CHAPTER 10

Criteria for IRB Approval of Research

DHHS regulations at 45 CFR 46.111, Federal regulations at 21 CFR 56.11, and the Federal Policy (Common Rule) delineate specific criteria for the approval of research.

The Prisma Health IRB will determine that all the following requirements are satisfied before approving proposed research:

- *Risks are minimized using sound research design,*
- *Risks are reasonable in relation to anticipated benefits*
- *The selection of subjects if equitable*
- *The informed consent of subjects will be obtained*
- *The informed consent of subjects will be documented*
- *The research includes adequate provisions for monitoring date to ensure the safety of subjects*
- *The research included adequate provisions to safeguard the confidentiality of data and the privacy of subjects*
- *The research includes adequate additional protection to safeguard the rights and welfare of subjects who*
- *may be vulnerable to coercion or undue influence.*

1. Risks Are Minimized

a) The Prisma Health IRB must consider the overall level of risk to participants in evaluating proposed research. The IRB is required to distinguish research that is "greater than minimal risk" from research that is "greater than minimal risk". Under specific circumstances, research that is no greater than minimal risk may be eligible for expedited review, waiver or alteration of consent requirements, or waiver of the requirement to obtain written documentation of consent.

b) Under Federal regulations at 45 CFR 46.102(j) and the Common Rule, "minimal risk means that the probability and magnitude of harm or discomfort in the research are not greater in and of themselves than those encountered in daily life or during the performance of routine physical or psychological examinations or tests."

c) The definition of minimal risk is based on activities "ordinarily encountered in daily life or during the performance of routine physical or physiological examination or test" and should not be interpreted to include the inherent risks that certain individuals/research participants may face in their everyday life.

d) To approve research, the IRB must determine that risks are minimized. To accomplish this assessment the IRB will review and determine:

   i. procedures that are consistent with sound research design,
   ii. procedures do not expose participants to unnecessary risks,
   iii. Whenever appropriate, the research should utilize procedures already being performed in the context or planned diagnostic or treatment purposes,
   iv. tests, procedures, data use, and sample size do not exceed that requirement to meet with objectives of the study,
   v. Design and methodology do not contain any issues or flaws that would place participants at unnecessary risk.

e) When research design presents unnecessary or unacceptable risks to participants without commensurate benefits to the participants or others, the research cannot ethically proceed and cannot be approved by the IRB.

f) The IRB reserves the authority to seek opinions from consultants on proposed research and its design. In requesting research re-design, the IRB may determine that re-design must enhance participant autonomy, maximize benefits, allow more equitable selection of subjects, minimize undue influence or coercions, or otherwise protect the rights and welfare participants.

g) The IRB will also consider the qualification of the research team. Clinicians are expected to maintain appropriate professional credentials and licensing privileges to include compliance to requirements for Human Subjects Protection training.

2. Psychological and Social Harms are Minimized

a) When evaluating research, the IRB will not only consider the risk of clinical/treatment harms, but also the risk of psychological and social harms.
b) The IRB will also consider the risks of criminal or civil liability or other risks that can result in serious social harms such as damage to financial or legal standing, employability, insurability, reputation, stigmatization, and damage to social relationships.
c) The IRB considers the potential for participants to experience stress, anxiety, or trauma that can result in genuine psychological harms. The Prisma Health IRB roster includes continuing consultants with expertise in Behavioral Sciences to bring expertise to the review of Social Behavioral Research and research that includes.
d) IRB will also consider risks related to data and biospecimen collection and retention as well as use of this information for future yet to be determined research.
e) To mitigate potential harms, the IRB will evaluate all submissions for appropriate preventive protections incorporated into study design, adequate disclosure of risks in the informed consent document and process, as well as appropriate safeguards to maintain the confidentiality and privacy of persons participating in the research.

3. Risks are Reasonable Relative to Anticipated Benefits.

The IRB must determine that the risks of the research are reasonable in relation to the anticipated benefits (if any) to subjects and/or to the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111(a)(2)).

