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OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

SOP Number: 14B

SOP Title: RESEARCH INVOLVING PREGNANT WOMEN, HUMAN FETUSES AND NEONATES

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

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SOP 14B RESEARCH INVOLVING PREGNANT WOMEN, HUMAN FETUSES AND NEONATES

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SOP 14B RESEARCH INVOLVING PREGNANT WOMEN, HUMAN FETUSES AND NEONATES

INTRODUCTION

This Standard Operating Procedure (SOP) highlights the most common issues that arise at NIH with regard to research with pregnant women, human fetuses and neonates, but the SOP is not a complete set of regulatory requirements. Therefore, please refer to 45 CFR Subpart B, attached as **Appendix A - 45 CFR 46, Subpart B**, which is hereby incorporated into this SOP.

14B.1 PURPOSE

This SOP discusses requirements for research involving pregnant women, fetuses and neonates.

14B.2 POLICY

This SOP incorporates protections required by the NIH Human Research Protection Program (HRPP) as set forth by Federal regulatory requirements at 45 CFR 46, Subpart B - Research Involving Pregnant Women, Human Fetuses and Neonates (**Appendix A**).

The exemptions at 45 CFR 46.101(b)(1) through (6) may apply to research involving pregnant women, human fetuses, and neonates (also see SOP 6 – Processes for Determinations Made by the Office of Human Subjects Research Protections (OHSRP)).

In addition to other responsibilities assigned to Institutional Review Boards (IRBs) under 45 CFR 46 and the relevant SOPs, each IRB shall review research covered by Subpart B and approve only research that satisfies the conditions of all applicable sections of this Subpart and the other applicable Subparts of 45 CFR 46.

In limited circumstances, Food and Drug Administration (FDA) and Department of Health and Human Services (DHHS) regulations allow for exception(s) from informed consent requirements for emergency research, but this waiver is not available for research involving pregnant women, human fetuses and neonates

(see SOP 12 - Requirements for Informed Consent and SOP 15 - Research Regulated by the Food and Drug Administration (FDA). General Procedures for Both IND and IDE Applications).

14B.3 DEFINITIONS

(Taken from 45 CFR 46.202)

A. **Fetus:** The product of conception from implantation until delivery.

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

C. **Delivery:** Complete separation of the fetus from the woman by expulsion or extraction or any other means.

D. **Neonate:** A newborn

E. **Nonviable neonate:** A neonate after delivery that, although living, is not viable.

F. **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.

G. **Secretary:** The Secretary of Health and Human Services and any other officer or employee of DHHS to whom authority has been delegated.

H. **Viable, as it pertains to the neonate:** 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 45 CFR 46 Subpart A (protection of human subjects) and Subpart D (research involving children).

14B.4 RESPONSIBILITIES OF PRINCIPAL INVESTIGATORS WHEN APPLYING FOR REVIEW OF RESEARCH INVOLVING PREGNANT WOMEN,

HUMAN FETUSES AND NEONATES, EITHER AT INITIAL REVIEW OR AS AN AMENDMENT

When conducting research protocols involving pregnant women, human fetuses and neonates, Principal Investigators (PIs) shall provide information to the IRB required by applicable HRPP SOPs and the applicable NIH Intramural Clinical Protocol Application (i.e., either the Initial or Amendment application). PIs can also use Supplement J, Research Involving Pregnant Women, Fetuses or Neonates as guidance in protocol writing (**Appendix B**).

14B.5 REGULATORY CRITERIA FOR RESEARCH INVOLVING PREGNANT WOMEN OR FETUSES

Pregnant women or fetuses may be involved in research if all the conditions of 45 CFR 46.204 are met (see 45 CFR 46.204 for more information on the applicable criteria.) For pregnant children (as defined in 46 CFR 46.402(a)) and considered minors by applicable law, Subpart D and SOP 14D - Research Involving Children, should also be followed.

14B.6 REGULATORY CRITERIA FOR RESEARCH INVOLVING NEONATES

A. Neonates of Uncertain Viability and Nonviable Neonates: May be involved in research if all the conditions of 45 CFR 46.205(a) are met (see 45 CFR 46.205(a) for more information on the applicable criteria).

