Marshfield Clinic

Criteria for IRB Approval

1. SCOPE

1.1. System-Wide

2. DEFINITIONS & EXPLANATIONS OF TERMS

2.1. Minimal risk

- The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life of a healthy individual, or during the performance of routine physical or psychological examinations or tests.

2.2. Viable fetus

- Means being able, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration.

2.3. Nonviable fetus

- Means a fetus ex utero which, although living, is not viable.

3. PROCEDURE BODY

This document provides investigators and IRB members with the criteria used by the Marshfield Clinic Research Foundation Institutional Review Board (MCRF IRB) when reviewing and approving research studies. The criteria for approving research is dictated by 45 CFR 46.111 and 21 CFR 56.111, with additional criteria for vulnerable subjects found at 45 CFR 46 Subparts B, C, and D, and 21 CFR 50 Subpart D. Wisconsin law is mute on the issue of what information must be included in research consent forms.

3.1. Basic Approval Criteria

a. The IRB will ensure that all of the approval criteria noted below are satisfied prior to approving a research project:

- (1) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks, the IRB will only consider those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB will not consider possible long-range effects of applying knowledge gained in the

research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

- (3) Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research involving populations such as children, prisoners, pregnant women, mentally disabled persons, economically or educationally disadvantaged persons, or minority populations such as the Hmong.
- (4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116.
- (5) Informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117.
- (6) When appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects.
- (7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

  Finding confidentiality protections to be adequate may be based on the presence of identifiers, sensitivity of the content, and risks of breach. The IRB will consider measures for maintaining confidentiality including de-identification of data, restricting PHI to a limited data set, physical and electronic storage protections, encryption of electronic data, statistical methods, and use of certificates of confidentiality. The investigator must document the data elements to be collected and the measures planned to secure the data, and design the protocols to minimize the need to maintain or share identifiable data if possible.

  Participant privacy will be protected by conducting study procedures, including informed consent, with the privacy of the individual in mind. Whenever possible, the informed consent discussion will take place in a private room. Research interventions and procedures will take place in areas that meet clinical standards for patient privacy.
- (8) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

3.2. Additional Approval Criteria for Research Involving Minors

a. If the proposed research involves children (under the age of 18), reviewers are asked to first make a risk determination and then apply criteria for approving the research specific to that risk determination. Reviewers are reminded of the

"minimal risk" definition above. The categories of risk as defined by regulations are:

- Research not involving greater than minimal risk (45 CFR 46.404 and 21 CFR 50.51);
- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject (45 CFR 46.405 and 21 CFR 50.52)
  - Note: The FDA indicates that it does "not consider the administration of a placebo to offer a prospect of direct benefit." Therefore, the placebo arm of a study does not meet the requirements under this citation.
- Research 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 (45 CFR 46.406 and 21 CFR 50.53); and
- Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407 and 21 CFR 50.54).

b. Once the research is assigned a risk category, the reviewer is asked to apply the following criteria from the appropriate risk category to the project to determine whether the project is approvable.

(1) Research not involving greater than minimal risk

- The IRB may approve research under this category only if it finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.
  - Does the investigator's plan include a requirement for obtaining assent from children judged to be capable of assent or a provision to encourage (but not require) assent when 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 or a request for waiver of assent (waiver form must adequately justify that criteria for waiver have been met)?
  - Does the investigator's plan include a requirement for permission (consent) from at least one parent or a request for waiver of consent (waiver form must adequately justify that criteria for waiver have been met) or (for non-FDA regulated studies only) can consent be waived because the IRB determines that the research protocol is designed for a condition or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (e.g., neglected or abused children)? If consent is waived under this provision, an appropriate mechanism for protecting the children who will participate as subjects must be substituted and the waiver cannot be inconsistent with Federal, State or local laws.

