Research Enrolling "Vulnerable" Individuals: What Investigators Need to Know

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OHSRP Education Series
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Topics

- Meaning of vulnerability
- Categorical vs. contextual vulnerability
- “Vulnerable populations” as per the HHS regulations
- Additional potentially vulnerable populations per OHSRP policy
- Considerations for identifying other populations that may be vulnerable
- Investigator’s role in Human Subjects Research that includes potentially vulnerable study participants

What Do We Mean By "Vulnerability"

Neither the Common Rule for the Protection of Human Subjects nor the subparts define vulnerability the characteristics that render persons vulnerable, what they may be vulnerable to, or what safeguards may be appropriate.

Suggested explanations include:

- Council for International Organizations of Medical Sciences (CIOMS): "persons are vulnerable because they are relatively (or absolutely) incapable of protecting their own interests" or "because some feature of the circumstances (temporary or permanent) in which they live makes it less likely that others will be vigilant about, or sensitive to, their interests."

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What Do We Mean By "Vulnerability" (continued)

National Bioethics Advisory Commission (NBAC)*

- ". . . vulnerability, in the context of research, should be understood to be a condition, either intrinsic or situational, of some individuals that puts them at greater risk of being used in ethically inappropriate ways in research."

Themes regarding vulnerability as to why individuals may be vulnerable in research include:

- They cannot provide voluntary, informed consent arising from limitations in their decisional capacity

  or

- Certain circumstances exist

  or

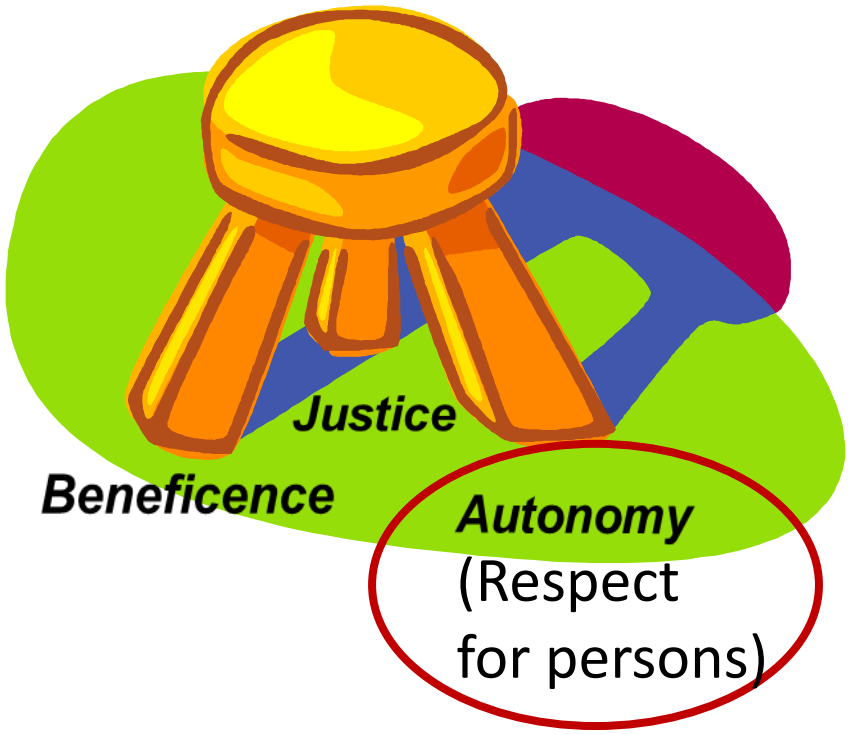
- They are especially at risk for exploitation

* NBAC. Ethical and Policy Issues in Research Involving Human Participants (2001)

The Belmont Report and HHS Regulations

Requirements regarding protection of vulnerable subjects are based, in part, on the Belmont Report.

- Reflecting the principle of respect for persons, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research wrote that “The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.”



What Do the HHS Regulations for Protection of Human Subjects Say?

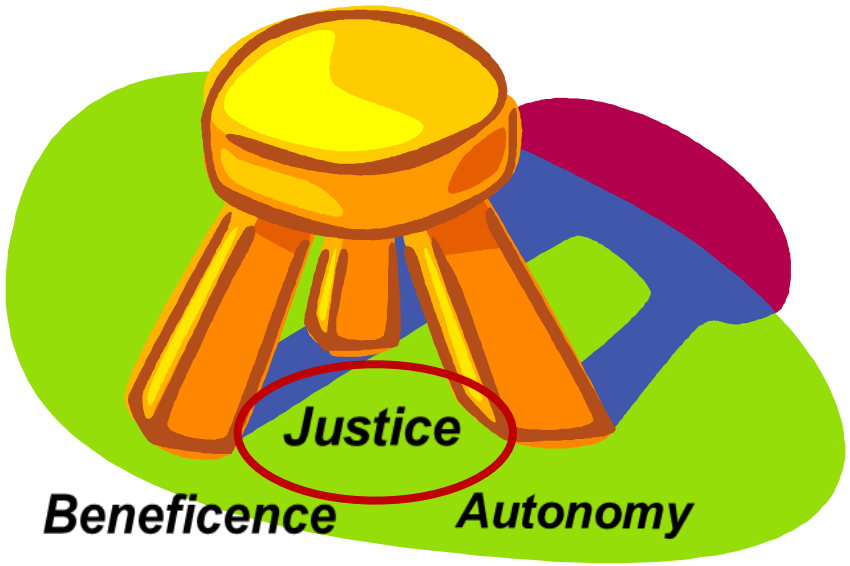
"When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects. "

(45 CFR 46.111(b))

The Belmont Report and HHS Regulations

Reflecting the principle of justice

- equals ought to be treated equally in the distribution of burden and benefits
- fair distribution of scarce benefits
- fair distribution of burdens



What Do the HHS Regulations for Protection of Human Subjects Say?

"Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons."

