RESEARCH INVOLVING VULNERABLE SUBJECTS

Introduction - *Elizabeth Kipp Campbell*

Pregnant Women & Neonates - *Kathy Seabolt*

Prisoners & Cognitively Impaired Individuals - *John Roberts*

Children - *Shahila Sriskanda*

Abusive Relationships - *Carter Church*

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Learning Objectives

- Define *vulnerability*
- Identify various types of *vulnerable subjects*
- Understand safeguards to protect the rights of vulnerable subjects
- Understand the role of the Investigator
- Understand the role of the IRB

Vulnerable subjects

45 CFR 46 has additional subparts designed to provide extra protections for vulnerable populations:

- 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

Group-based vulnerabilities

- Unemployed or impoverished persons,
- Patients
- Ethnic minorities
- Homeless
- Individuals in abusive relationships

Situation-based vulnerabilities

- Cognitive or communicative vulnerability (e.g., non-English speaking)
- Institutional vulnerability (e.g., nursing homes)
- Deferential vulnerability (e.g., doctor/patient)
- Medical vulnerability (e.g., life threatening illness)
- Economic vulnerability (e.g., inadequate income/heath care)
- Social vulnerability (e.g., undocumented immigrants)

National Bioethics Advisory Commission Report , August 2001

Additional considerations

Research should be conducted only in the following circumstances:

- Risk is low and benefit is high, or
- No alternatives to the study are possible (e.g., study of pregnancy require pregnant women)

Researcher Responsibilities

- Apply the ethical principal, *Respect for Persons*
- Identify the potential for enrolling vulnerable subjects, including those who are at risk for impaired decisional capacity
- Justify the inclusion of vulnerable subjects in the study
- Describe the safeguards to protect the rights and welfare of subjects

IRB Responsibilities

- Apply the ethical principal, *Respect for Persons*
- Assess the researcher's justification for including vulnerable subjects
- Ensure that the appropriate safeguards are in place, including obtaining informed consent from a legally authorized representatives and the plans for assent of child and/or adults unable to provide consent.
- Evaluate the research to determine the need for additional protections

SUBPART B:

Additional Protections for Women, Human Fetuses and Neonates Involved in Research

Why are Pregnant Women/Fetuses Considered a Vulnerable Population?

- Pregnant women are considered vulnerable because of the involvement of a third party (the fetus) that may be affected by the research and cannot give consent. Likewise, neonates (newborns) are not able to provide consent and are particularly vulnerable because of their often unknown health standing.

Definitions (45 CFR 46.202)

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

- Delivery - complete separation of the fetus from the woman by expulsion or extraction or any other means.

- Fetus means the product of conception from implantation until delivery.

- Neonate - means a newborn.

- Nonviable neonate - neonate after delivery that, although living, is not viable.

Definitions (45 CFR 46.202) (Cont.)

- Pregnancy - 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.

- Viable Neonate - as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of subparts A and D.

  - Subpart A – Basic HHS Policy for Protection of Human Research Subjects
  - Subpart D- Additional Protections for Children Involved as Subjects in Research

Research Involving Pregnant Women/Fetuses (45 CFR 46.204)

The IRB may approve research involving pregnant women or fetuses if all of the following conditions are met:

- Where scientifically appropriate, preclinical 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;
- 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 other means;
- Any risk is the least possible for achieving the objectives of the research;
- If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of 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, the woman's consent is obtained OR

Research Involving Pregnant Women/Fetuses (45 CFR 46.204) (Cont.)

- 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 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;
- Each individual providing consent under (d) or (e) is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
- For children who are pregnant, assent and permission are obtained in accord with the regulations for children in research (45 CFR 46, Subpart D);
- No inducements, monetary or otherwise, will be offered to terminate a pregnancy; 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
- Individuals engaged in the research will have no part in determining the viability of the neonate.

Research Involving Neonates (45 CFR 46.205)

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

- 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
- 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
- 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

Nonviable Neonates (45 CFR 46.205)

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

- Vital functions of the neonate will not be artificially maintained;
- The research will not terminate the heartbeat or respiration of the neonate;
- There will be no added risk to the neonate resulting from the research;
- The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
- The legally effective informed consent of both parents of the neonate is obtained (note: waiver or alteration of the consent does not apply here) if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements.

Note: The consent of the legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements.

Viable neonates (45 CFR 46.205)

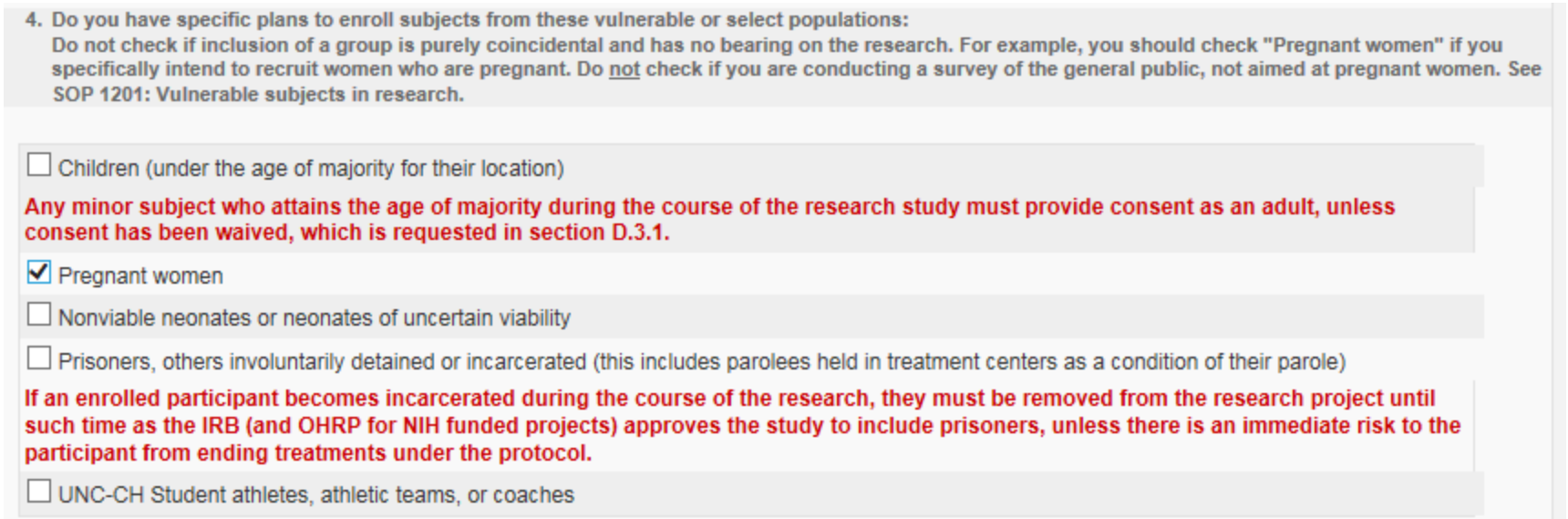
- A neonate, after delivery, that has been determined to be viable may be included in research in accord with the requirements of subparts A and D.

  - Subpart A – Basic HHS Policy for Protection of Human Research Subjects
  - Subpart D- Additional Protections for Children Involved as Subjects in Research

FDA Regulations

FDA regulations and the HIPAA Privacy Rule have no special provisions pertaining to research involving pregnant women, fetuses, or neonates.

How to fill out the application:



4. Do you have specific plans to enroll subjects from these vulnerable or select populations:
Do not check if inclusion of a group is purely coincidental and has no bearing on the research. For example, you should check "Pregnant women" if you specifically intend to recruit women who are pregnant. Do not check if you are conducting a survey of the general public, not aimed at pregnant women. See SOP 1201: Vulnerable subjects in research.

☐ Children (under the age of majority for their location)

Any minor subject who attains the age of majority during the course of the research study must provide consent as an adult, unless consent has been waived, which is requested in section D.3.1.

☑ Pregnant women

☐ Nonviable neonates or neonates of uncertain viability

☐ Prisoners, others involuntarily detained or incarcerated (this includes parolees held in treatment centers as a condition of their parole)

If an enrolled participant becomes incarcerated during the course of the research, they must be removed from the research project until such time as the IRB (and OHRP for NIH funded projects) approves the study to include prisoners, unless there is an immediate risk to the participant from ending treatments under the protocol.

☐ UNC-CH Student athletes, athletic teams, or coaches

Example: If you are including pregnant women in a survey/questionnaire that does not have anything to do with their status as a pregnant woman, do not check yes for this question.

