

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

OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

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**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

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

14E.1 PURPOSE

This Standard Operating Procedure (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 subjects who participate in research activities led by NIH investigators. Such research takes place mainly at NIH sites (i.e., NIH Clinical Center (CC) NIDA Baltimore, NIDDK Arizona, NIEHS North Carolina, NIA Baltimore) and is usually reviewed by an NIH IRB, however the research could occur at another location and NIH could rely on an outside IRB.

14E.3 BACKGROUND

Adults are presumed capable of giving legally effective informed consent ("consent"). When questions arise regarding an adult's ability to provide initial or on-going consent, further evaluation is warranted. 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 a legally authorized representative (LAR) (45 CFR 46.116) provides consent (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 unless the IRB determines that it is not required. Dissent should be respected.

14E.4 DEFINITIONS

A. **Assent:** The affirmative agreement to participate in research. Mere failure to object should not be construed as assent.

B. 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.

C. Greater Than Minimal Risk But Presenting The Prospect of Direct Benefit To The Individual Subjects: requires 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.

D. Legally Authorized Representative (LAR): is 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 (see, DHHS regulations at 45 CFR 46.102(c) and FDA regulations at 21 CFR 50.3(l)). Examples of LARs include when a competent person assigns an agent to make decisions on the person's behalf should he/she become incompetent (such as a DPA), agents named by a court order (such as legal guardians of the person), and those identified by statute or policy through the next of kin hierarchy.

E. Legally Effective Informed Consent: Informed consent is legally effective if it is both obtained from the subject or the subject's legally authorized representative (LAR) and documented in a manner that is consistent with the DHHS protection of human subjects regulations and with applicable laws of the jurisdiction in which the research is conducted. In general terms, the regulations stipulate that an investigator should seek consent only under circumstances that provide the prospective subject or the LAR sufficient opportunity to consider whether to participate and that minimize the possibility of coercion or undue influence. The information provided should be in language that is understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language.

F. 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.

G. 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.

H. NIH Ability to Consent Assessment Team (ACAT): is comprised of the Bioethics Consultation Service (“Bioethics”) and the Human Subject Protection Unit (HSPU). ACAT is a Clinical Center (CC) group trained to conduct assessments of whether an individual at the CC has the capacity to provide consent. Additionally, responsibilities of ACAT include but are not limited to: carrying out the LAR assessment in lieu of the PI/designee when applicable and evaluating whether an adult who is unable to consent has retained the ability to designate a DPA. ACAT can be contacted by calling Bioethics at 301-496-2429 or the HSPU can be paged at 102-11158 by calling the CC page operator at 301-496-1211.

I. NIH Advance Directive for Health Care and Medical Research Participation (Form NIH 200): A CC form that combines the essential components of a living will and a DPA for health care and research participation. Part I of the form allows research subjects to appoint a substitute decision maker (agent). Part II allows research subjects to document specific preferences they have concerning their medical research participation. Part III allows research subjects to document specific preferences they have concerning health care; this section is similar to a living will.

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 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 to an NIH IRB for initial review, the NIH Intramural Clinical Initial Protocol Application

will be completed and the Principal Investigator (PI) will ensure that the protocol contains all the information specified in Supplement K – Guidance Regarding Research Involving Adults Unable to Consent (Appendix 1). 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 K as guidance (Appendix 1). 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 identified and evaluated for his/her ability to provide consent for research based on the requirements of this SOP.
- D. That the permission of the LAR will be obtained if required by this policy.
- E. The risks of the research and prospect of direct benefit (if any) for adults unable to consent.
- F. The procedures for obtaining assent (written, oral, or by other means), if at all, and the procedures for respecting dissent. If assent will not be sought then the protocol must explain why assent is not possible or should not be required, and
- G. Any additional safeguards that will be used (e.g., consent monitoring).