(45 CFR 46.111(a)(3))

Vulnerability: Categorical vs. Contextual

CATEGORICAL (2018 Common Rule)*

- children
- prisoners
- individuals with impaired decision-making capacity
- economically or educationally disadvantaged persons

HHS Regulations for Protection of Human Subjects, include additional subparts with protections for the following

- Subpart B-Pregnant Women, Human Fetuses and Neonates Involved in Research
- Subpart C-Research Involving Prisoners as Subjects
- Subpart D-Children Involved as Subjects in Research

*45 CFR 46.111(b)

NIH HRPP Policies

Three policies have additional specific federal regulatory requirements which apply to all NIH research

- **400:** Research Involving Pregnant Women, Human Fetuses and Neonates (Subpart B)
- **401**: Research Involving Prisoners (Subpart C)
- **402**: Research Involving Children (Subpart D)

Two NIH policies do not have specific regulatory requirements beyond Subpart A, but investigators must comply with NIH policy requirements

- **403:** Research Involving Adults Who Lack Decision-making Capacity to Consent to Research Participation
- **404**: Research Involving NIH Staff as Subjects

Vulnerability: Categorical vs. Contextual

CONTEXTUAL APPROACH

- National Bioethics Advisory Committee (NBAC): “vulnerability is sensitive to context, and individuals may be vulnerable in one situation and not in another . . . “
- “Allows for a more nuanced understanding of the nature of the vulnerability than the categorical approach and therefore a more focused approach to safeguards.” (Gordon*)

*Gordon BG. Vulnerability in Research: Basic Ethical Concepts and General Approach to Review. Ochsner J. 2020 Spring;20(1):34-38.

Types of Vulnerability

- Institutional Vulnerability
- Deferential Vulnerability
- Medical Vulnerability
- Economic Vulnerability
- Social Vulnerability
- Cognitive or Communicative Vulnerability

Short Form Consent (SFC) Process

When the SFC process is used:

- The short form consent (SFC) has only generic headers that correspond to each of the required elements of consent, with no information about the actual study in which the person is enrolling
- The non-English speaking individual has no documentation to refer to as they decide whether to participate or, if they do enroll, to refer to during the study
- Given the ethical and regulatory requirements for obtaining valid informed consent and ensuring the safety of subjects, in many if not most cases, the short form process falls short
- The intent of permitting the short form process has been to provide a mechanism for the ***unanticipated or unexpected*** **enrollment of non-English speaking individuals** when there is no IRB approved translated full consent document, and when it is clearly in the participant's best interest to enroll prior to obtaining a translated consent

301-Guideline: Enrolling Non-English-Speaking Subjects

What Does the Short Form Consent Actually Say?

INSTITUTE/CENTER:

PRINCIPAL INVESTIGATOR:

STUDY NUMBER:

STUDY TITLE:

You are being asked to participate in a research study. Before you agree, you must first be provided with a summary of the research study. This summary must contain the key information to help you understand the reasons why you might or might not want to join the study.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to stop.

After presenting the summary, the study team will provide you with additional details about the study which must include:

1) the purposes, procedures, and duration of the research;
2) any procedures which are experimental;
3) any reasonably foreseeable risks, discomforts, and benefits of the research;
4) any potentially beneficial alternative procedures or treatments; and
5) how confidentiality will be maintained.

Where applicable, the study team must also tell you about:

1) any available compensation or medical treatment if injury occurs;
2) the possibility of unforeseeable risks;
3) circumstances when the investigator may halt your participation;
4) any added costs to you;
5) what happens if you decide to stop participating;
6) when you will be told about new findings which may affect your willingness to participate;
7) how many people will be in the study;
8) use of your biologic specimens for commercial profit;
9) whether you will be told about your research results;
10) whether the research might include whole genome sequencing; and
11) any future research use of your information or biologic specimens.
12) For clinical trials: A description of this clinical trial will be available on https://www.clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Further, a description of this clinical trial may be available on https://www.clinicaltrials.gov consistent with NIH policy.

If you agree to participate, you must be given a signed copy of this document and a written summary of the research.

You may contact (name) [redacted] at (phone number) [redacted] any time you have questions about the research.

You may contact (name) [redacted] at (phone number) [redacted] if you have questions about your rights as a research subject or what to do if you are injured.

Signing this document means that the research study, including the above information, has been described to you orally, and that you voluntarily agree to participate.

Signature of Research Participant	Print Name of Research Participant	Date
Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is:_____.

Short Form Consent (SFC) Process

- *Unanticipated enrollment* means that the study team could not have reasonably known that they might enroll a person who doesn't speak English
- Typically, at the time a clinic appointment is made, the study team will be aware that a potential subject does not speak English and that an interpreter is needed
  - ➢ At this time, the study team should have the informed consent translated into the language of that person
  - ➢ The prospective subject's appointment may need to be delayed to obtain the translated document, unless it is clearly in the prospective subject's best interest to not delay and proceed with enrollment using the short form process
- When the short form process must be used, the limitations of this process can be mitigated in part by translating the consent promptly after enrollment and providing it to the individual that was consented using the short form

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Short Form Consent (SFC) Process

FDA guidance (2023)* on informed consent indicates that this is an expectation of the FDA any time a short form consent process is used and notes the following

1. Determine that there is sufficient justification to enroll the subject without using a translated long form to document the subject's informed consent
2. The SFC process (as described in the regulations) means using a translated short form and the English Long Form as the written summary

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FDA. Informed Consent Guidance for IRBs, Clinical Investigators, and Sponsors (2023)

Short Form Consent (SFC) Process

3. Additional steps after subject is enrolled (continued)

- "The investigator **must** obtain a translated copy of the IRB-approved English version of the long form that served as the written summary, which should be done promptly.
- The investigator promptly submits it to the IRB for review and approval.
- Once the translated long form/written summary is approved by the IRB, the investigator **must provide it to the subject or LAR and should do so as soon as possible**.
- FDA considers this step essential to the requirement that informed consent be documented by use of a written consent document and that the subject be provided a copy (21 CFR 50.27). Many of the clinical investigations regulated by FDA involve ongoing interventions and may involve long-term follow-up. For this reason, translation of the long form is critically important as a means of providing subjects or their LAR an ongoing source of information understandable to them."