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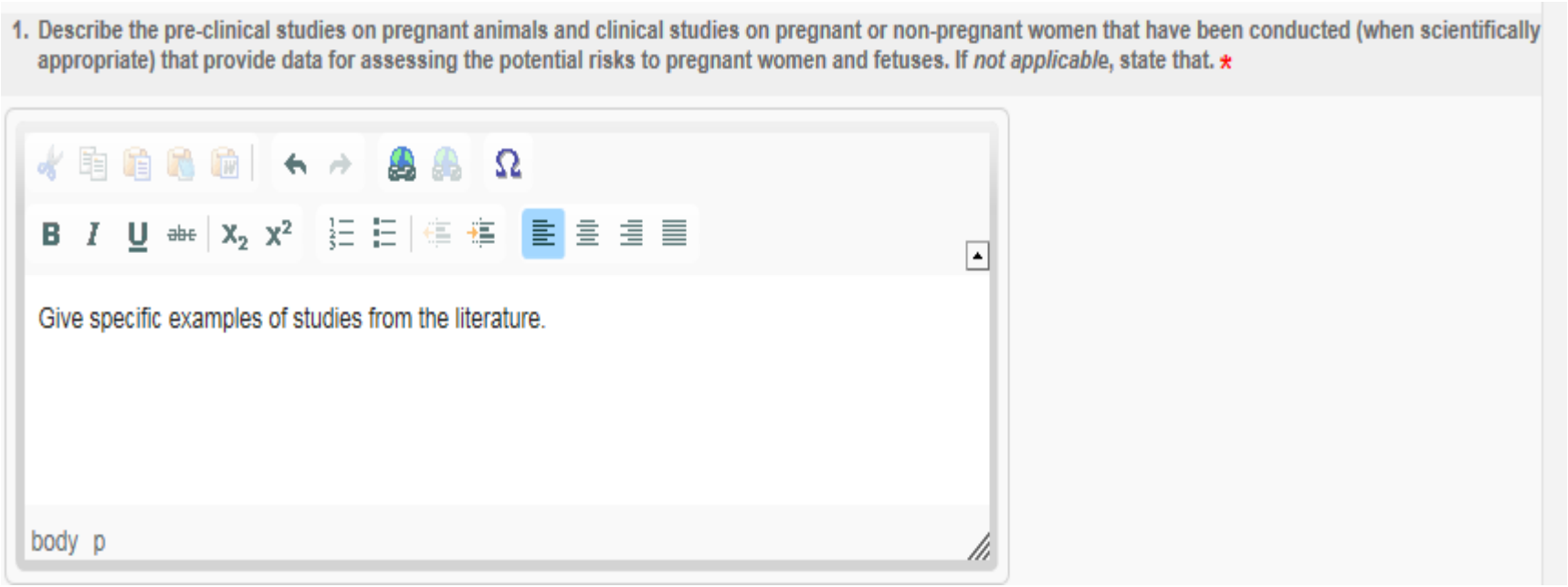
How to fill out the application:



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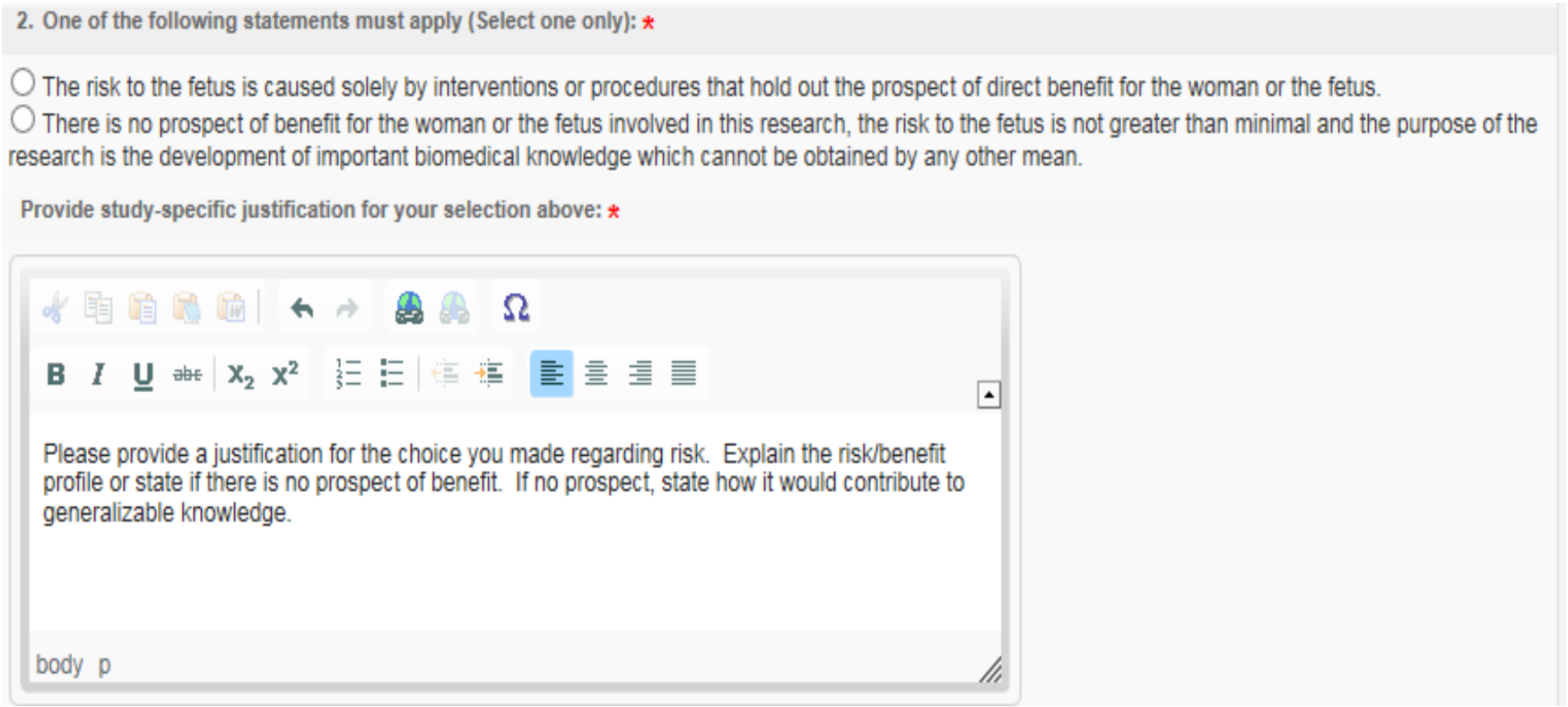

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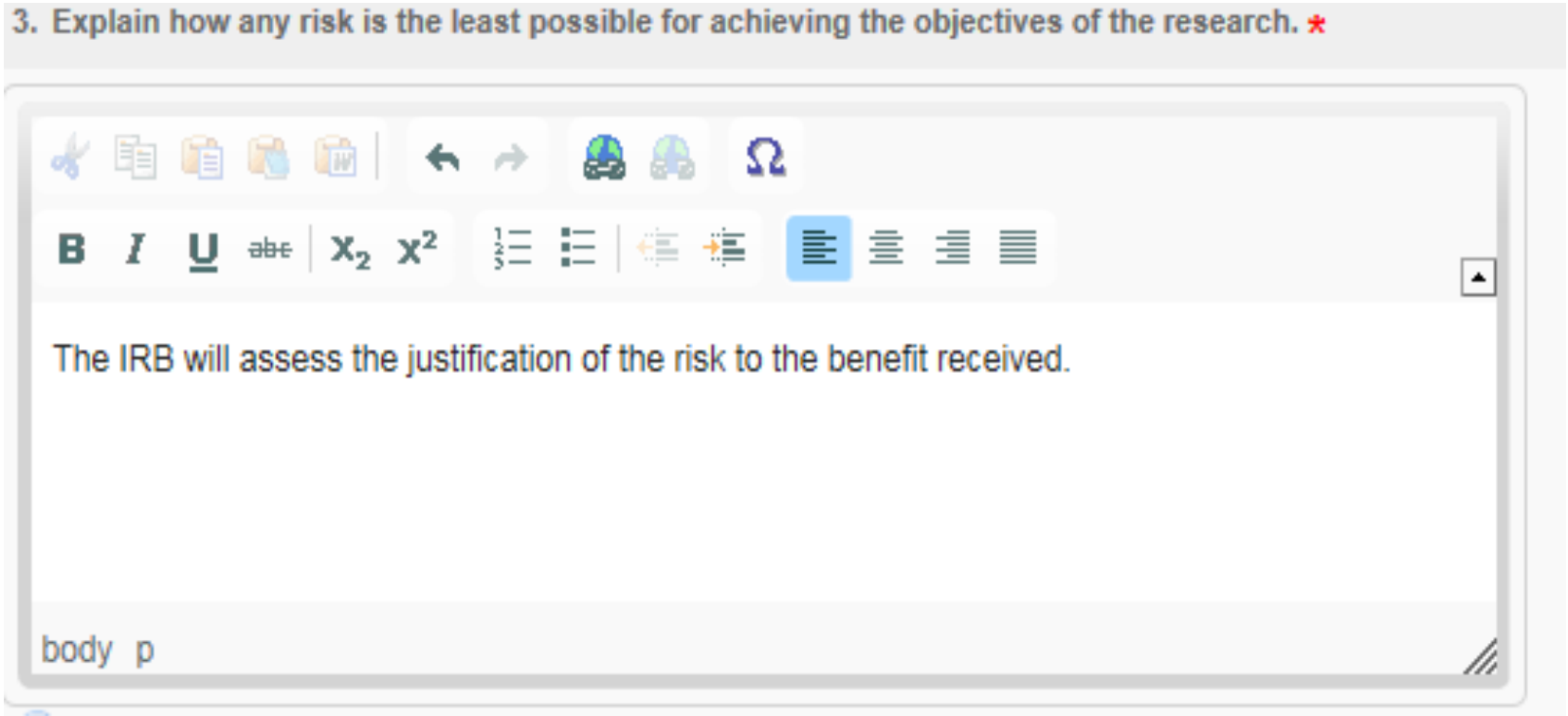