14E.5.4 RESEARCH ADVANCE DIRECTIVES

At the NIH CC, subjects may not have the ability to provide informed consent, but the individual may retain the ability to make an informed decision about the nature and effect of appointing a DPA and may appoint a DPA. Investigators conducting research in the CC shall encourage adult subjects, particularly those who are at risk of losing the ability to consent, in addition to those who have lost the ability to consent but retain the ability to appoint a DPA, to complete the NIH Advance

Directive For Health Care and Medical Research (Form NIH 200). This form is designed for use at the CC and combines the essential components of a living will and a DPA for health care and research participation. It may, however, provide guidance as to a person's preferences when they leave the CC. For further guidance refer to the CC Medical Administrative Policy 92-7 (rev) "Advance Directives" (see **References**). An outside DPA for healthcare can also be relied upon at the CC for research purposes unless there is a limitation of applicability as to research.

If at a non-CC NIH site, follow your Institute or Center (IC) policies and guidance on advance directives.

14E.5.5 IDENTIFYING A POTENTIAL LAR

The PI will identify a potential LAR as described in **14E.7**.

14E.6 NIH IRB RESPONSIBILITIES

14E.6.1 REVIEW REQUIREMENTS

When reviewing research protocols involving adults who are or may be unable to consent, 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 consistent with this policy.
- D. Assess and document the risks and prospect of direct benefit (if any) for adults unable to consent.
- E. Determine and document the category of research as specified in **14E.6.2** below.
- F. If applicable, ensure that the procedures for obtaining assent and respecting dissent are appropriate. If an IRB determines that assent will be obtained, it

shall determine whether, and how (written, oral, or by other means) it shall be documented (see SOP 12 - Requirements for Informed Consent), and

- G. Determine whether any additional safeguards will be used (e.g., consent monitoring).
- H. When an NIH IRB is serving as an IRB of record and the protocol involves adults who are or may be unable to consent, it should obtain information about how the consent process will be conducted if this vulnerable group of subjects is to be enrolled outside of the NIH CC. This information should be evaluated by the IRB as part of its local context considerations. See SOP 20B – NIH Responsibilities When Reviewing Local Context Considerations for Offsite Research.

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

NIH IRBs may approve the participation of adults who are or may be unable to consent in research that falls into one of the following categories only:

Category A - Research not involving greater than minimal risk.

Category B - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

Category C - Research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects.

Category D - Research not otherwise approvable under categories A-C in this policy.

1. In order to approve research in this category an NIH IRB must, in addition to fulfilling the other requirements of this SOP, determine and document that the knowledge to be obtained:
 - i. is of vital importance;
 - ii. cannot reasonably be obtained by studying only adults who can consent; and

- iii. cannot be obtained in a way that poses less risk.
2. The IRB must also identify a person(s) (ACAT at the CC) independent of the research team who will assess the appropriateness of the LAR to consent on behalf of the participant. See 14E.7.2 below.
 3. Additional review shall be conducted by the NIH Deputy Director for Intramural Research (DDIR) who will convene an independent panel of NIH employees with appropriate subject matter expertise and no conflicts. Conflicts may include but are not limited to: involvement in the development, scientific review, or implementation of the protocol under review; having a direct reporting relationship with the PI; and/or serving as a member of the IRB of record. The panel will provide to the DDIR a written determination regarding the following, whether:
 - i. the knowledge to be obtained: (a) is of vital importance, (b) cannot reasonably be obtained by studying adults who can consent, and (c) cannot be obtained in a way that poses less risk;
 - ii. the risks of the study are not excessive; and
 - iii. additional conditions or protections are needed, e.g., consent monitoring.

The DDIR can concur with the IRB's approval and may allow the conduct of the research or may disapprove implementing the IRB-approved research.

14E.7. PROCESS FOR ENROLLING AN ADULT WHO IS UNABLE TO CONSENT

This section of the SOP applies to instances where an adult subject has been determined to be unable to consent and *after* the approvals per 14E.6 have occurred.

14E.7.1. IDENTIFICATION OF THE LAR

- A. A LAR may be able to provide consent on behalf of a subject who is unable to consent to participation in a research protocol. The identification of a potential

LAR requires that the PI evaluate what information and individuals exist pertaining to the appointment of an LAR, including whether there is applicable state law, or CC policy, and/or whether the subject has the ability to designate a DPA at that time.