FDA. Informed Consent Guidance for IRBs, Clinical Investigators, and Sponsors (2023)

Reporting Short Form Consent (SFC) Use via RNI

Process for submitting the RNI for **ALL** uses of the short form

- Inform the IRB of the use of the short form within 7 calendar days by submitting an RNI form in PROTECT
- This should be done for each use of the short form
- Provide the **justification for using the short form consent** process in the description of the event (**for both minimal risk (MR) and greater than minimal risk studies (GTMR)**)

Reporting SFC Use via RNI-MR Studies

When the protocol is **minimal risk**:

- Track the number of times the SFC is used in each language and include this information in the submitted RNI form
- Submit an RNI form in PROTECT within 7 calendar days
- Provide the justification for using the short form consent process in the description of the event (item 5 of the RNI form)
- If not done previously, when the short form consent is used three times for a given language, the short form process may no longer be used for that language, and the consent must be translated for any future subjects that speak that language
- Upon IRB approval, the PI must provide the translated long form to any subjects previously enrolled using the short form consent process who speak that language and who are still on study
- Include this information in a note in the medical/research record

301-Guideline: Enrolling Non-English-Speaking Subjects

SFC When Study is Greater Than Minimal Risk (GTMR)

- If there is no translated consent document available, enrollment of that individual should be delayed and an IRB approved translated consent should be obtained, UNLESS it is determined by the PI that it is justified to proceed because it is in the prospective subject's best interest to enroll prior to the translation
- The **best interest of the subject** means that it is necessary to ensure the rights, welfare, and safety of the prospective subject

  For example:

  - A trial with therapeutic intent and there is insufficient time to obtain the translation due to the rapidity of disease progression or severity of disease
  - Delaying consent would pose undue hardship on the prospective subject, for example due to travel distance, need for time off work/away from home, etc.

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SFC When Study is GTMR (continued)

- If the PI determines it to be justified to proceed with informed consent prior to translating the consent, and the short form consent process is used, this determination and the reasons for it must be documented in the research record and/or CRIS as part of the consent note
- Submit an RNI form in PROTECT within 7 calendar days
- Provide the justification for using the short form consent process in the description of the event (item 5 of the RNI form)
- If the non-English speaking person has agreed to participate using the short form process, the consent MUST be promptly translated into the subject's language
- After translation of the long form consent, submit it to the IRB along with the certificate of translation

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301-Guideline: Enrolling Non-English-Speaking Subjects

SFC Process – GTMR Studies (continued)

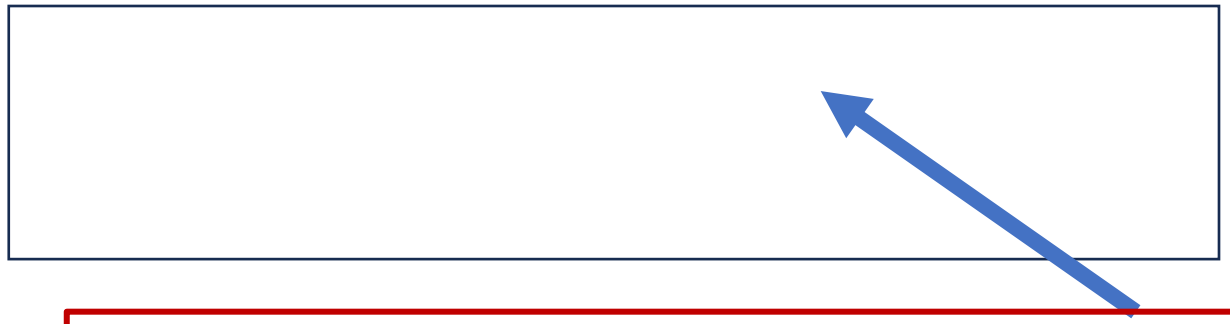
- After IRB approval, the translated long form should be provided to the subject
- Include this information in a note in the medical/research record
- Ideally, this should occur no later than 30 days following enrollment
- When the RNI is originally submitted, the Office of Compliance and Training will send a request for clarification asking for a response that reports the date that the translated long form consent is provided to the subject
- Respond to the request for clarification with the date the translated long form is provided to the subject and the RNI will be closed out

301-Guideline: Enrolling Non-English-Speaking Subjects

4. Identify the categories that represent the new information: (check all that apply)

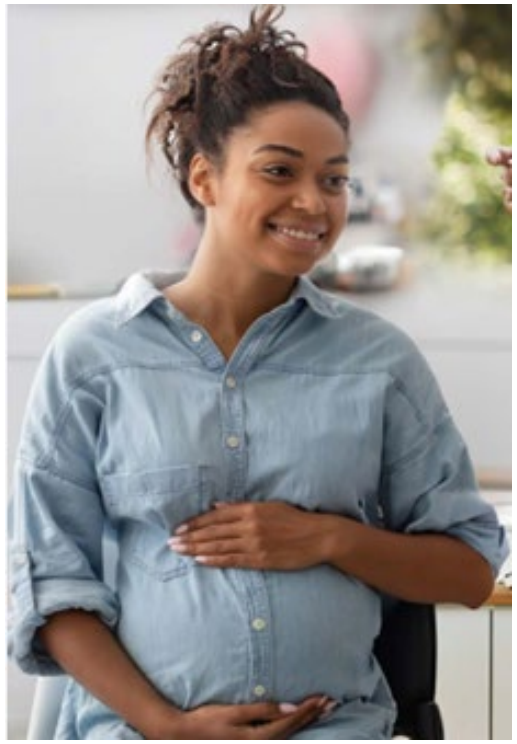
- Non-compliance: Failure of an investigator to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research, or the requirements or determinations of the Institutional Review Board (IRB), whether the failure is intentional or not.
- Major protocol deviation: Deviation from the IRB-approved protocol that has, or may have the potential to negatively impact, the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- New information that might affect a participant's willingness to enroll or remain in the study. Examples include, but are not limited to: (See examples on RNI form)
- Complaint: Complaint of a subject that cannot be resolved by the research team.
- Death of a subject deemed to be at least possibly due to the research.
- Unanticipated Problem involving risks to subjects or others (See specific criteria on RNI form)
- *Short Form Use: Use of the short form consent to enroll a non-English speaking subject.*
- Audit: Audit, inspection, or inquiry by a federal agency.
- Confidentiality: Breach of confidentiality
- Unreviewed change: Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.
- Incarceration: Incarceration of a subject in a study not approved by IRB to involve prisoners.
- Suspension: Premature suspension or termination of the research by the sponsor, investigator, or institution.