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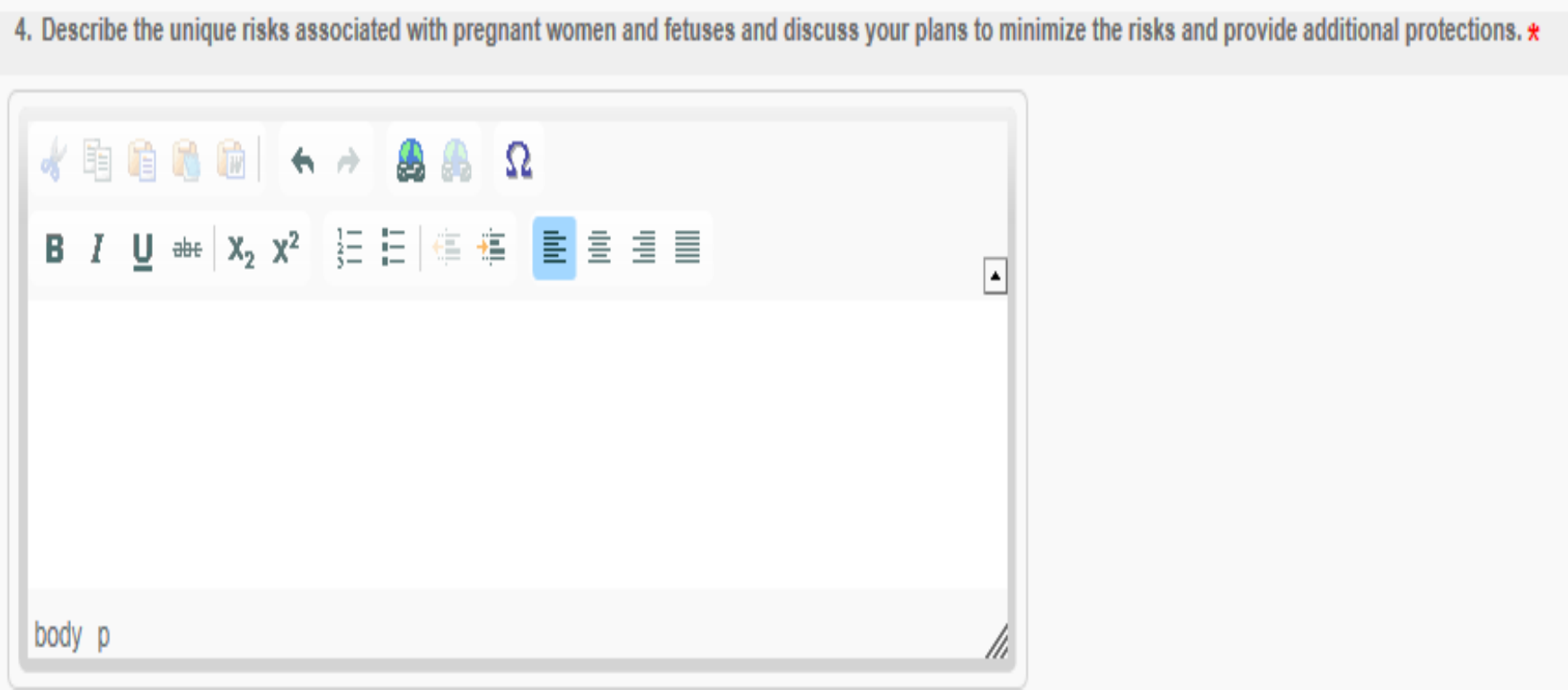
How to fill out the application:



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How to fill out the application:

- [ ] Children (under the age of majority for their location)

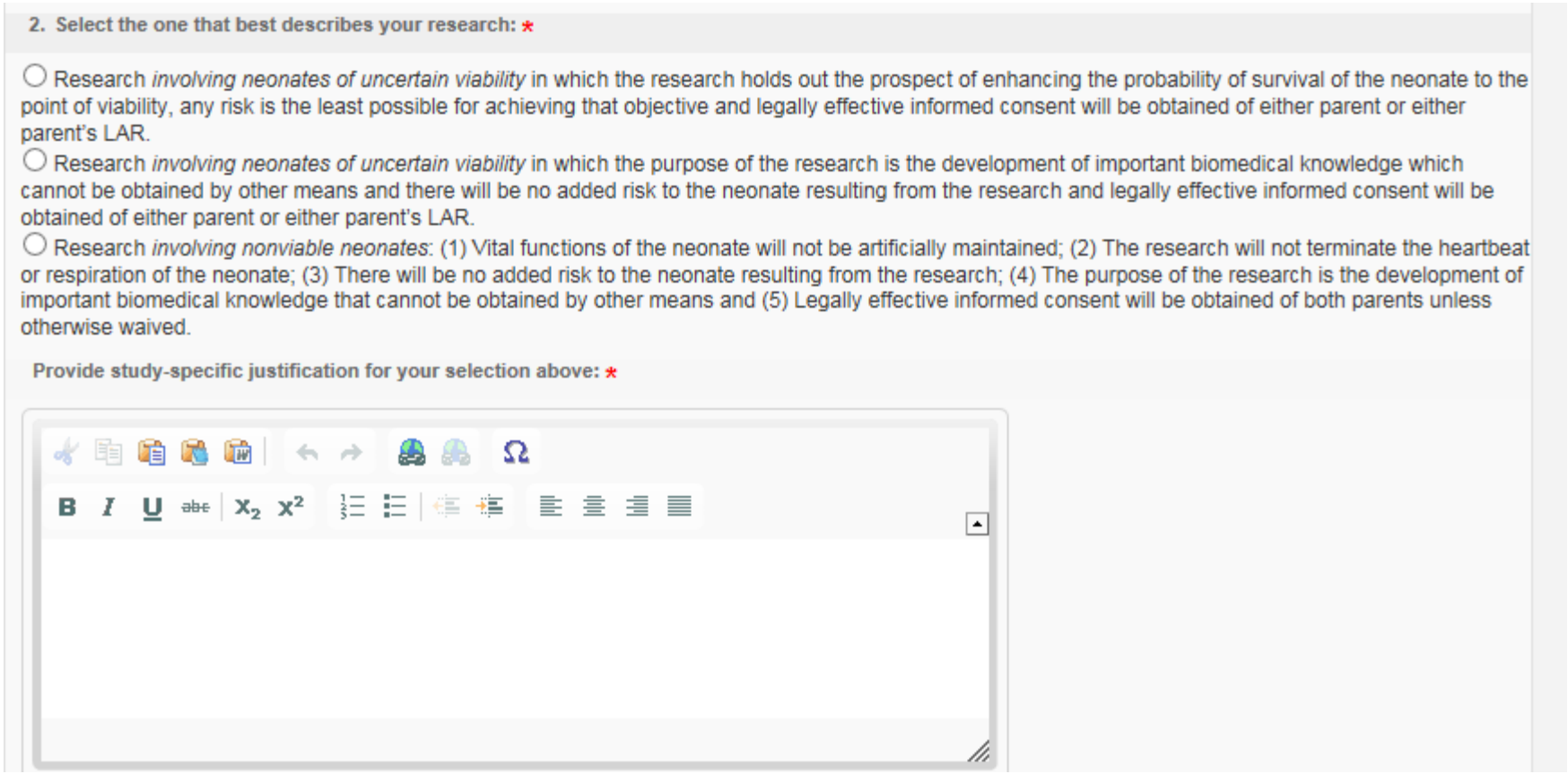
Any minor subject who attains the age of majority during the course of the research study must provide consent as an adult, unless consent has been waived, which is requested in section D.3.1.

- [ ] Pregnant women
- [x] Nonviable neonates or neonates of uncertain viability
- [ ] Prisoners, others involuntarily detained or incarcerated (this includes parolees held in treatment centers as a condition of their parole)

