



Title:	Vulnerable Subjects in Research		
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1 Purpose

When some or all of the participants in a research conducted under the auspices of the University of North Carolina at Chapel Hill (UNC-Chapel Hill) are likely to be vulnerable to coercion or undue influence or have diminished decision-making capacity, the research must include additional safeguards to protect the rights and welfare of these participants. The IRB must ensure that all of the regulatory requirements for the protection of vulnerable subjects are met and that appropriate additional protections for vulnerable subjects are in place.

The following procedures describe the requirements for involving vulnerable participants in research under the auspices of the UNC-Chapel Hill.

2 Procedure

2.1 Involvement of Vulnerable Populations

If the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process should include one or more individuals who are knowledgeable about or experienced in working with these participants. The IRB may include one or more individuals who are knowledgeable about or experienced in working with individuals from these populations or it may seek such expertise through the use of consultants.

45 CFR 46 has additional subparts designed to provide extra protections for vulnerable populations which also have additional requirements for IRBs.

Subpart B - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Subpart C - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Subpart D - Additional Protections for Children Involved as Subjects in Research

DHHS-conducted or supported research that involves any of these populations must comply with the requirements of the relevant subparts. Research funded by other federal agencies may or may not be covered by the subparts.

In its FWA, the UNC-Chapel Hill limits its commitment to apply Subparts B, C, and D to non-exempt human subjects research conducted or supported by DHHS or any other federal agency that requires compliance with the Subpart(s) (B, C, or D) applicable to the research.

The following policies and procedures, which are based on Subparts B, C, and D, apply to all research regardless of funding. The individual sections describe how the subparts apply specifically to DHHS-funded research.

2.2 Responsibilities

1. The investigator is responsible for identifying the potential for enrolling vulnerable subjects in the research proposal, including the possible inclusion of subjects who are at risk for impaired decisional capacity, and who are being asked to participate in a research study with greater than minimal risk.
2. The IRB shall include representation, either as members or through the use of consultants, of individual(s) who are knowledgeable about or experienced working with the vulnerable populations involved in the research proposal under review.
3. The IRB reviews the investigator's justifications for including vulnerable populations in the research to assess appropriateness for inclusion in the research proposal.
4. The IRB must ensure that appropriate additional safeguards have been included in each study to protect the rights and welfare of vulnerable subjects at the time of initial review of the research proposal.
5. Information reviewed as part of the continuing review process should include the number of participants considered to be members of specific vulnerable populations.

2.3 Review Procedures

2.3.1 Initial Review of Research Proposal

1. The investigator identifies the potential to enroll vulnerable subjects in the proposed research at initial review and provides the justification for their inclusion in the study.
2. The investigator describes safeguards to protect the subject's rights and welfare in the research proposal.
3. The IRB evaluates the proposed safeguards, including, if applicable, the proposed plan for obtaining consent from legally authorized representatives and the plans for assent of children and adults unable to provide consent.
4. The IRB evaluates the research to determine the need for additional protections and considers, if appropriate, the use of a data and safety monitoring board, consent monitor, or research subject advocate.

2.3.2 Continuing Review and Monitoring

At Continuing Review the investigator should identify the number and categories of vulnerable subjects enrolled and any problems that arose relevant to their rights and welfare.

2.4 Research Involving Pregnant Women, Human Fetuses and Neonates

The following applies to all research regardless of funding source. According to the UNC-Chapel Hill FWA, Subpart B of 45 CFR 46 applies only to DHHS-funded research, the funding-source specific requirements are noted in the appropriate sections.

2.4.1 Research Involving Pregnant Women or Fetuses

2.4.1.1 Research Not Conducted or Supported by DHHS

For research not funded by DHHS where the risk to the pregnant women and fetus is no more than minimal, no additional safeguards are required and there are no restrictions on the involvement of pregnant women in research.

Pregnant women or fetuses may be involved in research not funded by DHHS involving more than minimal risk to pregnant women and/or fetuses if all of the following conditions are met:

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant 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;
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, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent;
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 provisions for informed consent, 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 under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children (as defined in Section 2.6) who are pregnant, assent and permission are obtained in accord with the requirements of state law and the IRB;
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; and
10. Individuals engaged in the research have no part in determining the viability of a neonate.