5. * Briefly describe the new event



- Include justification for use of the short form process (*for both MR and GTMR studies*)
- Provide the language of the short form consent document that was used
- If protocol is **minimal risk**, include the number of times the short form consent in that specific language has been used
- If the protocol is **greater than minimal risk,** a request for clarification will be sent when the RNI is submitted asking you to add the date (in item #5) that the relevant translated long form was provided to the subject
- Reply to the request for clarification with the date the subject was provided the IRB approved translated long form

Subpart B: Research Involving Pregnant Women, Human Fetuses and Neonates (and HRPP Policy 400)



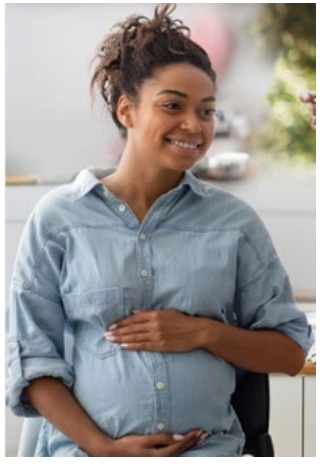
1975: HHS adopted regulations concerning pregnant women as research participants and included pregnant women as a "vulnerable population" deserving of special protection

- Regulations took a proscriptive approach: "No pregnant woman may be involved in research unless. . ."

Pre-2018 Common Rule and Pregnant Women

Pre-2018 Common Rule:

"When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, *pregnant women*, mentally disabled persons, and economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects."[Italics added.]



Pre-2018 Requirements

Ver en Español

Code of Federal Regulations

TITLE 45

PUBLIC WELFARE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 46

PROTECTION OF HUMAN SUBJECTS

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Revised January 15, 2009

Effective July 14, 2009

* * *

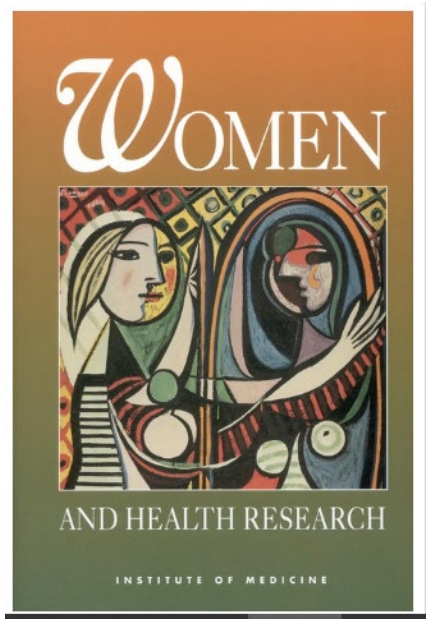
Historical Background

The Institute of Medicine (IOM) report, Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies (1994), commented on the HHS regulations related to research with pregnant women (Subpart B) noting the following:

- "Removal of pregnant women from the regulatory category of "vulnerable" potential participants would avoid any possible inference that pregnant women are less capable of making informed decisions by virtue of their pregnancy, than are other potential research participants."

The IOM:

- Urged that the prevailing presumption regarding the participation of pregnant women in clinical trials and other intervention studies be shifted from one of *exclusion* to one of *inclusion*



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IOM and Principle of Autonomy

The IOM:

- Unanimously endorsed the importance of recognizing in public policy and in the decisions made by IRBs and investigators, that pregnant women should be treated as competent adults capable of making their own decisions about participation in research
- Noted that it is the responsibility of investigators and IRBs to ensure that pregnant women are provided with adequate information about the risks and benefits to themselves, their pregnancies and their potential offspring

Why Should We Enroll Pregnant Persons in Clinical Trials?

Belmont Principle of Justice

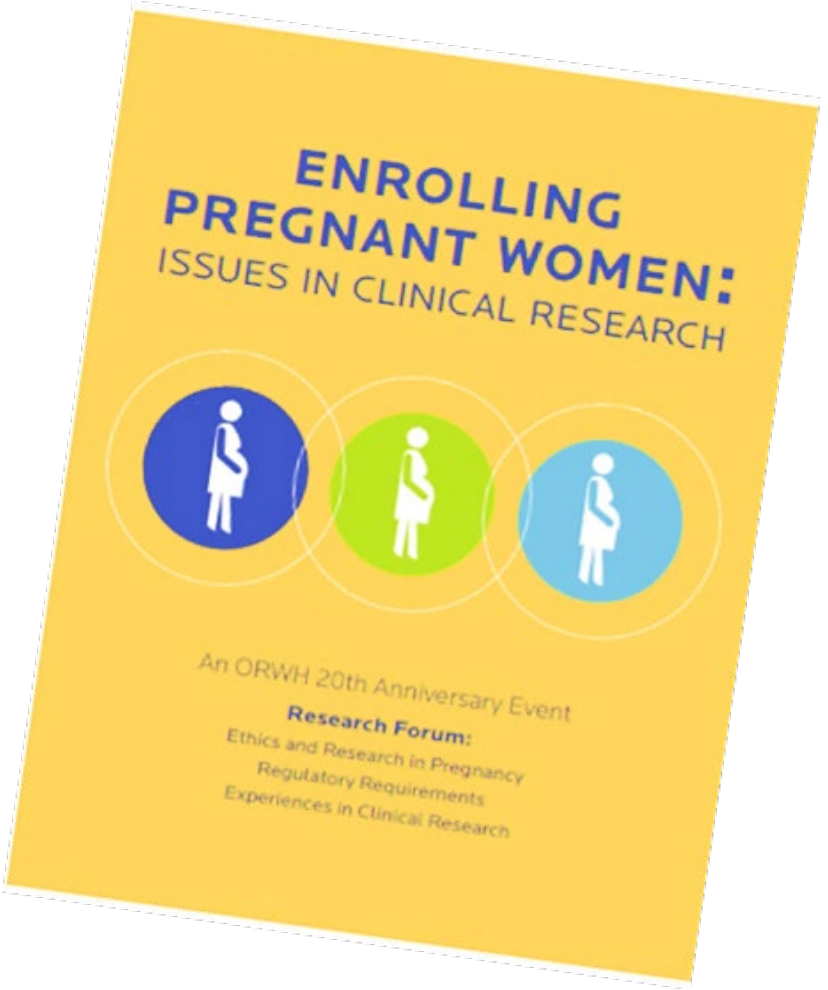
One of the three basic ethical principles discussed in the Belmont Report is Justice