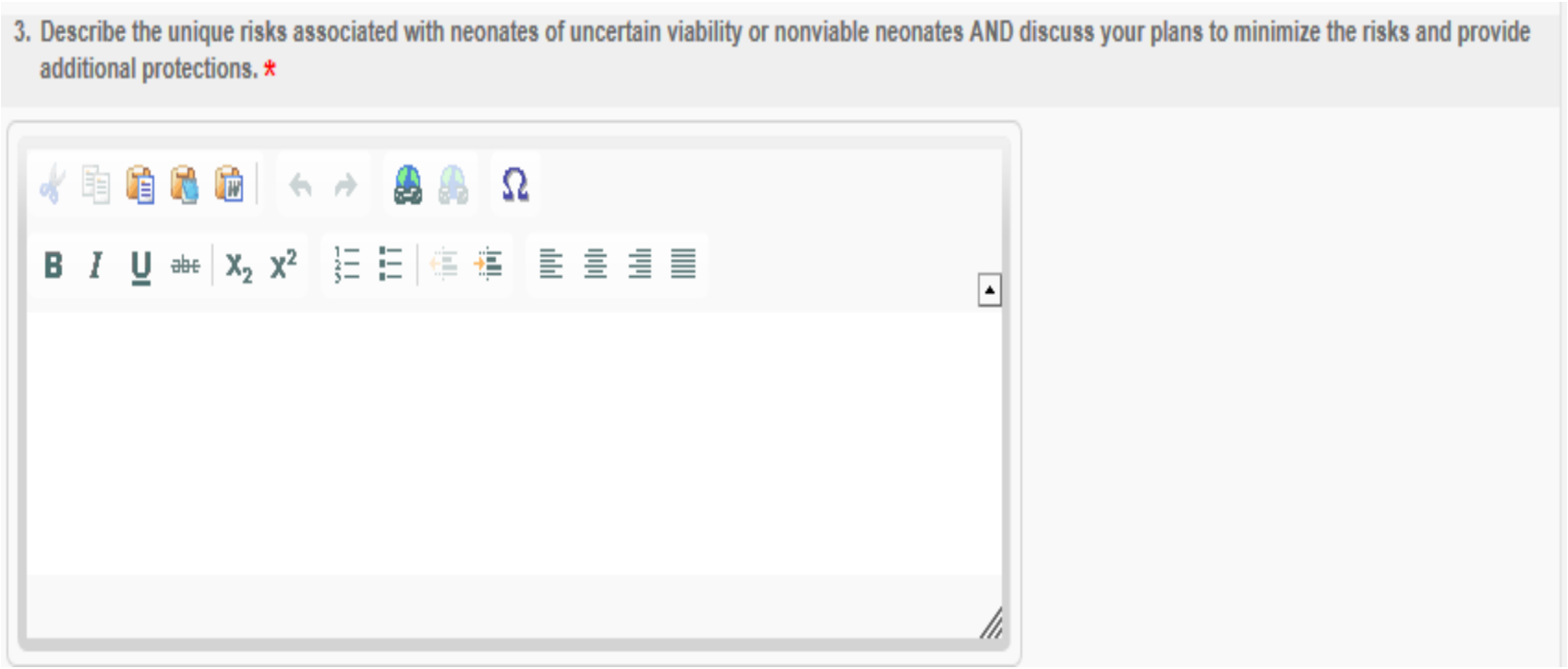
If an enrolled participant becomes incarcerated during the course of the research, they must be removed from the research project until such time as the IRB (and OHRP for NIH funded projects) approves the study to include prisoners, unless there is an immediate risk to the participant from ending treatments under the protocol.

- [ ] UNC-CH Student athletes, athletic teams, or coaches

How to fill out the application:



How to fill out the application:



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How to fill out the application:

A.3 – Inclusion/Exclusion Criteria

Excluding pregnant women because it is easier is not an acceptable response. Stating that the drug being studied has been proven harmful to pregnant women would be an acceptable response.

A.3.3 – Will pregnant women or women who become pregnant be excluded?

- If yes, provide justification and describe the type and timing of pregnancy testing to be used

Example: At screening all women of child-bearing potential will be given a pregnancy test. At visits X, X, X follow-up pregnancy tests will be obtained.

How to fill out the application:

A.6.9 – Physical risks to a nursing child or fetus (through either mother or father)

Example: Describe results of animal and pre-clinical studies that have already determined the risk or state that the risk is not known.

A.6.12 – Are there plans to withdraw or follow subjects (or partners of subjects) who become pregnant while enrolled in this study? If yes, explain

Provide specific information on follow-up of subjects who become pregnant during study participation


UNC
OFFICE OF HUMAN RESEARCH ETHICS
INSTITUTIONAL REVIEW BOARD (IRB)

SUBPART C:

Additional Protections for Prisoners Involved in Research

Applicability (45 CFR 46.301)

- (a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health and Human Services involving prisoners as subjects.
- (b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects, to the extent such research is limited or barred by applicable State or local law.
- (c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

Purpose (45 CFR 46.302)

- Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

Definitions (45 CFR 46.303)

- 46.303(c) - *Prisoner* means 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 which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Definition continued

'Prisoners' includes:

- individuals sentenced to such an institution under a criminal or civil statute
- individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution
- individuals detained pending arraignment, trial, or sentencing

Example – court appointed rehab treatment centers

Types of Research Involving Prisoners

- ***Targeted Research*** - Regulations apply to research specifically targeting prisoners, or the prison setting

- ***Accidental Prisoners*** - Regulations also apply to subjects who become incarcerated following their enrollment or subjects for whom their incarceration is coincidental with their research involvement, ***(***e.g., a prisoner with cancer enrolled in a treatment-oriented study that involves no other prisoners).

Considerations

All prisoners are regarded as being *vulnerable to coercion or undue influence* and therefore need additional safeguards to protect their rights and welfare as research participants.

How does the IRB protect their rights and welfare?

Board Composition (45 CFR 46.304)

- (a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.
- (b) At least one member of the Board shall 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 Board only one Board need satisfy this requirement.

Additional duties of IRB (45 CFR 46.305)

46.305(a) In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that:

(1) The research under review represents one of the categories of research permissible under §46.306(a)(2)

46.305 additional duties of IRB

(2) 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;

(3) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

46.305 additional duties of IRB

(4) 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 principal investigator provides to the Board 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;

(5) The information is presented in language which is understandable to the subject population;

46.305 additional duties of IRB

(6) 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

(7) Where the Board finds there may be a need for follow-up examination or care of participants 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 participants of this fact.

Permitted Research Involving Prisoners (45 CFR 46.306)

(a) Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if:

- (1) The institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under §46.305 of this subpart; and

Permitted Research Involving Prisoners (45 CFR 46.306)

(2) In the judgment of the Secretary the proposed research involves solely the following:

- (i) 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;
- (ii) 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;

Permitted Research Involving Prisoners (45 CFR 46.306)

(iii) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research; or

Permitted Research Involving Prisoners (45 CFR 46.306)

(iv) 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 approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of the intent to approve such research.

IRBIS Section A.2.4 (Subjects)

☐ Prisoners, others involuntarily detained or incarcerated (this includes parolees held in treatment centers as a condition of their parole)

If an enrolled participant becomes incarcerated during the course of the research, they must be removed from the research project until such time as the IRB (and OHRP for NIH funded projects) approves the study to include prisoners, unless there is an immediate risk to the participant from ending treatments under the protocol.

Checking “Prisoners” in Section A.2.4, triggers section A.2.D - Research involving prisoners and others involuntarily detained or incarcerated

The new section consists of seven questions, which correspond to the seven criteria which must be met as described in 45 CFR 46.305. For each question, you will be asked to Provide study specific justification to support this finding

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IRBIS Application A.2.D.1:

1. The research under review represents one of the categories of research permissible under §46.306(a)(2)

(Select the category which best describes your research)

(i) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior,

(ii) Study of prisons as institutional structures or of prisoners as incarcerated persons,

(iii) Research on conditions particularly affecting prisoners as a class

(iv) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject

OR

IRBIS Application A.2.D.1 (cont)

An additional option, not noted in 46.306.2a:

(v) **Research conducted under a waiver of epidemiology research** where the sole purposes of the research are 1) to describe the prevalence or incidence of a disease by identifying all cases, or, (2) to study the potential risk factor associations for a disease and the research involves no more than minimal risk and not more than inconvenience to the human subject participants and prisoners are not the a particular focus of the research.

A.2.D Prisoners, Questions 2 - 7

2. Any possible advantages or compensation to the prisoner for participation in research, when compared to the general living conditions and opportunities in the prison, are not so great that they impair the prisoner's ability to evaluate the risks and benefits of the research in the limited choice environment of the prison

3. The risks involved in the research are commensurate with risks that non-prisoner volunteers would accept;

A.2.D Prisoners, Questions 2 - 7

4. Procedures for the selection or recruitment of subjects are fair to all prisoners and cannot be arbitrarily influenced by prison authorities or prisoners. Unless the PI provides the IRB with written justification for following other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

5. The information is presented in language that is understandable to the subject population;

A.2.D Prisoners, Questions 2 - 7

6. 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

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

Accidental Prisoners

When the Investigator learns or discovers that a research participant has become a prisoner,

1. Stop research activities involving that person (you may analyze data already collected)
2. Submit a modification in IRBIS, Complete A.2.D; Prisoner representative will review protocol
3. IRB will determine if,

    a) it is possible to continue subject on the study

    b) research staff will have access to the subject in prison

    c) determine whether participation in the research does or does not present risk to the subject

IRB Finding, if federally funded

Finding will be printed on the approval letter:

In accordance with 45 CFR 46.304, the convened IRB committee included a board member who is a prisoner representative. This research, which involves prisoners, meets criteria set forth in section 45 CFR 46.305(a)(1-7) and is permitted according to 45 CFR 46.306. **Please note that the IRB must certify this approval to the federal Office for Human Research Protections (OHRP) and that NO RESEARCH INVOLVING PRISONERS MAY BEGIN UNTIL THE CERTIFICATION PROCESS IS COMPLETE.**

IRB Finding, no federal funding

Finding will be printed on the approval letter:

In accordance with 45 CFR 46.304, the convened IRB committee included a board member who is a prisoner representative. This research, which involves prisoners, meets criteria set forth in section 45 CFR 46.305(a)(1-7) and is permitted according to 45 CFR 46.306.

Certification of research - OHRP

All federally funded research involving prisoners must be certified with the Office of Human Research Protections (OHRP). UNC IRB sends a certification letter to OHRP, indicating that the IRB has made the seven findings required under 46.305, and include an approved research proposal.

OHRP confirms that the research fits into one of the permissible categories described in 46.306, and will publish in the federal register a notice of intent to approve the research.