4. Selection of Subjects is Equitable.

a) The IRB must determine that the selection of participants is equitable. The investigators must provide details of the proposed involvement of humans in research including:
    i. The characteristics of the participant population,
    ii. Anticipated number of participants enrolled, particularly at the local site,
    iii. Age ranges,
    iv. Health Status,
    v. Gender and racial/ ethnic composition,
    vi. Criteria for inclusion or exclusion of the study population and any subpopulation.
b) The IRB will evaluate the purposes of the research and the research setting being particularly cognizant of issues involving potentially vulnerable participant populations which may include:
    i. Children,
    ii. Pregnant women,
    iii. Prisoners,
    iv. Handicapped or mentally disabled persons,
    v. Economically or educationally disadvantaged persons,
    vi. The IRB may also determine any study participants may vulnerable based on position, disease state, or any other situation in which they may be coerced in the process by lack of understanding or need.
c) The IRB will carefully examine inclusion – exclusion criteria and recruitment procedures to determine that burdens and benefits of the research are equitably distributed.

5. Informed Consent, Parental Permission, and Child Assent Will be Obtained

a) Informed Consent will be sought and obtained from each prospective participant or the participants legally authorized representative (45 CFR 46.116 and 21 CRF 50.21), unless informed consent requirements can be waived or altered under Federal regulations. Any such waiver or alteration must be consistent with applicable Federal, and State laws and regulations.

b) To improve research involving children as participants, the IRB must determine the permission of the child's parent(s) or guardian(s) and the assent of the child will be sought and obtained (or formally waived or altered) in accordance with Subpart D of the HHS and FDA Human Subject regulations at *45 CFR 46.4-8* and *21 CFR 50.55.* Any waiver or alteration of these permission or assent requirements must be consistent with applicable Federal and State laws and regulations*. See Chapter 11 for consent requirements.*

c) The informed consent of adult participants, the informed consent of a participant's legally authorized representative, the permission of the parent(s) or guardian(s) of a child-participant may only be sought under circumstances that minimize the possibility of coercion or undue influence and that provide the parent(s), participant, or legally authorized representative with sufficient opportunity to consider whether the participant will participate.

d) Information for informed consent, permission, and assent must be presented in language that is understandable to the participant or legally authorized representative.

e) No informed consent, permission, or assent process may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights; through which the investigator, the sponsor, this Institution, or its employees are released from liability for negligence, or appear to be so released.

f) Informed consent, permission, and assent (as applicable) must be obtained prior to initiation of any clinical screening procedures that are performed solely for the purposed of determining eligibility for research.

g) Alternatives to obtaining and documenting informed consent, permission, or assent immediately before the start of the research include obtaining and documenting consent, permission, or assent during a reasonable interval prior to the start of the research that permits the individual sufficient time to make an informed choice about the requested participation.

h) When other alternatives are proposed, the IRB must determine that the alternative is appropriate under Federal and State law and the alternative is appropriate under Federal and State law and regulation in the jurisdiction in which the participant will be enrolled and participate. These instances will be evaluated on a case-by-case basis.

6. Consent Monitoring

a) In considering the adequacy of informed consent, permission, and assent procedures, the HRPP Director may require special monitoring of the process associated with consent. The IRB Committee or HRPP Director may require special monitoring of the process, particularly in situations where research may present significant risks, or the participant population may be particularly vulnerable or have difficulty understanding information provided.

b) Such monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a specific research project.

c) Monitoring of the consent process may include observation of the process, interview of research staff, investigators, and participants. Monitoring may be conducted by an IRB committee member, HRPP staff, or compliance auditor.

7. Advertisements and Recruitment Incentives

a) All advertisements and recruitment material associated with proposed research must be reviewed by the IRB prior to any posting or distribution at the start of a study as well as any ongoing materials developed for this purpose. In addition to that information contained in the materials, the IRB must also review the mode of their communication, the final copy of the printed, video, audio, email communications and web-based postings. These materials are

viewed as the initial phase of the consent process and must be consistent with prohibitions on coercion and undue influence.

b) These procedures must be designed so that informed consent and assent are given freely and there is no coercion or undue influence in the recruitment strategies or the process of consent.