- Exclusion of pregnant persons from clinical research may result in an unfair denial of benefits to the pregnant person or fetus that are unavailable outside the research setting
- Pregnant people need safe and effective treatment during pregnancy with pharmacokinetic information to identify appropriate therapeutic doses during pregnancy and to quantify risks of fetal exposure

NIH Office of Research on Women's Health

The NIH Office of Research on Women's Health (ORWH) published recommendations from a convened, *Enrolling Pregnant Women: Issues in Clinical Research* held in 2010

- As was the case in the IOM report, the ORWH emphasized the need to change the presumption of exclusion of pregnant women to one of inclusion
- Report reiterated that identifying pregnant women as a vulnerable population is a misnomer



Revised Common Rule (the 2018 Requirements)*

The IRB should be particularly cognizant of the special problems of research ~~involving~~ *that involves a category of subjects who are* vulnerable ~~populations~~ to coercion or undue influence, such as children, prisoners, ~~pregnant women, mentally disabled persons~~ *individuals with impaired decision-making capacity*, or economically or educationally disadvantaged persons

**Blue font* is new wording

45 CFR 46 (Subpart B): Enrollment of Pregnant Women or Fetuses in Trials Supported or Conducted by HHS

Must meet all 10 conditions:

1. Where scientifically appropriate, *preclinical studies*, including studies on pregnant animals, and clinical studies, including *studies on nonpregnant women*, have been conducted ***and*** provide data for assessing potential risks to pregnant women and fetuses
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of *direct benefit for the woman or the fetus*; OR, if there is *no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means*

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45 CFR 46 (Subpart B): Enrollment of Pregnant Women or Fetuses in Trials Supported or Conducted by HHS

3. Any *risk is the least possible* for achieving the objectives of the research
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, [and] *her consent is obtained* in accord with the informed consent provisions of Subpart A

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45 CFR 46 (Subpart B): Enrollment of Pregnant Women or Fetuses in Trials Supported or Conducted by HHS

5. If the research holds out the prospect of *direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained* in accord with the informed consent provisions of 45 CFR 46, subpart A, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest
6. Each individual providing consent is *fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate*

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45 CFR 46 (Subpart B): Enrollment of Pregnant Women or Fetuses in Trials Supported or Conducted by HHS

7. For *children as defined in §46.402(a) who are pregnant*, assent and permission are obtained in accord with the provisions of subpart D "*Additional Protections for Children Involved as Subjects in Research*"
8. *No inducements*, monetary or otherwise, will be offered to terminate a pregnancy
9. Individuals *engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy*
10. Individuals engaged in the research will have *no part in determining the viability of a neonate*

Can the Protocol be Approved Under Subpart B?

- Does the research have the prospect of direct benefit (DB) to the pregnant person and/or to the fetus?*
- Is the research no greater than minimal risk or does the research have a greater than minimal risk to the pregnant person and/or the fetus?**

(Respect for persons)

*Clinical Care is not considered a benefit of research

**Unlike HHS Subpart D regulations (research involving children), regulations for research involving pregnant people do not include consideration of research that represents a "minor increase over minimal risk." Addition of such a category was recommended in the 2018 report to the Secretary of HHS by the Task Force on Research Specific to Pregnant Women and Lactating Women that was established by the 21st Century Cures Act.

Research w/ Prospect of DB vs. No Prospect of DB

- Research that has the prospect of direct benefit (DB) to the pregnant person or the fetus is generally approvable even if greater than minimal risk when the other Subpart B requirements are also met
- When research involves pregnant people and there is no prospect of direct benefit to the pregnant person or fetus, the IRB may only approve the research if the risk to the fetus is no greater than minimal, and the "*purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means.*"
  - The PI must provide a justification in the protocol and the IRB must subsequently determine that the aim of gaining such knowledge cannot be achieved by enrolling only nonpregnant participants

Research > Minimal Risk with No Prospect of Direct Benefit

- Research involving pregnant people that is greater than minimal risk with no prospect of direct benefit to the pregnant person or the fetus cannot be approved by the IRB
- For studies that do not enroll pregnant people and that are greater than minimal risk, the protocol should address what will happen if participants become pregnant during the study

Interventional Studies

- For investigational treatment studies:
  - The protocol should indicate if pregnancy is an off-treatment criterion
  - If the participant's partner becomes pregnant and the intent is to continue to collect outcome data, the IRB must review and approve a consent form allows the partner to provide consent to have pregnancy outcome data collected, and the protocol should be revised to include a pregnant partner cohort
- For FDA regulated research, pregnancy outcome should be collected and reported

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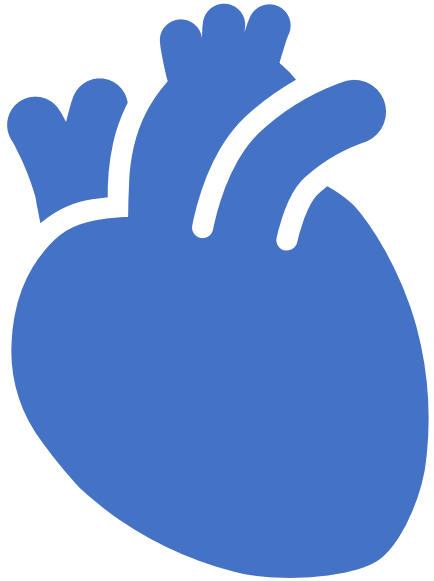
Interventional Studies: When a Participant Becomes Pregnant While on a Study with No Prospect of DB for the Pregnant Person or Fetus

If the protocol indicates that the participant will remain on study, it should include the following information:

- While pregnant, neither research interventions nor research tests or procedures that are greater than minimal risk will occur (because per the regulations, research with pregnant people that is > minimal risk is not approvable unless there is potential for direct benefit to the pregnant woman or fetus) **and**
- Explain the justification in the protocol for why the biomedical knowledge to be gained cannot be obtained from nonpregnant people

Participation of Pregnant People While on a Study with No Prospect of DB for the Pregnant Person or Fetus?