2.4.1.2 Research Conducted or Supported by DHHS

For DHHS-conducted or supported research 45 CFR Subpart B applies to all non-exempt human subject research involving pregnant women, fetuses, and neonates.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant 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;
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, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent.
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 provisions for informed consent, 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 under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children (as defined in Section 2.5) who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 2.6.2;
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; and
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

2.4.2 Research Involving Neonates of Uncertain Viability or Nonviable Neonates

Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
3. Individuals engaged in the research will have no part in determining the viability of a neonate.
4. The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below in this section) have been met as applicable.

2.4.2.1 Neonates of Uncertain Viability.

Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research unless the following additional conditions have been met:

The IRB determines that:

1. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
2. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
3. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with the provisions of permission and assent, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

2.4.2.2 Nonviable Neonates.

After delivery, nonviable neonates may not be involved in research unless all of the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained;
2. The research will not terminate the heartbeat or respiration of the neonate;
3. There will be no added risk to the neonate resulting from the research;
4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
5. The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply.

However, if either parent is unable to consent because of unavailability or incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph.

2.4.3 Viable Neonates

A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements for Research Involving Children (i.e., a viable neonate is a child for purposes of applying federal regulations and the UNC-Chapel Hill policies).

2.4.4 Research Involving, After Delivery, the Placenta, the Dead Fetus or Fetal Material

Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, must be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.

If information associated with material described above in this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent sections of these policies and procedures are applicable.

2.4.5 Research Not Otherwise Approvable

2.4.5.1 Research Not Conducted or Supported by DHHS

If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and the research is not approvable under the above provisions, then the IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on either:

1. That the research in fact satisfies the conditions detailed above, as applicable; or
2. The following:
 - a. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
 - b. The research will be conducted in accord with sound ethical principles; and
 - c. Informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of this manual.

2.4.5.2 Research Conducted or Supported by DHHS

DHHS conducted or supported research that falls in this category must be approved by the Secretary of Health and Human Services. If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and the research is not approvable under the above provisions, then the research will be sent to OHRP for DHHS review.

2.5 Research Involving Prisoners

The following applies to all research involving prisoners, regardless of funding source. The requirements in this section are consistent with Subpart C of 45 CFR 46, which applies to DHHS-funded or supported research. When following Department of Justice regulations, for research conducted within the Bureau of Prisons: implementation of Bureau programmatic or operational initiatives made through pilot projects is not considered to be research.

2.5.1 Applicability

This policy applies to all biomedical and behavioral research conducted under the auspices of the UNC-Chapel Hill involving prisoners as subjects. Even though the IRB may approve a research study involving prisoners as subjects according to this policy, investigators are still subject to the Administrative Regulations of the NC Department of Corrections and any other applicable State or local law. [45 CFR 46.301]

2.5.2 Minimal Risk

Minimal risk, in studies involving prisoners, means the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

2.5.3 Composition of the IRB

In addition to satisfying the general membership requirements detailed in other sections of these policies and procedures, when reviewing research involving prisoners, the IRB must also meet the following requirements:

- A majority of the IRB (exclusive of prisoner members) must have no association with the prison(s) involved, apart from their membership on the IRB
- At least one member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement
- The prisoner representative must be a voting member of the IRB. A comment may be added to the roster indicating that the prisoner representative will only count

towards quorum when he or she is in attendance and reviewing studies covered by subpart C

2.5.4 Review of Research Involving Prisoners

1. Initial Review

- a. The prisoner representative must review research involving prisoners, focusing on the requirements in Subpart C.
- b. The prisoner representative must receive all review materials pertaining to the research (same as primary reviewer).

2. Modifications

- a. Minor modifications to research may be reviewed using the expedited procedure described below, using either of the two procedures described based on the type of modification.
- b. Modifications involving more than a minor change reviewed by the convened IRB must use the same procedures for initial review including the responsibility of the prisoner representative to review the modification and participate in the meeting (as described above).

3. Continuing review

Continuing review must use the same procedures for initial review including the responsibility of the prisoner representative to review the continuing review materials and participate in the meeting (as described above).

4. Research Involving Prisoners, Reviewed by Expedited Review

- a. Research involving interaction with prisoners may be reviewed by the expedited procedure, if a determination is made that the research involves no greater than minimal risk for the prison population being studied and the research falls within the categories of research eligible for expedited review.
- b. The prisoner representative must concur with the determination that the research involves no greater than minimal risk.
- c. The prisoner representative must review the research as a reviewer, designated by the chair, or consultant. This may be as the sole reviewer or in addition to another reviewer, as appropriate.
- d. Review of modifications and continuing review must use the same procedures as initial review.
- e. Research that does not involve interaction with prisoners (e.g., existing data, records review, etc.) may be reviewed by the expedited procedure, if a determination is made that the research involves no greater than minimal risk for the prison population being studied. Review by a prisoner representative is not required. The prisoner representative may review the research as a reviewer (if designated by the IRB Chair as

an expedited reviewer) or consultant. Review of modifications and continuing review will follow these same procedures.