1. If a subject has a court appointed guardian from a state that allows it¹ or the subject has a DPA², that guardian or DPA may consent to the subject's participation in the research if the LAR is found to be appropriate.
2. If a subject does not have a court appointed guardian or a DPA but is capable of understanding the DPA process and can assign a DPA, then the subject may assign a DPA³. The assigned DPA may consent to the subject's participation in the research if the LAR is found to be appropriate.
3. If no guardian or DPA exists, and the subject is unable to appoint a DPA, rely as a guide on applicable state law to determine who can serve as the LAR,⁴ or CC policy if at the CC. At the CC, a person at the highest level on the following list may consent to the subject's participation in the research if the LAR is found to be appropriate:

1. spouse or domestic partner⁵
2. adult child
3. parent
4. sibling

¹ A court appointed guardian may only consent to enroll a subject in research if the guardian has authority to do so under the laws of the state that issued the guardianship order and the terms of the guardianship order. The Office of the General Counsel (OGC) should be asked to review guardianship orders to determine if the guardian has legal authority to consent to the subject's participation in the research. PIs are encouraged to seek an OGC consultation in advance of a potential subject with a guardianship order coming to an NIH research site to enroll on a study.

² Consult with OGC if concerned about the authority provided in a DPA.

³ At the CC, ACAT evaluates whether an adult who is unable to consent has retained the ability to designate a DPA. If at a non-CC NIH site, contact your IC leadership for policies and guidance which may refer to applicable state law.

⁴ For questions about applicable law, consult OGC.

⁵ 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.

5. other close relative.

B. Subject to **14E.7.1.A**, the ability of an LAR to consent on behalf of a subject who is unable to consent to participation in a research protocol is dependent on the risk level of the approved research. A court appointed guardian or DPA, assessed to be an appropriate LAR, can consent to an individual's enrollment in research in all risk categories, (**14E.6.2**). However, an LAR identified as being a person at the highest level of the next-of-kin hierarchy list (**14E.7.1.A.3** above) may only consent for a subject if they are found to be appropriate and the research is in category A or B, (**14E.6.2** above).

14E.7.2. DETERMINING APPROPRIATENESS OF LAR

After the 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 level of risk of the research and the location of the research.

An appropriate LAR is one who at least:

- a. Understands that the protocol involves research;
- b. Understands the risks, potential benefits (if any), and alternatives to the study; and
- c. Has sufficient reason to believe that participation in the study is consistent with the subject's preferences and values. For research in category D, the LAR must have *compelling evidence* (e.g. written research advance directive and no clear conflicting evidence) that participation in the study is consistent with the subject's preferences and values.

For studies approved in categories A and B (**14E.6.2** above), the appropriateness of the LAR will be evaluated by the PI/designee⁶ unless the IRB designates an independent person(s) to perform this role (e.g., ACAT if the protocol is taking place at the CC). In studies approved in category C, an independent person(s) identified by the IRB (e.g., ACAT if the protocol is at the CC) will decide if the PI/ designee or the independent

⁶ If the protocol is taking place at the CC, the PI's designee may be someone on the research team or a member of ACAT. If not at the CC, the PI's designee may be someone on the research team or an independent person outside of the research team if it is felt that the team does not have the required competencies to undertake the evaluation.

person(s) will evaluate the appropriateness of the LAR. For studies approved in category D, the appropriateness of the LAR must be evaluated by an independent person(s) designated by the IRB (e.g. ACAT if the protocol is taking place at the CC).

The PIs of CC protocols are encouraged to engage with ACAT before making arrangements to bring to the CC a potential subject who may be or is unable to consent to the research.

REFERENCES

- A. MAS 92-7 (rev) "Advance Directives": <http://cc-internal.cc.nih.gov/policies/PDF/M92-7.pdf>

LIST OF APPENDICES

Appendix 1: Supplement K - Guidance Regarding Research Involving Adults Who Are or May Be Unable to Consent.