Example:

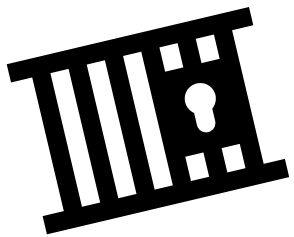
- In a natural history study of individuals with congenital heart disease, the PI explains that the only way to learn about critical physiologic differences between pregnant and nonpregnant individuals with this disease is to continue to follow pregnant people on study
- While pregnant, no research interventions, tests or procedures that are > minimal risk will be performed on the pregnant person

In this case, continued participation of a person who becomes pregnant can be approved by the IRB under the Subpart B regulations

Other NIH Policies

- When conducting research involving pregnant women, research with human fetuses or human fetal tissue, Principal Investigators (PIs) should be aware that other regulations and NIH policies apply
- These other requirements, including prohibited research, are not covered in Policy 400. Therefore, PIs should also review the *OIR Sourcebook: Special Research Considerations* when conducting research involving:
  - human embryonic stem cells (hESCs)
  - human induced pluripotent stem cells (iPSCs), or
  - human fetal tissue

Subpart C: Research Involving Prisoners (and HRPP Policy 401)



Prisoner*– Any individual who is:

- Involuntarily confined or detained (ability to leave the institution is restricted) in a penal institution (e.g., prison) having been sentenced to such an institution under a criminal or civil statute
- Detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution
- Detained pending arraignment, trial or sentencing

*45 CFR 46.303(c)

Research Involving Prisoners: Investigator Responsibilities

- When investigators anticipate the participation of prisoners on the research, this intent must be indicated in the protocol and any safeguards for prisoner-subjects must be described
- If a subject becomes incarcerated and the IRB and OHRP have not approved prisoner participation, the IRB must be notified ASAP, and all research interventions must cease until IRB and OHRP approval have been obtained
- However, in special circumstances if the PI believes it is in the best interest of the subject to remain on study, the PI must promptly notify IRBO and obtain permission from the IRB Chair to continue activities needed to ensure the safety and welfare of the now prisoner-subject until the IRB and OHRP approval is obtained

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Research Involving Prisoners: Investigator Responsibilities (continued)

- The PI must submit a modification requesting permission for the prisoner-subject to remain on study and include any additional safeguards and changes to procedures (if any) needed for the now-prisoner-subject to remain on the research
- If the IRB disapproves continued participation of the prisoner-subject, the subject must be taken off study

Subpart D: Research Involving Children (and HRPP Policy 402)

- **Children** – Are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted (45 CFR 46.402(a))
- For consent purposes, when research is conducted at an **NIH site**, children are less than 18 years of age
- Children who are legally emancipated are considered adults and the requirements of Policy 402 do not apply: Investigators **MUST** consult OHSRP who will contact OGC for guidance before considering a minor to be emancipated

(continued)

Research Involving Children

- Research involving children may not begin prior to IRB approval of the research
- Investigators must ensure the protocol and research comply with the basic protections for human subjects specified at 45 CFR 46 Subpart A and the additional requirements of 45 CFR 46 Subpart D
  - When research involves pregnant children (Subpart B), or child prisoners (Subpart C), the other subparts also apply
- For FDA-regulated research, investigators must also comply with all applicable FDA requirements

Subpart D Risk: Benefit Categories

46.404/50.51	research not involving > minimal risk
46.405/50.52	> minimal risk but with prospect of direct benefit (DB) to the individual subjects
46.406/50.53	no more than a minor increase over minimal risk and no PDB but likely to yield generalizable knowledge about the subject's disorder or condition
46.407/50.54	not otherwise approvable

§46.404 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
- Examples of Minimal Risk Activities:
  - Physical assessment, small volume routine
  - venipuncture for blood collection,
  - non-invasive specimen collection
  - non-contrast MRI without sedation
  - a single skin biopsy of < 3mm
- The regulations only permit healthy children to participate only when research involves no greater than minimal risk

§46.405 Research Involving Greater Than Minimal Risk But Presenting Prospect of Direct Benefit to Individual Subjects

- The IRB must find that the protocol meets the following points:
  - The risk is justified by the anticipated benefit to the subjects
  - The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches

§46.406 Research Involving Greater Than Minimal Risk and No Prospect of Direct Benefit to Individual Subjects, but Likely to Yield Generalizable Knowledge about the Subject's Disorder or Condition

The IRB must find that the protocol meets the following points:

- The risk represents a minor increase over minimal risk
- The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations
- The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition

§46.407 Research Not Otherwise Approvable Which Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Children

The following conditions must be met:

- The Secretary of HHS, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either

  (1) Research satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, OR

  (2) The following:

  (i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children

  (ii) The research will be conducted in accordance with sound ethical principles

  (iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in the regulations

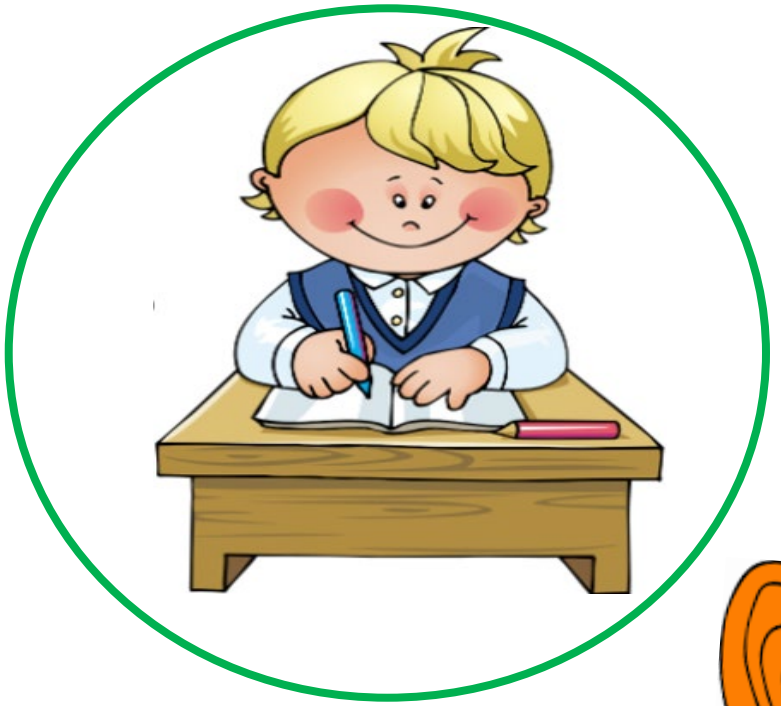
Parental Permission and Assent from the Minor