5. Research Involving Prisoners, Reviewed by the Convened IRB

a. The prisoner representative must present his/her review either orally or in writing at the convened meeting of the IRB when the research involving prisoners is reviewed.

b. Continuing review – must use the same procedures for initial review including the responsibility of the prisoner representative to review the continuing review materials and participate in the meeting (as described above).

c. If no subjects have been enrolled, the research may receive continuing review using the expedited procedure under expedited category #8.

2.5.5 Incarceration of Enrolled Subjects

If a participant becomes a prisoner while enrolled in a research study that was not reviewed according to Subpart C, the investigator must promptly notify the IRB and the IRB shall:

1. Confirm that the participant meets the definition of a prisoner.

2. Consult with the investigator to determine if it is in the best interests of the participant to continue participation in the study, in part or in full, and if so, if there are specific study activities which are in the best interests of the subject and should continue until the IRB is able to review the research study under Subpart C.

3. If the participant should continue, one of two options are available:

a. Keep the participant enrolled in the study and review the research under Subpart C. If some of the requirements of Subpart C cannot be met or are not applicable (e.g., procedures for the selection of subjects within the prison), but it is in the best interests of the participant to remain in the study, keep the participant enrolled and inform OHRP of the decision along with the justification.

b. Terminate enrollment of the participant from the study and keep the participant on the study intervention under an alternate mechanism such as compassionate use, off label use, etc.

4. If a participant is incarcerated temporarily while enrolled in a study:

a. If the temporary incarceration has no effect on the study (i.e., there is no need for study activities to take place during the temporary incarceration), keep the participant enrolled.

b. If the temporary incarceration has an effect on the study, follow the above guidance.

2.5.6 Additional Duties of the IRB

In addition to all other responsibilities prescribed for IRB in other sections of this manual, the IRB will review research involving prisoners and approve such research only if it finds that:

- The research falls into one of the following permitted categories [45 CFR 46.306(a)(2)]:
 - Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
 - Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
 - Research on conditions particularly affecting prisoners as a class (for example, research on diseases or social and psychological problems much more prevalent in prisons) provided that the study may proceed only after the DHHS Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research;
 - Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols/research plans approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the DHHS Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research
- Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
- The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
- Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the investigator provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
- The information is presented in language which is understandable to the subject population;
- Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is

clearly informed in advance that participation in the research will have no effect on his or her parole; and

- Where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing subjects of this fact.

2.5.7 Certification to DHHS

Under 45 CFR 46.305(c), the institution responsible for conducting research involving prisoners that is conducted or supported by DHHS shall certify to the Secretary (through OHRP) that the IRB has made the seven findings required under 45 CFR 46.305(a) and receive OHRP authorization prior to initiating any research involving prisoners. Certifications, and requests for DHHS Secretarial consultation, do not need to be submitted to OHRP for research not conducted or supported by DHHS, regardless of whether the institution has chosen to extend the applicability of its FWA and Subparts B, C, and D to all research.

For all DHHS conducted or supported research, OHRE Director will send to OHRP a certification letter to this effect, which will also include the name and address of the institution and specifically identify the research study in question and any relevant DHHS grant application or protocol/research plan. DHHS conducted or supported research involving prisoners as subjects may not proceed until OHRP issues its authorization in writing to the UNC-Chapel Hill on behalf of the Secretary under 45 CFR 46.306(a)(2).

Under its authority at 45 CFR 46.115(b), OHRP requires that the institution responsible for the conduct of the proposed research also submit to OHRP a copy of the research proposal so that OHRP can determine whether the proposed research involves one of the categories of research permissible under 45 CFR 46.306(a)(2), and if so, which one.

The term "research proposal" includes:

- The IRB-approved protocol/research plan; any relevant DHHS grant application or proposal;
- Any IRB application forms required by the IRB;
- And any other information requested or required by the IRB to be considered during initial IRB review.

OHRP also encourages the organization to include the following information in its prisoner research certification letter to facilitate processing:

- The OHRP Federalwide Assurance (FWA) number;
- The IRB registration number for the designated IRB; and
- The date(s) of IRB meeting(s) in which the study was considered, including a brief chronology that encompasses:
 - The date of initial IRB review; and

- The date of subpart C review, if not done at the time of initial IRB review.