Federally funded research involving prisoners may not proceed until OHRP issues it's approval in writing to UNC on behalf of the Secretary of the Department of Health and Human Services (DHHS).

SUBPART D:

Additional protections for Children and Children who are wards of the state

CHILDREN

Subpart D: 45 CFR 46.401-409 (Federal) and 21 CFR 50.50-56 (FDA), UNC IRB SOP 35

Children as 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,

North Carolina age of consent is 18 years old.

https://www.hhs.gov/ohrp/regulations-and-policy/guidance/special-protections-for-children/index.html

Other definitions under 45 CFR 46.402

- Assent- a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.
- Permission- the agreement of parent(s) or guardian to the participation of their child in research.
- Parent- a child's biological or adoptive legal guardian.
- Guardian- an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.

The IRB will consider:

- Justification
  - Application section A.2.A., question 1
- Benefits
  - Application section A.2.A., question 2
- Risks
  - Application section A.2.A., question 3

Research Involving Children (Subpart D: 45 CFR 46.404)

- Research not involving greater than minimal risk.
  - Minimal risk- Likelihood of anticipated harm is not greater than what a healthy child would encounter in daily life or through routine tests.
- Adequate provisions are made for soliciting the assent of the children
- Adequate provisions are made for soliciting parental permission from legal guardian.
  - 1 parent signature is sufficient.

Research Involving Children (Subpart D: 45 CFR 46.405)

- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
- Direct benefit- The benefit to a subject's health and well-being, received directly from participation in the study.
  - (a) The risk is justified by the anticipated benefit to the subjects;
  - (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
  - (c) Adequate provisions are made for soliciting the assent of the children and permission from parent or legal guardian.
- 1 parent signature is sufficient.

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Research Involving Children (Subpart D: 45 CFR 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.
  - (a) The risk represents a minor increase over minimal risk;
  - (b) 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;
  - (c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition; and
  - (d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.

Research Involving Children (Subpart D: 45 CFR 46.406) continued…

- 2 parent signature is required, unless one parent is:
  - Deceased
  - Unknown
  - Incompetent or not reasonably available (for example, one parent is incarcerated)
  - has legal responsibility for the care/custody of the child

Research Involving Children (Subpart D: 45 CFR 46.407)

- Research not otherwise approvable and doesn't fall under the first 3 categories

- Research represents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.
- Consultation with secretary of the department of health and human services must be made to make final determination if study is approvable.
  - (a) Adequate provisions are made for soliciting the assent of children
  - (b) Adequate provisions are made for soliciting permission of their parents or legal guardians

Research Involving Children (Subpart D: 45 CFR 46.407) continued…

- 2 parent signature is required, unless one parent is:
  - Deceased
  - Unknown
  - Incompetent or not reasonably available (for example, one parent is incarcerated)
  - has legal responsibility for the care/custody of the child

Research Involving Children (Subpart D: 45 CFR 46.408)

- **Requirements for assent by children.**
  - Age, maturity, and psychological state of the children involved.
  - At UNC, age of assent is 7 years old.
  - Assent may be waived by the IRB if child's capability is so limited, the research holds out a prospect of direct benefit, or adequate justification is provided
  - Consent using an adult informed consent process required for newly 18 years olds.

- **Requirements for permission by parents or guardians.**
  - Permission of one parent is sufficient for research to be conducted under categories 404 or 405
  - Permission of both parents must be obtained for research to be conducted under categories 406 or 407, unless reasonably unable to do so.
  - Permission may be waived if it is not a reasonable requirement to protect the subject.

How to complete your application?

section A.2. Subjects

4. **Do you have specific plans to enroll subjects from these vulnerable or select populations:**
Do not check if inclusion of a group is purely coincidental and has no bearing on the research. For example, you should check "Pregnant women" if you specifically intend to recruit women who are pregnant. Do not check if you are conducting a survey of the general public, not aimed at pregnant women. See SOP 1201: Vulnerable subjects in research.

- [x] Children (under the age of majority for their location)

Any minor subject who attains the age of majority during the course of the research study must provide consent as an adult, unless consent has been waived, which is requested in section D.3.1.

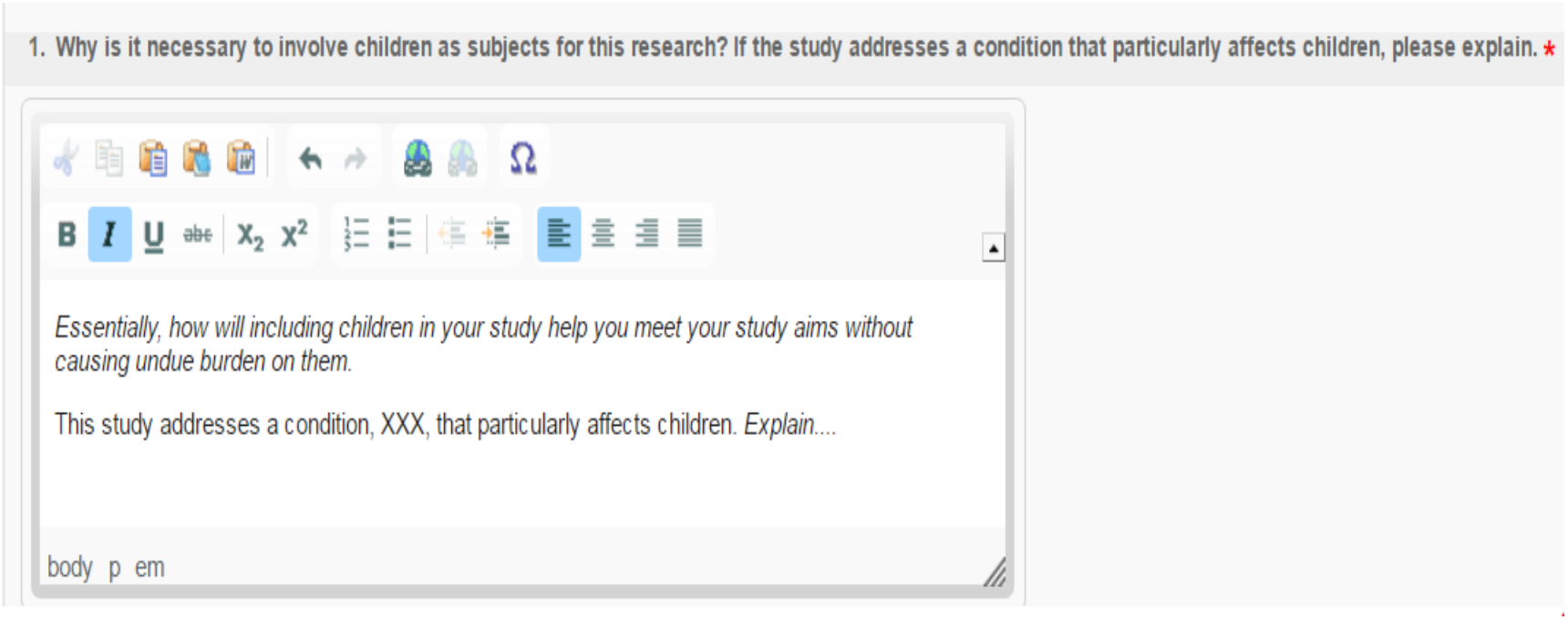
- [ ] Pregnant women
- [ ] Nonviable neonates or neonates of uncertain viability
- [ ] Prisoners, others involuntarily detained or incarcerated (this includes parolees held in treatment centers as a condition of their parole)

If an enrolled participant becomes incarcerated during the course of the research, they must be removed from the research project until such time as the IRB (and OHRP for NIH funded projects) approves the study to include prisoners, unless there is an immediate risk to the participant from ending treatments under the protocol.

- [ ] UNC-CH Student athletes, athletic teams, or coaches

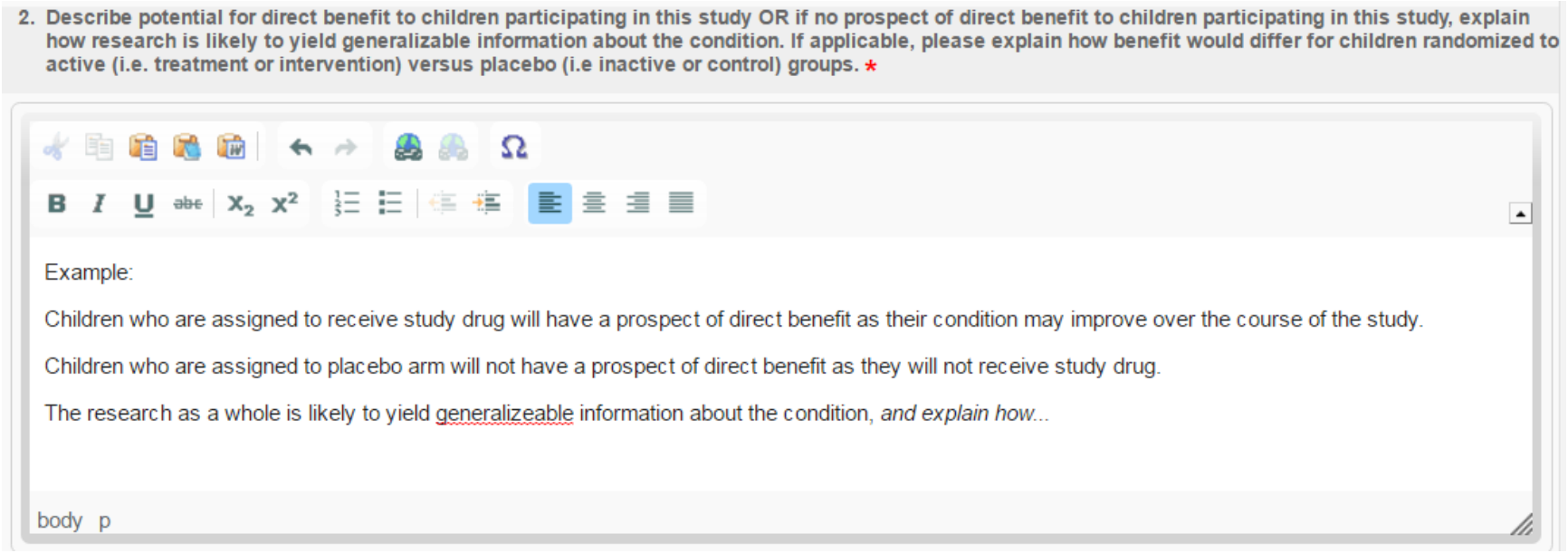
How to complete your application? Continued…