No child may be enrolled, screened, or have research procedures initiated unless parental permission and child assent are obtained consistent with the Common Rule and as applicable, FDA regulations

- Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under § 46.404 or § 46.405
- However, for research taking place at an NIH site, in cases where parents share joint legal custody for medical decision-making of a child (e.g., by a custody agreement or court order), **both** parents must give their permission regardless of the risk level of the research. Exceptions may include if one parent has since died, become incompetent, or is not reasonably available. Both parents must give their permission for research covered under §46.406 and 46.407 unless one parent is deceased, unknown, or not reasonably available
- Consult with the OHSRP, when questions arise about what constitutes being "not reasonably available"
- Note that federal regulations require additional steps if wards of the state will be enrolled. Consult policy 402 and OHSRP for additional information

Assent

- Assent in terms of the federal regulations for protection of research subjects means:
  - *. . . a child's affirmative agreement to participate in research*
  - *Mere failure to object should not, absent affirmative agreement, be construed as assent*



Assent

- The IRB requires **child assent** unless it can be appropriately waived, or if the child is not capable of providing assent. If an investigator wishes for the IRB to waive assent for some or all the participants, this should be described in the protocol and the conditions under which the waiver will apply.
- When the IRB determines that assent is required, it determines whether and how assent must be documented: The assent process may be either verbal or written.
- The IRB may only waive assent of the child if it determines that specific conditions are met:
  - if the capability of some or all the children is so limited that they cannot reasonably be consulted
  - if the intervention or procedure involved in the research holds out the prospect of direct benefit to the health or well-being of the children and is available only in the context of the research
  - if the research meets the same conditions as those for waiver or alteration of informed consent in research involving adults

PI Responsibilities When Enrolling Minors: Protocol

Protocol

- Describe how parental permission and assent from the minor subject will be obtained
- In cases where the participant is a minor, Policy 402 states “When the IRB determines that assent is required, it shall determine whether and how assent must be documented. The assent process may be either verbal or written.”
  - PI should submit a proposal in the protocol, describing which age groups will be able to provide assent, and which will not provide assent
  - Written assent should be obtained whenever possible
  - Use the appropriate consent and assent templates from the OHSRP website
  - If you will enroll older minors and do not have a separate assent form, the “Assent” block on the long form ICF can be used but this plan be described in the protocol.
- Address consent processes for children who become adults or emancipated during a study

Obtaining Assent from Older Minor Subjects

Parent/Guardian of a Minor Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I give permission for my child to take part in this study.

Signature of Parent/Guardian	Print Name of Parent/Guardian	Date
Signature of Parent/Guardian	Print Name of Parent/Guardian	Date

Assent: I have had this study explained to me in a way that I understand, I have been given the opportunity to discuss it, and I have had the chance to ask questions. I agree to take part in this study.

Assent of Minor:

Signature of Minor	Print Name of Minor	Date

PI Responsibilities When Enrolling Minors: Processes

Parental Permission and Assent Processes

- All investigators are responsible for complying with IRB requirements for obtaining and documenting parental permission and assent, as applicable, or they must provide a justification in the protocol for requesting a waiver of parental permission and/or assent
- When child subjects reach the age of majority, investigators must seek legally effective informed consent from the now-adult subject or withdraw the subject from the research
  - Alternatively, the investigator may request a waiver of consent from the IRB for the subject's continued participation if the ongoing research meets the criteria for a waiver specified in federal regulations*
  - If the now-adult subject is unable to provide legally effective informed consent, the requirements of Policy *3014-403 Research Involving Adults Who Lack Decision-making Capacity to Consent to Research Participation* must be followed

* 45 CFR 46.116(f)(3) of the 2018 Common Rule

HRPP Policy 403: Research Involving Adults Who Lack Decision-Making Capacity to Consent to Research Participation

- Factors impacting an adult's capacity to consent to research participation
  - dementia
  - stroke
  - traumatic brain injury
  - developmental disorders
  - intellectual disabilities
  - serious mental illness

- Why Enroll Potential Subjects Who Lack Consent Capacity?
  - There is a need for research intended to improve detection, diagnosis and treatment of these conditions and this requires inclusion of these individuals in this research
  - Additionally, individuals who lack consent capacity may be eligible for protocols that are unrelated to their cognitive capacity but for which there may be prospect of direct benefit

HRPP Policy 403: Research Involving Adults Who Lack Decision-Making Capacity to Consent to Research Participation

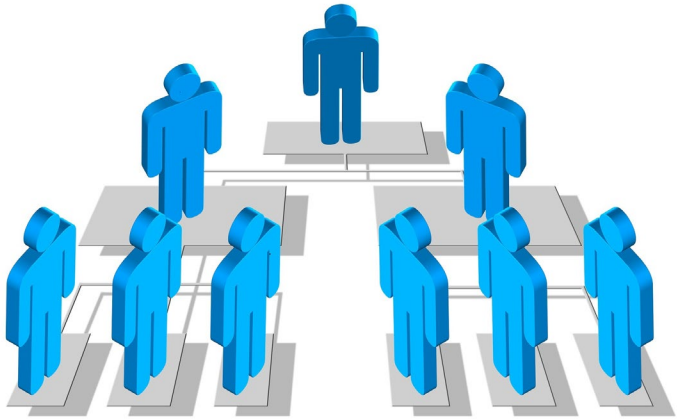
- NIH investigators will not initiate research that enrolls subjects without capacity or include subjects who lose capacity during the research without IRB approval unless a subject with capacity consented to the research and has a temporary loss of capacity (e.g., they are expected to regain capacity)
- The NIH IRB will only approve research that permits the participation of subjects without capacity if it has determined and documented that the research meets one of four specific risk/benefit categories
- NIH policy outlines the hierarchy for determining who may serve as the legally authorized representative (LAR) at an NIH site (for research conducted at non-NIH sites this may vary due to state law or institutional policy)

Research Involving Adults Who Lack Decision-making Capacity to Consent to Research Participation

Category	Risk: Benefit
Category A	Minimal risk
Category B	> Minimal risk but with a prospect of direct benefit to the participant
Category C	> minimal risk without a prospect of direct benefit, if the risk is no more than a minor increase over minimal, and it does not adversely affect the rights, safety or welfare of the subject
Category D	> minimal risk with no prospect of direct benefit if it has undergone additional institutional review and approval by the NIH Institutional Official