2.5.8 Waiver for Epidemiology Research

The DHHS Secretarial waiver for certain epidemiological research conducted or supported by DHHS functions as a fifth category of permissible research [68 FR 36929]. The criteria for this category are that the research must have as its sole purpose (i) to describe the prevalence or incidence of a disease by identifying all cases, or (ii) to study potential risk factor associations for a disease, and where the IRB has approved the research and fulfilled its duties under 45 CFR 46.305(a)(2)-(7) and determined that (i) the research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and (ii) prisoners are not a particular focus of the research. The specific type of epidemiological research subject to the waiver involves no more than minimal risk and no more than inconvenience to the human subject participants. The waiver would allow the conduct of minimal risk research that does not now fall within the categories set out in 45 CFR 46.306(a)(2).

The organization still must review the research under subpart C and certify to OHRP that an appropriately constituted IRB has reviewed the proposal and made all other required findings under DHHS regulations at 45 CFR 46.305(a) and receive OHRP authorization prior to initiating any research involving prisoners. All of the other requirements of subpart C apply to research in this category.

2.6 Research Involving Children

The following applies to all research involving children, regardless of funding source. The requirements in this section are consistent with Subpart D of 45 CFR 46, which applies to DHHS-funded research and Subpart D of 21 CFR 50, which applies to FDA-regulated research involving children. The IRB determines whether the criteria for approval of research are met when research involves children.

2.6.1 Allowable Categories

In addition to the IRB's normal duties, research involving children must be reviewed by the IRB to determine if it fits within and is permissible under one or more federally-defined categories (OHRP/FDA). Each procedure or intervention that the child will undergo for the research must be taken into consideration. The categories are as follows:

1. [45 CFR 46.404/21 CFR 50.51] Research/Clinical Investigations not involving greater than minimal risk. Research determined to not involve greater than minimal risk to child subjects may be approved by the IRB only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in Section 2.6.2.
2. [45 CFR 46.405/21 CFR 50.52] Research/Clinical Investigations involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a

monitoring procedure that is likely to contribute to the subject's well-being, may be approved by the IRB only if the IRB finds and documents that:

- 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 options; and
- Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 2.6.2.

3. [45 CFR 46.406/21 CFR 50.53] Research/Clinical Investigations involving greater than minimal risk and no prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition. Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, may be approved by the IRB only if the IRB finds and documents that:

- 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; and
- Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 2.6.2.

4. [45 CFR 46.407/21 CFR 50.54] Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children.

When the IRB does not believe that the research meets the requirements of any of the above categories, and the IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the IRB shall refer the research for further review as follows:

- HHS conducted or supported research in this category will be referred for review by the Secretary of Health and Human Services. However, before doing so the IRB must determine and document that the proposed research also meets all of the requirements of the Common Rule.
- FDA-regulated research in this category will be referred for review by the Commissioner of Food and Drugs.

- The federal agency, 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, determined either:
 - That the research fell into categories [45 CFR 46.404/21 CFR 50.51], [45 CFR 46.405/21 CFR 50.52] , [45 CFR 46.406/21 CFR 50.53]; or
 - The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children and the research will be conducted in accordance with sound ethical principles.
 - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 2.6.2.

2.6.2 Parental Permission and Assent

2.6.2.1 Parental Permission

The IRB must determine that adequate provisions have been made for soliciting the permission of each child's parent or guardian.

Parents or guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary, as described in SOP 1101.2.5.

The IRB may find that the permission of one parent is sufficient for research to be conducted under Categories 1 [45 CFR 46.404/21 CFR 50.51] & 2 [45 CFR 46.405/21 CFR 50.52] above. The IRB's determination of whether permission must be obtained from one or both parents will be documented in the reviewer's notes when a study receives expedited review, and in meeting minutes when reviewed by the convened committee.

Permission from both parents is required for research to be conducted under Categories 3 [45 CFR 46.406/21 CFR 50.53] & 4 [45 CFR 46.407/21 CFR 50.54] above unless

1. One parent is deceased, unknown, incompetent, or not reasonably available; or
2. When only one parent has legal responsibility for the care and custody of the child.

For research not covered by the FDA regulation, the IRB may waive the requirement for obtaining permission from a parent or legal guardian if:

- The research meets the provisions for waiver in SOP 1101.2.9 or
- If the IRB determines that the research is designed to study conditions in children or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children) provided that an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal, State, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described

in the protocol/research plan, the risk and anticipated benefit to the research subjects, and the child's age, maturity, status, and condition.