NEW section A.2.A Children



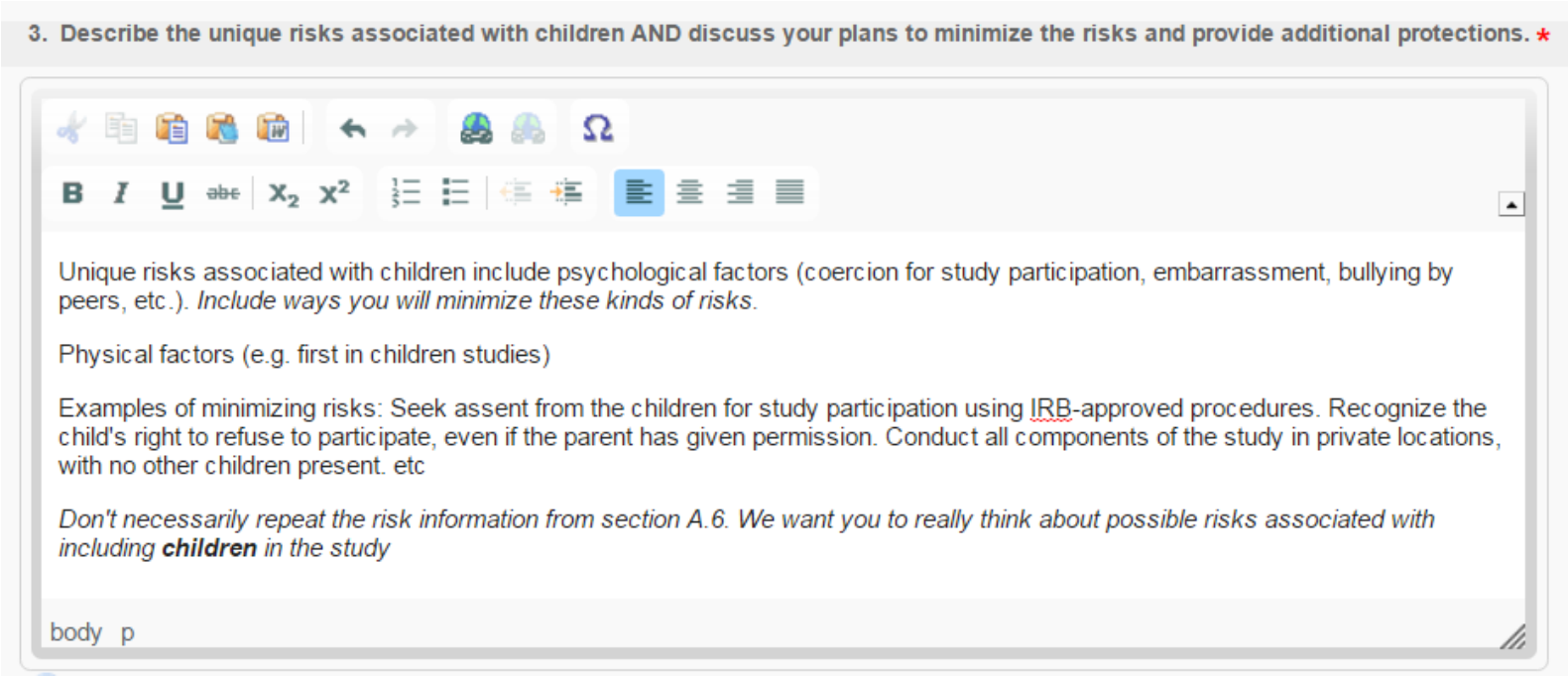
How to complete your application? Continued…

section A.2.A Children continued…



How to complete your application? Continued…

section A.2.A Children continued…



CHILDREN WHO ARE WARDS OF THE STATE

Subpart D: 45 CFR 46.409 (Federal) and 21 CFR 50.56 (FDA), UNC SOP 35.3.5.

Ward- An individual placed under the protection of a legal guardian.

Wards of the State- An individual placed under the protection of the court in the state where the individual resides.
-Children who are in foster care

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https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/#subpartd

Wards continued…

- Research Approved Under 45 CFR 46.404 or 405:
  - Adequate provisions are made for soliciting the assent of the children
  - The investigator should obtain the consent of the new legal guardian (legally authorized representative) appointed for the child.

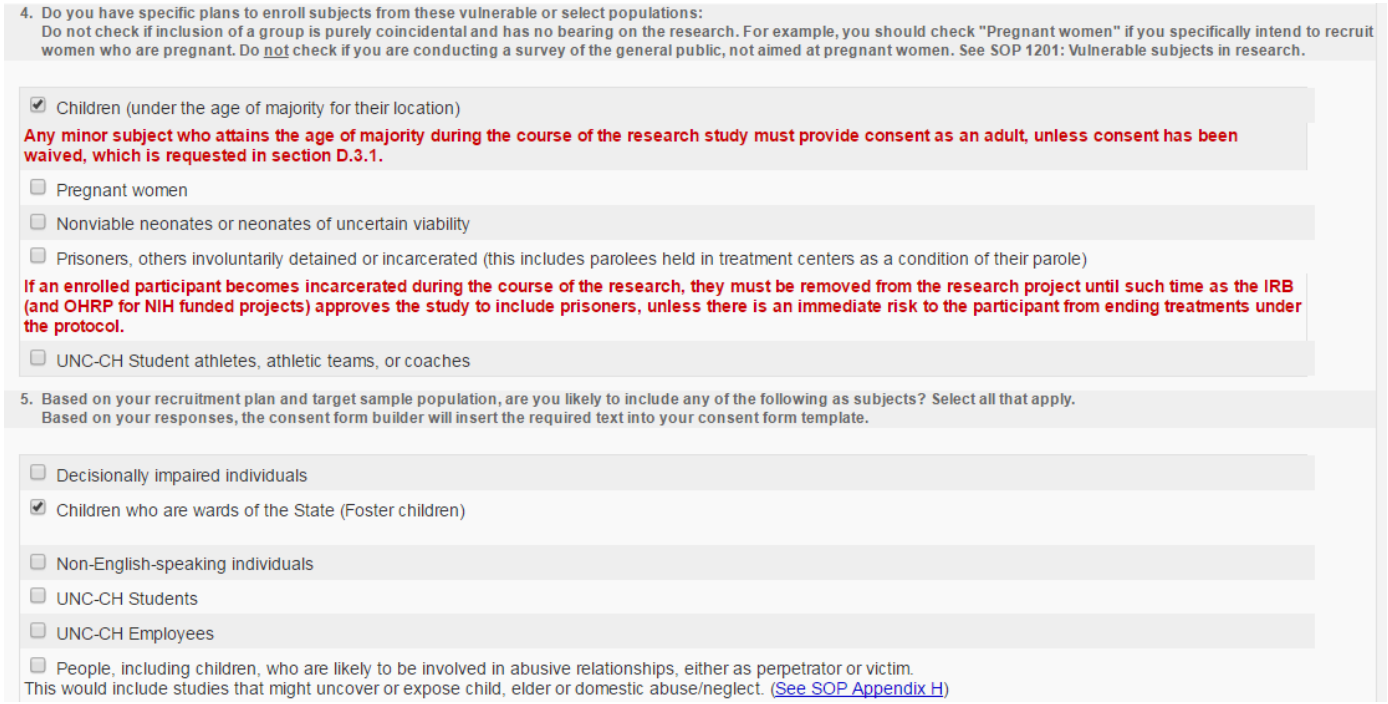
Wards (Subpart D: 45 CFR 46.409) continued…

- Research Approved Under 45 CFR 46.406 or 407:
- The research must be:
  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.

- The IRB shall require appointment of an advocate for each child who is a ward, in addition to the child's legal guardian
  - One individual may serve as advocate for more than one ward of the state.
  - The advocate shall 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."

How to complete your application?

section A.2. Subjects



4. Do you have specific plans to enroll subjects from these vulnerable or select populations:
Do not check if inclusion of a group is purely coincidental and has no bearing on the research. For example, you should check "Pregnant women" if you specifically intend to recruit women who are pregnant. Do not check if you are conducting a survey of the general public, not aimed at pregnant women. See SOP 1201: Vulnerable subjects in research.