c) Any advertisement to recruit participants should be limited to the information the prospective participants, legally authorized representatives, parents, or guardians need to determine eligibility and interest. The following items may be included:
    i. The name and contact information of the clinical investigator or organization where the research will be conducted,
    ii. The purpose of the research,
    iii. The criteria that will be used to determine eligibility for the study in summary form,
    iv. The time or other commitment required of the participants,
    v. The person or office to contact for further information.

d) The IRB must ensure that advertisements and recruitment efforts:
    i. Do not state or imply favorable outcomes or other benefits beyond what is state in the protocol or consent document,
    ii. Do not include exculpatory language,
    iii. Do not emphasize payments or amounts to be paid i.e., using large or bold print to highlight this information,
    iv. Do not promise "free treatment" when the intent is only to say participants will not be charged for taking part in the investigation.

e) For FDA-regulated research
    i. Do not make claims, either explicitly or implicitly, about the drug, biologic, or device under investigation that are inconsistent with FDA labelling,
    ii. Do not use terms, such as "new treatment," "new medication," or "new drug" without explaining that the test article is investigational,
    iii. Do not include any type of "offer for discount" once the product has been approved for marketing.

8. Payment for Research Participation

a) The Prisma Health IRB must review all plans/proposals for payments to research participants (or parents, guardians, or legally authorized representatives) associated with the research that it oversees.

b) The IRB will review payments to determine that:
    i. Payments are not of an amount as to result in coercion or undue influence one's decision to participate or continue participation,
    ii. Payments are not on a schedule that results in coercion or undue influence on the decision,
    iii. The research does not offer "raffle" or prizes to participants,
    iv. Credit for payment accrues as the study progresses and not be contingent upon the participant completing the entire study,
    v. Any amount paid as a bonus for completion is reasonable and not so large as to unduly induce participants to stay in a study when they would otherwise have withdrawn,
    vi. All information concerning payment, including the amount and schedule of payments, is set forth in the consent document.

9. Investigators Incentives

Investigators may not receive special incentives, monetary or material, for enrolling participants.

10. Indemnity and Liability Provisions (Exculpatory Language)

Participants in research may not be asked to waive or appear to waive any of their legal rights. The IRB staff and/or committee members will review to identify and remove any such language that might be present in submitted consent forms.

11. Other Requirements

a) For FDA regulated research, the consent from must include a statement that FDA may inspect the participants research records.

b) For research studies that are posted on Clinical Trials.gov the consent form will include the required statement:

"A description of this clinical trial will be available on https://clinicaltrials.gov , as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time."

12. Informed Consent, Permission, and Assent Will Be Documented

a) The IRB must determine that informed consent of adult participants (or the participants legally authorized representative) and/or the permission of the parent(s) or guardian(s) of child participants, will be documented in writing, unless documentation can be waived under Federal regulations.
b) Chapter 16 details the requirements for documents of permission for the involvement of children in research.
c) The method of documenting the assent of a child participant will be determined by the IRB in accordance with Subpart D of the DHHS and FDA regulations at 45 CFR 46.408 and 21 CFR 50.55, respectively.
d) Long Form and Short Form Documentation:
Federal regulations at 45 CFR 46.117 and 21 CFR 50.27 provide methods for documenting informed consent and/or permission:

i. Consent or permission may be document through use of a written document that embodies all the required elements of informed consent. The document must be signed by the subject (or the subject's legally authorized representative, parent(s), or guardian(s) in compliance with all regulatory requirements), and a copy must be provided to the individual signing the consent document. FDA regulations required that the signature be dated, or

ii. Consent or permission may also be documented through use of a short form document which state that the elements of informed consent have been presented orally to the subject (or the legally authorized representative, parent(s), or guardian(s)) in compliance with all regulatory requirements, and that the key information required by 45 CFR 46.116(a)(5) be presented to the subject first. When this method is used:
   - There must be a witness to the oral presentation,
   - The IRB must approve a written summary of what is to be presented orally,
   - Only the short form must be signed by the subject, representative, parent(s), or guardian(s),
   - The witness much sign both the short form and the summary. The summary must include the basic elements of disclosure,
   - The person obtaining the consent must sign the summary,
   - A copy of the signed summary and the signed short form will be given to the subject, the representative, the parent(s) or guardian(s).