Parental permission may not be waived for research covered by the FDA regulations.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by SOP 1101.2.7.

2.6.2.2 Assent from Children

The IRB is responsible for determining that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. This judgment may be made for all children to be involved in the study, or for each child, as the IRB deems appropriate.

When the IRB determines that assent is not a requirement of some children, the IRB determines and documents which children are not required to assent. When the IRB determines that assent is not a requirement for some or all children, the IRB determines and documents one or more of the following:

- The children are not capable of providing assent based on the age, maturity, or psychological state. UNC does not require *written* assent from children six years of age or younger.
- The capability of the children is so limited that they cannot reasonably be consulted.
- The intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the child and is available only in the context of the research.
- Assent can be waived using the criteria for waiver of the consent process.

It is important to note that the FDA regulations do permit the IRB to waive the assent requirement if it finds and documents that:

1. The clinical investigation involves no more than minimal risk to the subjects;
2. The waiver will not adversely affect the rights and welfare of the subjects;
3. The clinical investigation could not practicably be carried out without the waiver; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Because "assent" means a child's affirmative agreement to participate in research, the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way.

The IRB should take into account the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects. For research activities involving adolescents whose capacity to understand resembles that of

adults, the assent procedure should likewise include information similar to what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity, but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (for example, what the experience will be, how long it will take, whether it might involve any pain or discomfort). The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve.

Parents and children will not always agree on whether the child should participate in research. Where the IRB has indicated that the assent of the child is required in order for him or her to be enrolled in the study, dissent from the child overrides permission from a parent. Similarly, a child typically cannot decide to be in research over the objections of a parent. There are individual exceptions to these guidelines but in general, children should not be forced to be research subjects, even when permission has been given by their parents.

2.6.2.2.1 Documentation of Assent

When the IRB determines that assent is required, it also is also responsible for determining whether and how assent must be documented. When the research targets the very young child or children unable or with limited capacity to read or write, an oral presentation accompanied perhaps by some pictures with documentation of assent by the person obtaining assent in a research note is likely more appropriate than providing the child a form to sign. In this case, the investigator should provide the IRB with a proposed script and any materials that they intend to use in explaining the research.

When the research targets children who are likely able to read and write, investigators should propose a process and form that is age appropriate and study specific, taking into account the typical child's experience and level of understanding, and composing a document that treats the child respectfully and conveys the essential information about the study. The assent form should:

1. Tell why the research is being conducted;
2. Describe what will happen and for how long or how often;
3. Say it's up to the child to participate and that it's okay to say no;
4. Explain if it will hurt and if so for how long and how often;
5. Say what the child's other choices are;
6. Describe any good things that might happen;
7. Say whether there is any compensation for participating; and
8. Ask for questions.

Whenever possible, the document should be limited to one page. Illustrations might be helpful, and larger type and other age appropriate improvements are encouraged when they have the potential to enhance comprehension. Studies involving older children or adolescents should include more information and may use more complex language.

2.6.3 Children Who are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406/21 CFR 50.53 or 45 CFR 46.407/21 CFR 50.54 (Categories 3 & 4 in Section 2.6.1), only if such research is:

1. Related to their status as wards; or
2. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

If the research meets the condition(s) above, an advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in loco parentis.

The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

2.7 Adults with Impaired Decision Making Capacity

The requirements in this section apply to all research involving adults who cannot provide consent or with impaired decision-making capacity regardless of funding source.

Research involving subjects without the ability to provide consent or with impaired decision-making capacity should only be conducted when the aims of the research cannot reasonably be achieved without their participation. Participation of such subjects in research cannot be justified solely on their availability or the convenience for the investigator.

When an investigator seeks to include such subjects in research, they must disclose this to the IRB and provide justification for why inclusion is necessary. If capacity to consent is questionable, or may fluctuate, investigators should include provisions for determining capacity to provide informed consent (See SOP 1101.2.4), and, if appropriate to reevaluate capacity during participation. When capacity to consent may diminish, the procedures should include, when possible and appropriate, designation of a legally-authorized authorized representative (LAR), inclusion of the future LAR in the initial consent discussion and process, and memorialization of the participant's wishes regarding the research in writing. When the research includes subjects likely to regain capacity to consent, the investigator should include provisions to inform the subject regarding their participation and to seek consent for ongoing participation, if applicable.