B. 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 additional conditions of 45 CFR 46.205(b) have been met (see 45 CFR 46.205(b) for more information on the applicable criteria).

C. Nonviable Neonates: After delivery nonviable neonates may not be involved in research unless all of the additional conditions of 45 CFR 46.205(c) are met (see 45 CFR 46.205(c) for more information on the applicable criteria).

D. 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 of 45 CFR 46 Subparts A and D (45 CFR

46.205(d))(also see SOP 14D - Research Involving Children) (see 45 CFR 46.205(d) for more information on the applicable criteria).

14B.7 REGULATORY CRITERIA AND NIH REQUIREMENTS FOR RESEARCH INVOLVING, AFTER DELIVERY, THE PLACENTA, THE DEAD FETUS OR FETAL MATERIAL

Research in this category may only be conducted in accord with 45 CFR 46.206 (see 45 CFR 46.206 for more information on the applicable criteria). Additionally, please also refer to the Office of Intramural Research (OIR) Sourcebook (see **References**) for NIH policy requirements for the research use of fetal tissue and SOP 5 – Required Review for NIH Research Activities with Human Subjects and Specimens/ Data.

14B.8 REGULATORY CRITERIA FOR RESEARCH NOT OTHERWISE APPROVABLE WHICH PRESENTS AN OPPORTUNITY TO UNDERSTAND, PREVENT, OR ALLEVIATE A SERIOUS PROBLEM AFFECTING THE HEALTH OR WELFARE OF PREGNANT WOMEN, FETUSES, OR NEONATES

A. Research that falls in this category must be approved by the Secretary.

B. The Secretary will conduct or fund research that the IRB does not believe meets the criteria of **14B.5** (45 CFR 46.204) or **14B.6** (45 CFR 46.205) only if the requirements of 45 CFR 46.207 are met (see 45 CFR 46.207 for more information on the applicable criteria).

C. Proposed research in this category will be sent from the NIH IRB to the NIH Office of Human Subjects Protections (OHSRP). OHSRP will forward the research protocol other relevant documents, e.g., the IRB minutes, to the DHHS Office for Human Research Protections (OHRP) for review by the Secretary, after consultation with a panel of experts in accord with 45 CFR 46.207.

REFERENCES

A. 45 CFR 46, Subpart B:
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html

B. Office of Intramural Research Sourcebook:
https://oir.nih.gov/sourcebook/ethical-conduct/research-ethics/fetal-tissue-research

LIST OF APPENDICES

Appendix A: 45 CFR 46, Subpart B

Appendix B: Supplement J – Research Involving Pregnant Women, Fetuses or Neonates

APPENDIX A: 45 CFR 46, SUBPART B

Source: 66 FR 56778, Nov. 13, 2001, unless otherwise noted.

§46.201 To what do these regulations apply?

(a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates conducted or supported by the Department of Health and Human Services (DHHS). This includes all research conducted in DHHS facilities by any person and all research conducted in any facility by DHHS employees.

(b) The exemptions at §46.101(b)(1) through (6) are applicable to this subpart.

(c) The provisions of §46.101(c) through (i) are applicable to this subpart. Reference to State or local laws in this subpart and in §46.101(f) is intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.

(d) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.202 Definitions

The definitions in §46.102 shall be applicable to this subpart as well. In addition, as used in this subpart:

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

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

(c) Fetus means the product of conception from implantation until delivery.

(d) Neonate means a newborn.

(e) Nonviable neonate means a neonate after delivery that, although living, is not viable.

(f) 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.

(g) Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(h) Viable, 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. The Secretary may from time to time, taking into account medical advances, publish in the FEDERAL REGISTER guidelines to assist in determining whether a neonate is viable for purposes of this subpart. 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 of this part.

§46.203 Duties of IRBs in connection with research involving pregnant women, fetuses, and neonates.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart and the other subparts of this part.

§46.204 Research involving pregnant women or fetuses.

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

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) 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;

(c) Any risk is the least possible for achieving the objectives of the research;

(d) 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, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, 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.

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(i) 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

(j) Individuals engaged in the research will have no part in determining the viability of a neonate.

§46.205 Research involving neonates.

(a) 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 under paragraph (b)(2) or (c)(5) of this section 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 paragraph (b) or (c) of this section have been met as applicable.