- [x] Children (under the age of majority for their location)

Any minor subject who attains the age of majority during the course of the research study must provide consent as an adult, unless consent has been waived, which is requested in section D.3.1.

- [ ] Pregnant women
- [ ] Nonviable neonates or neonates of uncertain viability
- [ ] Prisoners, others involuntarily detained or incarcerated (this includes parolees held in treatment centers as a condition of their parole)

If an enrolled participant becomes incarcerated during the course of the research, they must be removed from the research project until such time as the IRB (and OHRP for NIH funded projects) approves the study to include prisoners, unless there is an immediate risk to the participant from ending treatments under the protocol.

- [ ] UNC-CH Student athletes, athletic teams, or coaches

5. Based on your recruitment plan and target sample population, are you likely to include any of the following as subjects? Select all that apply.
Based on your responses, the consent form builder will insert the required text into your consent form template.

- [ ] Decisionally impaired individuals
- [x] Children who are wards of the State (Foster children)
- [ ] Non-English-speaking individuals
- [ ] UNC-CH Students
- [ ] UNC-CH Employees
- [ ] People, including children, who are likely to be involved in abusive relationships, either as perpetrator or victim.
This would include studies that might uncover or expose child, elder or domestic abuse/neglect. (See SOP Appendix H)

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How to complete your application?

section A.2.F Wards of the State

REPORTING ABUSE AND NEGLECT

Purpose of the Reporting Law

A fourth-grade student comes to school with a black eye. The teacher talks privately with the student, who says: “My dad hit me because I was late for swim practice.”

A researcher conducting interviews related to dental health among elderly subjects is told by a participant that their caretaker has been using their credit cards without permission.

A police officer notices a five year old walking down the down the street at night without a jacket on in winter.

Purpose of the Reporting Law

YES

In North Carolina, reporting laws apply to everyone. Each person has a legal duty to intervene and to at minimum make a report to a county department of social services, on behalf of children and disabled adults who may be “abused,” “neglected,” “dependent,” or “exploited.”

County social services departments can then conduct assessments of reported cases and protect children or disabled adults in emergencies and begin any court proceedings if necessary.

Definitions - Children

Abused juveniles. - Any juvenile less than 18 years of age whose parent, guardian, custodian, or caretaker:

a. Inflicts or allows to be inflicted upon the juvenile a serious physical injury by other than accidental means;

b. Creates or allows to be created a substantial risk of serious physical injury to the juvenile by other than accidental means;

c. Uses or allows to be used upon the juvenile cruel or grossly inappropriate procedures or cruel or grossly inappropriate devices to modify behavior;

d. Commits, permits, or encourages the commission of a violation of the following laws by, with, or upon the juvenile: See resources.

e. Creates or allows to be created serious emotional damage to the juvenile; serious emotional damage is evidenced by a juvenile's severe anxiety, depression, withdrawal, or aggressive behavior toward himself or others;

f. Encourages, directs, or approves of delinquent acts involving moral turpitude committed by the juvenile; or

g. Commits or allows to be committed an offense under G.S. 14-43.11 (human trafficking), G.S. 14-43.12 (involuntary servitude), or G.S. 14-43.13 (sexual servitude) against the child.

Definitions - Children

Neglected juvenile - A juvenile who does not receive proper care, supervision, or discipline from the juvenile's parent, guardian, custodian, or caretaker; or who has been abandoned; or who is not provided necessary medical care; or who is not provided necessary remedial care; or who lives in an environment injurious to the juvenile's welfare; or the custody of whom has been unlawfully transferred under G.S. 14-321.2; or who has been placed for care or adoption in violation of law.

Definitions - Children

Dependent juvenile - A juvenile in need of assistance or placement because (i) the juvenile has no parent, guardian, or custodian responsible for the juvenile's care or supervision or (ii) the juvenile's parent, guardian, or custodian is unable to provide for the juvenile's care or supervision and lacks an appropriate alternative child care arrangement.

Definitions – Disabled Adults

Abuse – willful infliction of physical pain, injury or mental anguish, unreasonable confinement, or the willful deprivation by a caretaker of services necessary to maintain mental and physical health.

Neglect – a disabled adult who is either living alone and not able to provide for himself the services necessary to maintain his mental or physical health or is not receiving services from his caretaker**.**

Exploitation – illegal or improper use of a disabled adult or his resources for another's profit or advantage.

How to Report

The researcher must report the case of the participant to the Director of the Department of Social Services in the county where the child or disabled adult resides or is found.

After reporting to the Department of Social Services, consult the IRB for additional reporting requirements.

What if I don't report?

For children:

Any person or institution who knowingly or wantonly fails to report the case of a juvenile as required by subsection (a) of this section, or who knowingly or wantonly prevents another person from making a report as required by subsection (a) of this section, is guilty of a Class 1 misdemeanor.

IRB Application - Subjects A.2.5

5. **Based on your recruitment plan and target sample population, are you likely to include any of the following as subjects? Select all that apply. Based on your responses, the consent form builder will insert the required text into your consent form template.**

- [x] Decisionally impaired individuals

  Required document(s): Cognative Assessment Tool

  (e.g., Mini mental state examination (MMSE), Montreal cognitive assessment (MOCA))

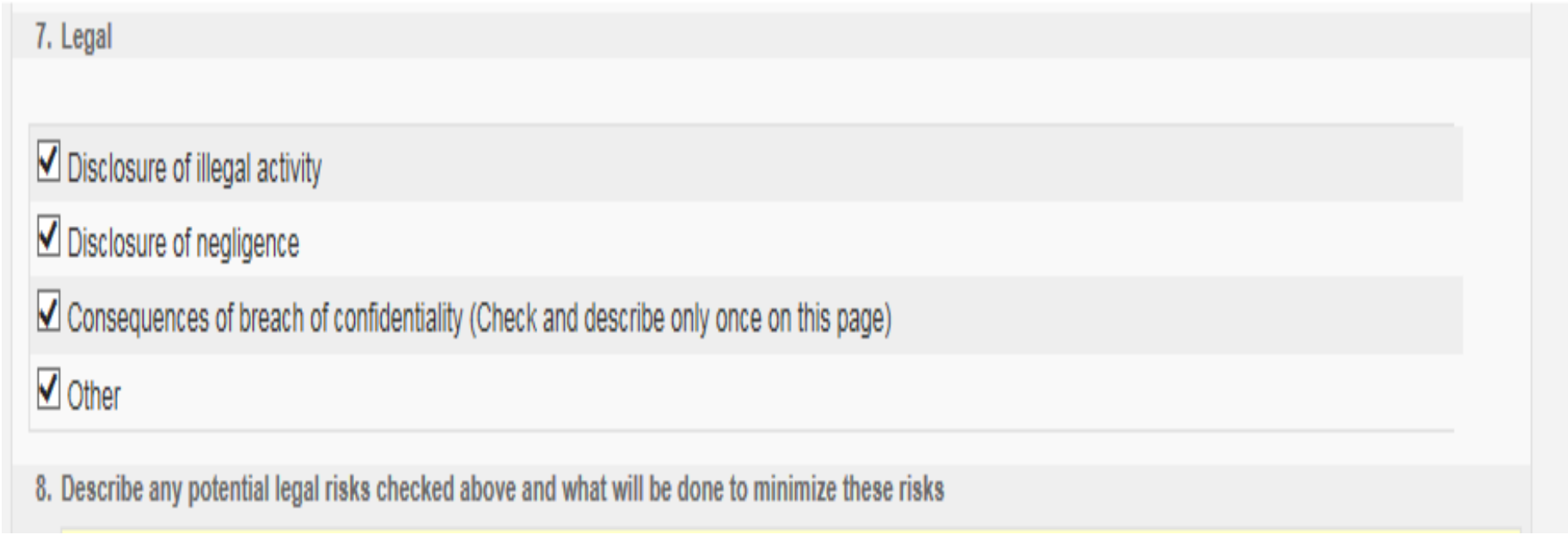
- [x] Children who are wards of the State (Foster children)

- [ ] Non-English-speaking individuals
- [ ] UNC-CH Students
- [ ] UNC-CH Employees
- [ ] People, including children, who are likely to be involved in abusive relationships, either as perpetrator or victim. This would include studies that might uncover or expose child, elder or domestic abuse/neglect. (See SOP Appendix H)

Consent Form Language

Under North Carolina law, confidentiality does not extend to information about abuse or neglect of a child or disabled adult. If the researchers become aware of such information, they are required to report it to state authorities.

IRB Application – Risks A.6


7. Legal

- [x] Disclosure of illegal activity
- [x] Disclosure of negligence
- [x] Consequences of breach of confidentiality (Check and describe only once on this page)
- [x] Other

8. Describe any potential legal risks checked above and what will be done to minimize these risks

IRB Application – Data and Safety Monitoring A.7

1. When appropriate, describe the plan for monitoring the data to ensure the safety of participants. These plans could range from the investigator monitoring subject data for any safety concerns to a sponsor-based data and safety monitoring board or committee (DSMB, DSMC, DMC), depending on the study. For studies that do not raise obvious safety concerns, you may still describe your plans for monitoring the study as it progresses. *

Certificates of Confidentiality

A certificate does not prevent an investigator from notifying the authorities if he or she obtains evidence of child or disabled adult abuse or a subject's threatened violence to self or others.