13. Participants with Limited Literacy or are Unable to Sign Consent Documents

These individuals may have information consent or permission information read to them and may "make their mark" to document their consent in a manner consistent with the laws of the state. This process must be witnessed by someone who is present during the consent discussion and can attest to the accuracy of the presentation and the understanding of the participant, legally authorized representative, parent(s), guardian(s). The witness, by virtue of their signature, attests to these facts and the validity of the individual's signature.

14. Date Stamp Required

All informed consent and permission documents will have an approval data applied by the IRB indicating the approval date. An expiration date will be applied to those protocols that required continuing review and the expiration date will coincide with the expiration date of the protocol. Only the IRB approved informed consent documents can be used for research consent. The investigator is responsible for storing consent documents for at least three years following the completion of the research. The investigator must also assure that a copy of the signed consent document is attached to the participants EPIC record if applicable.

15. Copy to Participant and/or Decision Maker

At the time that the informed consent or permission information has been presented, a copy of the consent document is given to the participant, legally authorized representative, parent(s) or guardian(s) for further review. The potential participant and/or decision maker must be provided time necessary to speak with family or others to assist in their decision-making process. Once the determination has been made to participate in the study the document will be signed.

16. Safety Monitoring Is Adequate

The Prisma Health IRB must determine that, where appropriate, the research plan makes adequate provisions of monitoring the data to protect the safety of participants. A detailed description of the data and safety monitoring plan should be submitted to the IRB as part of any proposal for research in which risks are substantial. This plan should include procedures for reporting adverse events and the monitoring plan.

The IRB has the authority to require a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) as a condition for approval of research where it determines that such monitoring is needed.

In the instance of multi-site externally sponsored studies, the IRB may rely on ongoing updates from a duly constituted DSMB/DMC indicated that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research and has determined that continuation of the research is justified.

17. Privacy and Confidentiality Provisions Are Adequate

The IRB must determine that, where appropriate, there are adequate provisions to protect the privacy of participants and the confidentiality of data.

Methods utilized to identify potential participants or to gather information about participants are conducted under conditions of participant authorization or with appropriate waivers of authorization issued by the IRB in its role of Privacy Board for research or the Institutional Privacy Officer.

In general, identifiable information may not be obtained from private (non-public) records without the approval or waiver from the IRB and/or the informed consent of the participants.

Plans to manage identifiable private information and/or identifiable biospecimens once it has been collected to must be in place and provided in the submitted protocol for IRB review. In reviewing the confidentiality protections, the IRB will consider the nature, probability, and magnitude of harms that would likely result from a disclosure of information collected. The effectiveness of proposed anonymizing techniques, coding systems, encryption methods, storage facilities, access limitation, and other relevant factors in determining the adequacy of confidentiality protections.

18. Certificate of Confidentiality (CoC)

The CoC protects the privacy of research participants again the involuntary release of sensitive information about individual participants for use in Federal, State, or local civil, criminal, administrative, legislative, or other legal proceedings.

Where the research involved the collection of highly sensitive information about individual identifiable participants, the IRB may determine that special protections are needed to protect participants from the risks of investigative or judicial processes. In such situations, the IRB ay require that any investigator obtain a DHHS Certificate of Confidentiality (CoC).

Effective October 1, 2017, the National Institute of Health (NIH) will automatically issue CoCs to all research funded by the NIH for research that is collecting or using identifiable, sensitive information. NIH funded researchers are automatically issued a CoC through their award.

CoCs may also be issued to other HHS funded research. If the research is funded be one of these agencies, or is operating under the authority of the FDA, investigators must contact the Certificate Coordinator at the funding agency to determine how to obtain the CoC.

Research not Federally funded can apply to the NIH or FDA as appropriate to request a CoC for HHS-missions relevant research or for a specific project that involves sensitive, identifiable information.

The CoC does not prohibit voluntary disclosure of information by an investigator, such as voluntary reporting to local authorities issues of suspect child abuse of communicable disease. In addition, the CoC does not protect against the release of information to DHHA or FDA for audit purposes.
The IRB will require that these conditions for release be state clearly and explicitly in the informed consent document.

19. Additional Safeguards for Vulnerable Participants

The IRB must determine that, when appropriate, additional safeguards are included the research plan and consent to protect the rights and welfare of participants who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, persons with mental disabilities or economically or educationally disadvantaged.