LAR Hierarchy

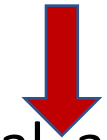
- Court appointed guardian
- Appointed Durable Power of Attorney (DPA) for Healthcare
- If subject does not have either of the above but understands the DPA process, they may appoint at DPA
- If the above LARs do not apply, next of kin applies (in this order, and for Categories A, B and C **only**)
    - Spouse or domestic partner
    - Adult child
    - Parent
    - Adult Sibling
    - Other Relative



When Subjects Who Previously Had Consent Capacity Lose It : Temporary vs. Permanent Loss

Investigator Responsibilities: Process Implications

- When a subject with capacity who provided initial consent for research participation has a subsequent **temporary** loss of capacity (e.g., they are expected to regain capacity), reconsent of the subject by the LAR is **not** required for the subject's continued participation in the research
- If the research has not been approved by the IRB for inclusion of subjects without capacity, and a subject who had capacity previously provided consent for themselves subsequently loses capacity **permanently, AND**
- The research involves continued interactions or interventions with the subject (excluding only data or specimen analysis)



- The PI **must** obtain IRB approval, and consent from the LAR for the subject without capacity to remain on the research

HRPP Policy 403 Research Involving NIH Staff as Subjects

- NIH staff and immediate family members of the study team are generally permitted to participate in NIH research, but must comply with NIH Policy including:
  - Prohibitions or restrictions by the staff member's Institute or Center
  - NIH compensation requirements
  - NIH leave requirements (See NIH Manual Chapter: 2300-630-3)
- NIH staff interested in participating in NIH Research should review the NIH Frequently Asked Questions (FAQs) for Staff Who are Considering Participation in NIH Research

Research Involving NIH Staff as Subjects: Studies with Prospect of Direct Benefit (DB) vs. No Prospect of DB

- For research with **prospect of DB**, NIH PIs are not required to obtain IRB approval for enrollment of NIH staff or the immediate family members of the study team
- When research offers **no prospect of direct benefit**, the IRB must prospectively approve inclusion of this group, and the protocol must describe:
  - Whether staff or family members will be included
  - Safeguards for this population
  - Recruitment plan
    - Solicitation of subordinates should not be direct
    - Recruitment materials may be displayed only where public announcements are permitted

NIH Staff as Subjects: Additional Concerns

There may be potential for undue pressure on potential subjects to participate the research in some situations:

- Immediate family members of the study team are recruited or enrolled on NIH research
- NIH staff have a subordinate relationship to an investigator on the study team or is part of the work unit where the research is taking place

(continued)

NIH Staff as Subjects: Additional Concerns (continued)

If a member of the study team participates as a subject on their own research, or if they are in a subordinate relationship with an investigator of part of the work unit where the research is taking place, there may be potential adverse effects such as the following:

- Scientific integrity
- Subject safety

NIH Staff Member in a Subordinate Relationship: Investigator Responsibilities

If the potential participant is an NIH staff member who is in a subordinate relationship with an investigator on the research team or is part of the work unit where the research is taking place:

- PI must ensure that the potential participant is informed that neither participation nor refusal to participate as a research subject will have an effect, either beneficial or adverse, on the subject's employment, training, or position at the NIH
- Whenever possible, consent should be obtained by an individual in a non-supervisory relationship with the subject
- A consent monitor or other qualified investigator must be present to observe the consent

Vulnerability Related to Third Party Risk

- **Terminology**
  - Non-subjects: “living individuals who are, or who are likely to be, exposed to research risk and who do not meet the regulatory definition of human subject (SACHRP)*
  - Bystander risk: “The prospect of harm to identifiable individuals or groups of individuals, other than research subjects themselves, that is a direct consequence of the research activities (as opposed to the knowledge such research activities generate and their application)”**

- *SACHRP. The Protection of Non-Subjects from Research Harm (2022)
- ** Kimmelman J. OHRP Exploratory Workshop. *Review of the Third-Party Research Risk: Is there a role for IRBS?* (2021)

One Way to Divide Potential Third-party Risks

3rd party is affected by a research intervention

vs.

Harms to the larger community from which subjects are drawn resulting from

- study design or conduct
- results/conclusions and dissemination of results

Types of 3rd Party Risks

Physical

Social, legal, and psychological

Cultural/Community

References and Links

NIH POLICIES

400: Research Involving Pregnant Women, Human Fetuses and Neonates

401: Research Involving Prisoners

402: Research Involving Children

403: Research Involving Adults Who Lack Decision-making Capacity to Consent to Research Participation

404: Research Involving NIH Staff as Subjects

GENERAL references and regulations

- Belmont Report (1978)
- 45 CFR 46 (2018 Requirements)
- Kipnis K. Vulnerability in research subjects: a bioethical taxonomy. In: *Ethical and Policy Issues in Research Involving Human Participants. Volume II: Commissioned Papers.* National Bioethics Advisory Commission. (2001)
- Gordon BG. Vulnerability in Research: Basic Ethical Concepts and General Approach to Review. Ochsner J. 2020 Spring;20(1):34-38.

References and Links

Research Involving Pregnant Persons

- NIH Office of Research on Women's Health, *Enrolling Pregnant Women: Issues in Clinical Research* (2010)

Research Involving Prisoners

- OHRP Guidance- Prisoner Involvement in Research (2003)
- OHRP Prisoner Research FAQs

Research Involving Children

- OHRP Research with Children FAQs
- OHRP Special Protections for Children as Research Subjects
- Children as Research Subjects and the HHS "407" Process

Research With Subjects Who Lack Capacity To Consent To Research

- Clinical Center (CC) Bioethics Consultation Service (including the Ability to Consent Assessment Team (ACAT))
- NIMH Human Subjects Protection Unit

References and Links

Research With Subjects Who Are Non-English Speaking

- Guidance for obtaining consent to participate in research from non-English speaking participants (Accompanies NIH Policy 301, Informed Consent. Download the pdf)
- FDA. Informed Consent Guidance for IRBs, Clinical Investigators, and Sponsors (2023)

Third Party Research Risk

- SACHRP. *The Protection of Non-Subjects from Research Harm* (2022)

Questions?

Thank You

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