This should be made clear in the consent language.

Other Considerations

- Positive drug tests or reports of drug use among minors may indicate abuse or neglect.
- Implications of false reporting.
- Waivers of Parental Permission.


UNC
OFFICE OF HUMAN RESEARCH ETHICS
INSTITUTIONAL REVIEW BOARD (IRB)

DECISIONALLY IMPAIRED SUBJECTS

Requesting use of legally authorized representatives to enroll research subjects

Considerations

- 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*.
- When an investigator seeks to include such subjects in research, they provide justification for why inclusion is necessary.

Decision-making capacity

- A participant's ability to make a meaningful decision about whether or not to participate. Generally includes:
  1. Understanding (the ability to comprehend the disclosed information)
  2. Appreciation (the ability to appreciate the significance of the disclosed information
  3. Reasoning (the ability to engage in a reasoning process about risk versus benefit
  4. The ability to express a choice about whether or not to participate.

Examples of individuals with diminished capacity

- Cognitive impairment due to dementia, Alzheimer's, brain injury or other medical conditions
- Mental Illness – schizophrenia, psychosis
- Effects of medication and treatment for cancer patients may impact decision making capabilities

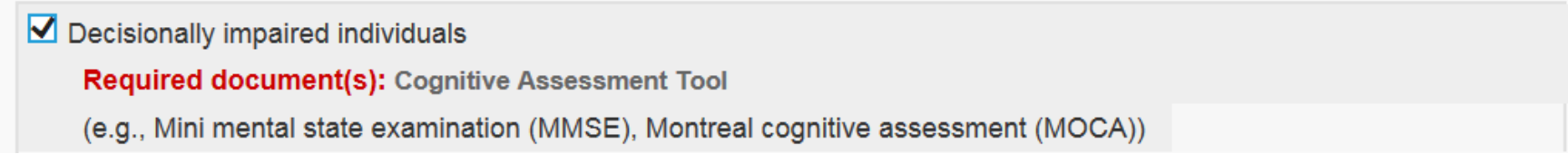
Impairment may be temporary,

- Suffer physical trauma, loss of consciousness, emergency situations (heart attack, stroke)
- Burn victims who are intubated

When the diminished capacity is temporary…

- It is important to note that consent is an ongoing process. Participants' decision making abilities may fluctuate during the course of the research and the investigators should continue to assess capacity for the duration of participation. If a participant is found to have regained decision making capacity, they must be re-consented for continued participation in the research.

IRBIS Section A.2.4



Checking “Decisionally impaired individuals” in Section A.2.4, triggers:

1. NEW section **A.2.E** - Questions specific to research involving decisionally impaired individuals
2. Required document: Cognitive assessment tool

Cognitive assessment tools

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

***Instructions:* Ask the questions in the order listed. Score one point for each correct response within each question or activity.**

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.

NEW Section A.2.E – Decisionally impaired individuals

1. Why is it necessary to involve individuals who are decisionally impaired as subjects for this research?

2. Explain the procedures proposed for evaluating the mental status of prospective subjects to determine whether they are capable of providing legally effective informed consent. Include who (by role) will evaluate mental status.

NEW Section A.2.E – Decisionally impaired individuals

3. Explain how you will identify persons authorized to give legally effective consent on behalf of any individual(s) judged incapable of legally effective consent on their own behalf.
4. Is it reasonable to expect that during the course of the study, subjects may lose or regain their capacity to provide legally informed consent? Yes or No
5. IF yes, What provisions have been made to protect the participant's rights (e.g., reconsent of participant)?

On to Part D – The Consent Process

Question D.1.3 – Will decisionally impaired subjects be enrolled in your study? (includes unconscious patients, some psychiatric disorders, others who lack the capacity to give consent) Yes or No

If yes, Describe the process for obtaining surrogate consent from a legally authorized representative.

IRBIS Application A.2.4

NOTE: Selecting ‘decisionally impaired individuals’ from the list of vulnerable populations triggers signature lines for the legally authorized representative in the consent:

_____ _____

Signature of Legally Authorized Representative Date

_____

Printed Name of Legally Authorized Representative

IRB Finding (documentation)

Finding will be printed on the approval letter:

The IRB has determined that decisionally impaired subjects may be enrolled in this research with the consent of a Legally authorized representative (LAR). The following individuals may give surrogate consent for another to participate, in order of priority: (1) a court appointed guardian, (2) an agent pursuant to a health care power of attorney, or (3) in some circumstances, a person appointed under a durable power of attorney. If one of these LARs is used, the PI should obtain a copy of the documentation granting the authority. If the first three LARs do not exist, and as long as there is no evidence to the contrary, the following members of the immediate family may give surrogate consent, again in order of priority: (4) the subject's spouse, (5) a majority of the subject's reasonable available parents and adult children, (6) a majority of the subject's reasonably available adult siblings, or (7) another individual with an established relationship with the subject who is acting in good faith on behalf of the subject and can reliably convey the subject's wishes. Investigators should consult with the Office of University Counsel with any questions as to who can legally serve in this capacity.

IRB Finding (documentation)

Finding will be printed on the approval letter:

The IRB has determined that decisionally impaired subjects may be enrolled in this research with the consent of a Legally authorized representative (LAR). The following individuals may give surrogate consent for another to participate, in order of priority: (1) a court appointed guardian, (2) an agent pursuant to a health care power of attorney, or (3) in some circumstances, a person appointed under a durable power of attorney. **If one of these LARs is used, the PI should obtain a copy of the documentation granting the authority**. If the first three LARs do not exist, and as long as there is no evidence to the contrary, the following members of the immediate family may give surrogate consent, again in order of priority: (4) the subject's spouse, (5) a majority of the subject's reasonable available parents and adult children, (6) a majority of the subject's reasonably available adult siblings, or (7) another individual with an established relationship with the subject who is acting in good faith on behalf of the subject and can reliably convey the subject's wishes. Investigators should consult with the Office of University Counsel with any questions as to who can legally serve in this capacity.

Who can act as a legally authorized representative?

As is the case for most states, North Carolina does not have State legal statutes that specifically address research enrollment. In accordance with federal regulations and guidance from the OHRP, UNC-Chapel Hill has established that the informed consent laws applicable to clinical care in North Carolina (North Carolina General Statute 90- 21.13) will be followed to determine who would be considered an acceptable LAR for purposes of providing surrogate consent for decisionally impaired subjects in studies conducted in North Carolina. Although the statute is specific to medical care, it may reasonably be applied to research participation as well.

Order of Priority

- (1) **Court-appointed legal guardian** (except to the extent any appointed health care agent has authority, unless the health care agent's authority has been suspended by a court order) is a court appointed guardian granted "general" guardianship or "guardian of the person" may provide surrogate consent for all activities of the individual; therefore, this guardian may provide surrogate consent for research participation of the individual.
- (2) **A health care power of attorney (HCPOA)** is a health care agent pursuant to the execution of health care power of attorney document. A HCPOA document (to the extent of authority granted) grants the agent power to make health care decisions for the…

Oder of Priority

…individual following a physician's determination that the individual lacks adequate capacity to make her/his own health care decisions. Therefore, if such a physician determination has been made, the agent under an HCPOA may provide surrogate consent for research participation; to the extent this does not contradict the written HCPOA.

Order of Priority

- (3) **A durable general power of attorney** grants the agent whatever authority is specified in the power of attorney document and is referred to as an attorney-in fact. Where the power of attorney includes a specific provision stating that it shall survive any period of incapacity or mental incompetence of the principal it is considered a "durable" power of attorney, and the person holding power of attorney may provide surrogate consent for research participation unless the research participation includes an activity expressly excluded from the power of attorney. NOTE that a general power of attorney is only valid when registered with the register of deeds in either the county named in the power of attorney or the county in which the principal resides. Before relying on the decision of a person holding a general power of attorney, investigators should require proof that the power of attorney has been registered and should examine the document to ensure that it expressly survives any period of incapacity or mental incompetence of the principal. For assistance with these determinations, please contact the Office of University Counsel.

Order of Priority

- (4) In the event that there is neither a court appointed guardian nor an agent under a durable general power of attorney or HCPOA, surrogate consent for research may be given, as long as there is no evidence to the contrary, by the other individuals listed below, in order of priority. When surrogate consent will be sought from one of these individuals, in the absence of a legal designation, their authority would be no broader (and may be more limited) than that of a duly appointed health care agent:
  - (**4a) The subject's spouse;**
  - **(4b) A majority of the subject's reasonably available parents and adult children;**
  - **(4c) A majority of the subject's reasonably available adult siblings; or (4d) Another individual with an established relationship with the subject who is acting in good faith on behalf of the subject and can reliably convey the subject's wishes.**

Order of Priority

- NOTE: In the case of designations (1), (2) or (3) above, the investigator should obtain a copy of the court order, HCPOA, or durable power of attorney and should maintain the copy with the research records as documentation of the authority of the surrogate decision maker.

Reporting Abuse and Neglect - Resources

NC Department of Social Services

NC Juvenile Code

Reporting Child Abuse and Neglect in North Carolina

Protection of the Abused, Neglected or Exploited Disabled Adult Act

UNC OHRE SOPs

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