.