When the IRB reviews research involving greater than minimal risk and the proposed subject population includes adults who cannot provide consent, may have impaired capacity to provide consent, or whose capacity can be expected to fluctuate over time, the IRB review process will include at least one member, or a consultant, who is experienced with or otherwise knowledgeable about the population.

In evaluating research, the IRB must be able to determine that the risks to subjects are reasonable not only in relation to any benefits, but also in relation to the importance of the knowledge that may reasonably be expected to result. In considering the risks of research involving subjects unable to provide informed consent or with diminished capacity to do so, the IRB should consider whether any components of the research involve risks that are greater for participants with diminished capacity. For example, the population might experience increased sensitivity or discomfort to certain stimuli or may not be able to verbalize or otherwise demonstrate when they are experiencing discomfort or pain.

As appropriate to the research, the IRB will consider the following in evaluating greater than minimal risk research involving adults unable to consent or with impaired decision-making capacity:

1. Whether the aims of the research cannot reasonably be achieved without inclusion of the population
2. Whether the research is likely to improve the understanding of the condition, disease, or issue affecting the subject population
3. Whether any experimental procedure or interventions have undergone pre-clinical testing or human testing on other populations and whether the data from that testing supports its use in the proposed research
4. Whether the procedures or interventions that the subject will undergo in the research place them at increased risk and if appropriate mechanisms are in place to minimize risks, when possible
5. Whether the data and safety monitoring plan, including any stopping rules, is appropriate given the risks of the research and the vulnerability of the population
6. Whether the procedures for withdrawing individual subjects from the research are appropriate
7. Whether the recruitment procedures, consent process, and any plans for financial compensation support voluntariness and minimize the likelihood of undue influence or coercion
8. Whether the subjects will be exposed to financial or other risks that they might not consider acceptable if they had the capacity to provide consent, and whether appropriate mechanisms have been put into place to minimize these risks
9. Whether the procedures for determining capacity to provide consent, and for evaluating capacity on an ongoing basis, if applicable, are appropriate

10. Whether the procedures for informing subjects who regain capacity about their involvement in the research, and for obtaining consent for on-going participation, if applicable, are appropriate
11. Whether assent should be required when possible, and, if so, if the proposed procedures to obtain and document assent are appropriate
12. Whether a research subject advocate or consent monitor should be required, for some or all subjects

3 Definitions

Children. 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.

According to North Carolina (NC) State Law, minors are persons under the age of eighteen. The general rule is that a person may consent for his or her own medical care at the age of eighteen. Therefore, the UNC-Chapel Hill IRB defines children as persons who are under eighteen years of age. Certain statutes and case law, however, provide minors with "majority" status in some circumstances, giving them the right to consent to their own medical care. For example: emancipated minors. NC law enumerates certain categories of individuals who, although under the age of 18, have the right to make medical decisions on their own behalf, such as minors who are married, widowed or divorced, minors who are parents, etc.); mature minors NC law recognizes that some minors may be sufficiently "mature" to give consent to medical treatment, even though they do not qualify as "emancipated"); or certain minors seeking care for drug addiction, sexually transmitted diseases, emotional disorders, or abortion or mental health treatment. Because NC law does not specifically address consent of children with majority status to research, the UNC-Chapel Hill will review issues of consent related to enrollment of these children in research on a case-by-case basis.

NOTE: For research conducted in jurisdictions other than NC, the research must comply with the laws regarding the legal age of consent in the relevant jurisdictions. The UNC-Chapel Hill's Legal counsel will be consulted with regard to the laws in other jurisdictions.

Guardian. A guardian is an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.

In NC a "Guardian" of a child means the a court-appointed person with the duty and authority to act in the best interests of the minor, subject to residual parental rights and responsibilities, to make important decisions in matters having a permanent effect on the life and development of the minor and to be concerned with his or her general welfare. [NCGS 7B-3507 and NCGS 90-21.5(a,b).]

NOTE: For research conducted in jurisdictions other than NC, the research must comply with the laws regarding guardianship in all relevant jurisdictions. The UNC-Chapel Hill's Legal counsel will be consulted with regard to the laws in other jurisdictions.

Fetus. A fetus means the product of conception from implantation until delivery.

Dead fetus. A fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

Delivery. A delivery is a complete separation of the fetus from the woman by expulsion or extraction or any other means.

Neonate. A neonate is a newborn.

Viable. As it pertains to the neonate, viable means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.

Nonviable neonate. A nonviable neonate means a neonate after delivery that, although living, is not viable.

Pregnancy. A pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

Prisoner. A prisoner is any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.