The IRB may also determine any study participants may be vulnerable based on position, disease state, or any other situation in which they may be coerced in the process by lack of understanding or need.

The IRB will include individuals who are knowledgeable about and experienced in working with these vulnerable participants. Should the reviewing IRB not include someone with the requisite expertise to conduct any such review, a consultant will be requested to review and study materials and provide guidance and recommendations for the committee to consider so that

issues of vulnerability may by appropriately and effectively addresses.

20. Research Involving Data Sets and Repositories

The use of existing data sets requires IRB review when they contain identifiable private information about living individuals. In such cases, the IRB must determine whether or information can be used without informed consent from the participants.

The IRB will consider the conditions of informed consent under which the data were originally obtained to determine if the proposed research is permissible under the original terms of consent,The IRB will then consider whether it is permissible to waive informed consent requirements in accordance with 45 CFR 46.116(f)(3).

The IRB may also determine that the research can proceed only if the data is provided by an "honest broker", an individual not involved in the research that can remove identifiers prior to release to the investigator so that the data set only include de-identified data.

Guidance on maintain a data repository is available at the OHRP website: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/biological-materials-and-data/index.html

The Prisma Health Data Support Core can also provide support and direction in the development and maintenance of data registries: https://academics.prismahealth.org/research-and-innovation/research-administration/research-data-services-and-data-support-core

21. Epidemiology Research

a) Epidemiology research often makes use of sensitive, individually identifiable, private information (usually obtained from medical or other private records) and links this information with additional information obtained from other public or private records such as employment, insurance, or police records. Epidemiology research may also combine historical research with survey and interview research. These studies often present significant issues regarding both privacy and confidentiality.
b) The IRB must be satisfied that the research does not constitute unwarranted invasion of the participants privacy.
c) Once it is determined that confidentiality protections are appropriate to the nature and sensitivity of information obtained, the IRB will consider informed consent requirements.
d) In most cases the numbers of participants and the utilization of previously collected information, a waiver of consent will typically be requested by the investigator. To approve such a waiver that IRB will see to establish that confidentiality protections are appropriate and must find and document that the first three criteria at 45 CFR 46.116(f)(3) for a waiver of informed consent have been met; specifically, that:
    i. The research presents no more than minimal risk to subjects.
    ii. The waiver will not affect the rights and welfare of the subjects.
    iii. The research could not practicably be carried out without the waiver; and
    iv. If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in ana identifiable format.

22. Issues in Genetic Research

a) Information obtained through genetic research may have serious repercussions for the participant or participant's family members. Genetic information can adversely affect an individual's insurability and employability.
b) The protection of private information gathered for and resulting from genetic research is a major consideration. Any protocol submitted will required the investigator to describe in detail how privacy will be protected, how confidentiality of obtained

information will be maintained.

c) The *Genetic Information Nondiscrimination Act of 2008* in conjunction with 45 CFR 46.116 require the informed consent include appropriate information related to:

   Research involving biospecimens will, or might include whole genome sequencing (sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen)

d) The IRB will also require the inclusion of approved GINA language in the informed consent document. This required language is available in the Prisma Health Main Informed Consent Template and further information about *GINA* requirements are available on the OHRP website as noted below.

23. Participant Withdrawal from Clinical Research

Should a participant choose to withdraw from clinical research, the primary concern will be for safe transition to an appropriate standard of care should their enrollment in the study involve specific, unique treatment. Another concern for the IRB is the continued use of the individuals' data that has already been collected.

The consent document will clearly explain the process and implications of withdrawal, while clearly maintaining that participation is voluntary and can withdraw if they choose. Appropriate steps for follow up and transition to other care options will be provided to participants as part of their decision process. While not required, template ICF language for withdrawal from clinical research is included in the IRB provided ICF Template and is available on the IRBNet site. Guidance is also available on the OHRP website:
https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-withdrawal-of-subject/index.html

24. Compliance with All Applicable Laws

All human subject research conducted at Prisma Health or by its employees must comply with all applicable laws and regulations of the United State and the State in which the research is conducted, as well as any local requirements.