Appendix 2: Tables regarding the identification of a legally authorized representative (LAR) and the determination of the LAR's appropriateness to consent on behalf of an adult who is unable to consent to participation in a research protocol.

APPENDIX 1 - SUPPLEMENT K - GUIDANCE REGARDING RESEARCH INVOLVING ADULTS WHO ARE OR MAY BE UNABLE TO CONSENT

Indicate your responses below and explain your selections in the protocol. Do not provide details in this document.

1. For research involving adults who are or may be unable to consent, provide the following information in the protocol (**SOP 14.E**):
 - a. Provide the justification for the inclusion of this population in this research.
 - b. Are any of these subjects institutionalized? (if applicable, complete Supplement H).
 - i. If yes, describe the setting. (Provide documentation of permission from the institution.)

2. Risk/Benefit Assessment

- a. Are the risks to subjects in this research no more than minimal? Yes
 No
 - i. If no, and the research involves greater than minimal risk to subjects, are there direct benefits to the individual subjects?
Yes No

3. Consent and Assent

When questions arise regarding an adult's ability to provide consent, the decision-making capacity of individual subjects should be determined through the use of a standardized measure or by consultation with a qualified professional.

- a. Describe in the protocol the procedures to be used to determine the individual subject's capacity to provide consent.
- b. For subjects where it has been determined that they lack the capacity to give consent, describe the provisions for obtaining consent from the subjects' legally authorized representative.
- c. Describe how the assent, if any, of the subjects will be obtained and documented.

APPENDIX 2: TABLES REGARDING THE IDENTIFICATION OF A LEGALLY AUTHORIZED REPRESENTATIVE (LAR) AND THE DETERMINATION OF THE LAR'S APPROPRIATENESS TO CONSENT ON BEHALF OF AN ADULT WHO IS UNABLE TO CONSENT TO PARTICIPATION IN A RESEARCH PROTOCOL.

Instructions: These tables should be followed where an adult subject has been determined to be unable to consent and *after* the approvals per 14E.6 have occurred.

TABLE 1: REQUIREMENTS FOR THE DETERMINATION OF AN LAR'S APPROPRIATENESS TO CONSENT TO RESEARCH NOT INVOLVING GREATER THAN MINIMAL RISK (CATEGORY A) AND FOR RESEARCH INVOLVING GREATER THAN MINIMAL RISK BUT PRESENTING THE PROSPECT OF DIRECT BENEFIT TO THE INDIVIDUAL SUBJECTS (CATEGORY B) (14E.6.2).

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

Cognitively Impaired Adults and Identification of a LAR	Requirements for Determining Appropriateness of LAR to Consent to Research at Clinical Center (CC) and non- CC sites	Role of the LAR at all sites
<p>1. Adults who cannot consent and have a court-appointed guardian from a state that allows itⁱ or a DPAⁱⁱ for healthcare and/or research participation.</p>	<p>PI/designeeⁱⁱⁱ, unless the IRB designates an independent person(s) to perform this role (e.g., ACAT^{iv} if the protocol is taking place at the CC), must assess appropriateness of LAR to consent to research.</p>	<p>LAR may give permission for the research and sign the consent form for the protocol on behalf of the subject.</p>
<p>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^v.</p>	<p>An appropriate LAR is one who at least:</p> <ul style="list-style-type: none"> (a) Understands that the protocol involves research; (b) Understands the risks, potential benefits (if any), and alternatives to the study; and (c) Has sufficient reason to believe participation in the study is consistent with the subject's preferences and values. 	
<p>3. Adults who cannot consent, who do not have a DPA or court-appointed guardian, and cannot appoint a DPA:</p> <p>At the CC: A person at the highest level of the following may consent to research participation if found to be appropriate: 1) spouse or domestic partner^{vi}, 2) adult child, 3) parent, 4) sibling, 5) other close relative</p> <p>At non-CC sites: Consult with OGC to identify applicable state law.</p>		

TABLE 2: REQUIREMENTS FOR THE DETERMINATION OF AN LAR’S APPROPRIATENESS TO CONSENT TO RESEARCH INVOLVING A MINOR INCREASE OVER MINIMAL RISK AND NO PROSPECT OF DIRECT BENEFIT TO INDIVIDUAL SUBJECTS (CATEGORY C) AND RESEARCH NOT OTHERWISE APPROVABLE UNDER CATEGORIES A-C (CATEGORY D) (14E.6.2).