(b) Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:

(1) The IRB determines that:

(i) 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

(ii) 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

(2) 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 subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

(c) Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart 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 subpart A of this part, except that the waiver and alteration provisions of §46.116(c) and (d) do not apply. However, 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 of this paragraph (c)(5), 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 (c)(5).

(d) 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 of subparts A and D of this part.

§46.206 Research involving, after delivery, the placenta, the dead fetus or fetal material.

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

(b) If information associated with material described in paragraph (a) of 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 subparts of this part are applicable.

§46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.

The Secretary will conduct or fund research that the IRB does not believe meets the requirements of §46.204 or §46.205 only if:

(a) 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

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the FEDERAL REGISTER, has determined either:

(1) That the research in fact satisfies the conditions of §46.204, as applicable; or

(2) The following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;

(ii) The research will be conducted in accord with sound ethical principles; and

(iii) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.

APPENDIX B: SUPPLEMENT J – RESEARCH INVOLVING PREGNANT WOMEN, FETUSES OR NEONATES

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

1. Research involving Pregnant Women and Human Fetuses (SOP 14.B)

In order to be approved, the level of risk must be the least possible for achieving the objectives of the research. If research is greater than minimal risk, it must provide prospect of direct benefit for the pregnant mother or fetus (45 CFR 46.204.)

a. **Does this research pose a greater than minimal risk to the:**

Woman ☐ Yes ☐ No
Fetus ☐ Yes ☐ No

b. **Does the research hold out the prospect of direct benefit for the:**

Woman ☐ Yes ☐ No
Fetus ☐ Yes ☐ No

For research that does not hold out the prospect of direct benefit to the fetus or woman, explain in the protocol how the purpose of the research is the development of important biomedical knowledge, which cannot be obtained by any other means.

c. **Where scientifically appropriate, have preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, been conducted to provide data for assessing potential risks to pregnant women and fetuses?**
☐ Yes ☐ No

Informed Consent

Describe how you will ensure that individuals providing consent are fully informed regarding the reasonably foreseeable impact of the research on the fetus.

If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father must be 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. Otherwise, the consent of the mother is sufficient.

The legally effective informed consent of either parent, when required as above, may be waived because of unavailability, incompetence, or temporary incapacity, in which case the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of CFR 45 part 46.

Check off that the Principal Investigator assures that:

- ☐ 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 a neonate.

2. Research involving Neonates (45 CFR 46.202(d)) (see 14.B.3)

Newborns are only considered neonates until they are determined to be viable. Once they are determined to be viable, they are considered children. (Supplement A should be completed for viable newborns).

When neonates of uncertain viability and nonviable neonates are to be involved in research please answer the following questions, provide information in the protocol to support your responses:

a. **Will there be any added risk to the neonate resulting from the research?** ☐ Yes ☐ No

b. **The Principal Investigator assures that individuals engaged in the research will have no part in determining the viability of the neonate:** ☐ Yes ☐ No

c. **Where scientifically appropriate, have preclinical and clinical studies been conducted to provide data for assessing potential risks to neonates?** ☐ Yes ☐ No

d. **Does the research hold out the prospect of enhancing the probability of survival of the neonate to the point of viability, and is any risk the least possible for achieving that objective?** ☐ Yes ☐ No

e. **Is the purpose of the research the development of important biomedical knowledge that cannot be obtained by other means and will there be no added risk to the neonate as a result of the research?** ☐ Yes ☐ No

f. **Will legally effective informed consent from either parent[1] be obtained in the case of a neonate of uncertain viability?** ☐ Yes ☐ No

g**. Will legally effective informed consent from both parents[2] be obtained in the case of nonviable neonates?** ☐ Yes ☐ No

i. **In the case of nonviable neonates, will vital functions of the neonate be artificially maintained?** ☐ Yes ☐ No

ii. **In the case on nonviable neonates, will the research terminate the heartbeat or respiration of the neonate?** ☐ Yes ☐ No

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[1] 45 CFR 46.205(b)(2) 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 subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest. Nonviable neonate means a neonate after delivery that, although living, is not viable.

[2] 46 CFR 46.205(c)(5) The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of §46.116(c) and (d) do not apply. However, 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 of this paragraph (c)(5), 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 (c)(5).