(2) Research Involving Greater than Minimal Risk but Presenting the Prospect of Direct Benefit to the Individual Subject

- The IRB may only approve research under this category if it answers affirmatively to the following:
  - Risk(s) are justified by the anticipated benefit to the subjects;
  - Relation of the anticipated benefit to the risk is at least as favorable to the subject as that presented by available alternative approaches; and
  - Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians (see questions under (3.2.c) above)

(3) Research 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

- The IRB may only approve research falling under this category if it answers affirmatively to the following:
  - 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;
  - Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians. Does the investigator's plan include a requirement for obtaining assent from children judged to be capable of assent or a provision to encourage (but not require) assent when 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 or a request for waiver of assent (waiver form must adequately justify that criteria for waiver have been met); and
  - The investigator's plan includes a requirement for permission (consent) from both parents unless one parent is deceased, unknown, incompetent, not reasonably available, or when only one parent has legal responsibility for the care and custody of the child or a request for waiver of consent (waiver form must adequately justify that criteria for waiver have been met) or (for non-FDA regulated projects) consent can be waived because the IRB determines that the research protocol is designed for a condition or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (e.g., neglected or abused children). If consent is waived under this provision, an appropriate mechanism for protecting the children who will participate as subjects must be substituted and the waiver cannot be inconsistent with Federal, State or local laws.

(4) Research Not Otherwise Approvable which Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Children

- The IRB may approve research under this category only if it answers affirmatively to the following:
  - 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 and welfare of children, and
  - As applicable, the Secretary of the Department of Health and Human Services or the Commissioner of the FDA has given approval as outlined in 45 CFR 46.407(b) and 21 CFR 50.54(b).

3.3. Additional Approval Criteria for Research Involving Children Who are Wards

a. Children who are wards of the state or any other agency, institution, or entity can be included in research involving greater than minimal risk and no prospect of direct benefit to individual subject or research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children, only if such research is
   - Related to their status as wards; or
   - Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

b. For the research described above to be reviewed by MCRF IRB, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian. One individual may serve as advocate for more than one child. This advocate shall have the background and experience to act in, and must agree to act in, the best interest of the child for the duration of the child's participation in the study. The advocate must not be 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.

3.4. Additional Approval Criteria for Research Involving Pregnant Women, Human Fetuses and Neonates

a. If a project pertains to research, development, and related activities involving pregnant women, human fetuses, or neonates, the IRB may approve the activity only if it answers affirmatively to all of the following applicable statements:
   - **If the research involves pregnant women or fetuses:** The IRB may only 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 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;

- 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 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 be any other means, her consent is obtained in accord with the informed consent provisions of subpart A of 45 CFR 46;
- If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant women and the father is obtained in accordance with the informed consent provisions of subpart A of 45 CFR 46, 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 paragraph (d) or (e) above is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
- For children as defined in Sec. 46.402 (a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of 45 CFR 46;
- 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.

b. **If the research involves neonates:** Neonates of uncertain viability and nonviable neonates may be involved in research only if all of the following conditions are met:

c. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

d. Each individual providing his or her consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

e. Individuals engaged in the research will have no part in determining the viability of a neonate.

f. The requirements of the following paragraphs have been met as applicable.

☐ **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 are met:

- The IRB determines that:

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 in accord with subpart A of 45 CFR 46, 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 neonates:** After delivery nonviable neonate 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 in accord with subpart A of 45 CFR 46, except that the waiver and alteration provisions of Sec. 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, 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.

☐ **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 45 CFR 46.

g. **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, tissues, 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. If information associated with material described above is recorded for research purpose 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 45 CFR 46 are applicable.

h. Research involving pregnant women, fetuses, or neonates 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 may not be approved or conducted unless:

- ☐ The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of serious problem affecting the health or welfare of pregnant women, fetuses, or neonates; and
- ☐ The Office for Human Subject Protection, after consultation with a panel of experts in pertinent disciplines and following opportunity for public review and comment, including a public meeting announced in the Federal Register, has determined either:
  - That the research in fact satisfies the conditions of Sec. 46.204, as applicable; or
  - The following:

    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;

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

    Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of 45 CFR 46.

3.5. Additional approval criteria for research involving prisoners

a. MCRF IRB does not currently review research involving prisoners, and therefore this policy does not detail the additional approval criteria. If, however, a protocol should come before the IRB that involves prisoners, the additional approval criteria in Subpart C of the DHHS regulations (45 CFR 46) will be applied.

4. ADDITIONAL RESOURCES

4.1. References:
- None.

4.2. Supporting documents available:
- None.

5. DOCUMENT HISTORY

Version No.	Revision Description
1.0	New Document in Document Control System transferred from Policy & Handbook Library - #779.4. (No changes made)
2.0	
3.0	

6. DOCUMENT PROPERTIES

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