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

Cognitively Impaired Adults and Identification of a LAR	Requirements for Determining Appropriateness of LAR to Consent to Research at CC and non-CC sites	Role of the LAR at all sites
<p>1. Adults who cannot consent and have a court-appointed guardian from a state that allows it^{vii} or a DPA^{viii} for healthcare and/or research participation.</p> <p>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^{ix}</p>	<p>For research in Category C: An independent person(s) identified by the IRB (e.g. ACAT if the protocol is at the CC) will decide if the PI/ designee^x or the independent person(s) will evaluate the appropriateness of the LAR to consent to research.</p> <p>An appropriate LAR is one who at least:</p> <ul style="list-style-type: none"> (a) Understands that the protocol involves research; (b) Understands the risks, potential benefits (if any), and alternatives to the study; and (c) Has sufficient reason to believe that participation in the study is consistent with the subject’s preferences and values. <p>For research in Category D: The appropriateness of the LAR to consent to research must be evaluated by an independent person(s) designated by the IRB (e.g. ACAT if the protocol is taking place at the CC).</p> <p>An appropriate LAR is one who at least:</p> <ul style="list-style-type: none"> (a) Understands that the protocol involves research; (b) Understands the risks, potential benefits (if any), and alternatives to the study; and (c) Has compelling evidence (e.g. written research advance directive and no clear conflicting evidence) that participation in the study is consistent with the subject’s preferences and values. 	<p>LAR may give permission for the research and sign the consent form for the protocol on behalf of the subject.</p>
<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>	<p>LAR consent in these circumstances is not permitted for Category C or D research.</p>	

ⁱ A court appointed guardian may only consent to enroll a subject in research if the guardian has authority to do so under the laws of the state that issued the guardianship order and the terms of the guardianship order. The Office of the General Counsel (OGC) should be asked to review guardianship orders to determine if the guardian has legal authority to consent to the subject's participation in the research. PIs are encouraged to seek an OGC consultation in advance of a potential subject with a guardianship order coming to an NIH research site to enroll on a study.

ⁱⁱ DPA means the individual holding the durable power of attorney for healthcare. Consult with OGC if concerned about the authority provided in a DPA.

ⁱⁱⁱ If the protocol is taking place at the CC, the PI's designee may be someone on the research team or a member of ACAT. If not at the CC, the PI's designee may be someone on the research team or an independent person outside of the research team if it is felt that the team does not have the required competencies to undertake the evaluation.

^{iv} NIH Ability to Consent Team. For definition please see **14E.4**.

^v At the CC, ACAT evaluates whether an adult who is unable to consent has retained the ability to designate a DPA. If at a non-CC NIH site, contact your IC leadership for policies and guidance which may refer to applicable state law.

^{vi} 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.

^{vii} A court appointed guardian may only consent to enroll a subject in research if the guardian has authority to do so under the laws of the state that issued the guardianship order and the terms of the guardianship order. The Office of the General Counsel (OGC) should be asked to review guardianship orders to determine if the guardian has legal authority to consent to the subject's participation in the research. PIs are encouraged to seek an OGC consultation in advance of a potential subject with a guardianship order coming to an NIH research site to enroll on a study.

^{viii} DPA means the individual holding the durable power of attorney for healthcare. Consult with OGC if concerned about the authority provided in a DPA.

^{ix} At the CC, ACAT evaluates whether an adult who is unable to consent has retained the ability to designate a DPA. If at a non-CC NIH site, contact your IC leadership for policies and guidance which may refer to applicable state law.

^x If the protocol is taking place at the CC, the PI's designee may be someone on the research team or a member of ACAT. If not at the CC, the PI's designee may be someone on the research team or an independent person outside of the research team if it is felt that the team does not have the required competencies to undertake the evaluation.