Chapter 9

Procedures for IRB Review

All human subject research conducted at Prisma Health Institutions must be prospectively reviewed by an approved reviewer in the Prisma Health IRB. No human subjects research may be initiated or continued without prospective approval of the Prisma Health IRB.

All IRB review records will include documentation specifying the responsibilities that a relying organization and an organization operating an IRB will undertake to ensure compliance with the requirements of the Common Rule.

The Prisma Health statement of compliance can be found on the HRPP website and all review determination letters.

1. REVIEW BY THE CONVENED IRB

A. The Common Rule, DHHS regulations, and FDA regulations all require that the IRB conduct initial and continuing review of all non-exempt research during convened IRB meetings at which a majority of members are present, unless the research falls into one or more of the categories appropriate for expedited review.
B. Meeting dates and agenda submission deadlines are posted on the HRPP website.
C. One week, at a minimum, prior to the convened meeting, all IRB members will be provided with the meeting agenda and access to all protocol submission materials to be discussed at the convened meeting and prior meeting minutes for review.
D. IRB committee members may contact the IRB Coordinator, Committee Chair, or Principal Investigator if they require additional information to effectively complete their review assignments. Committee members will have access to all protocol records and documents in the Prisma Health protocol management system.
E. IRB members are required to document their recommendation and reviewer notes in the protocol management system prior to the convened meeting so that all committee members may review them.
F. A majority of the Prisma Health IRB members (or their designated alternates), including at least one member whose primary concerns are in non-scientific areas, must be present to conduct a convened meeting. For research to be approved, it must receive the approval of a majority of those members present at the meeting. If quorum is lost during a meeting, the IRB cannot record votes until the quorum is restored.
G. When research involves participants who may be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, fetuses or neonates, research that addresses social behavioral issues or any population individuals with diminished capacity, at least one member or non-member

consultant, the HRPP Director, or IRB Chair shall ensure that at least one individual who is knowledgeable about or experienced in working with such participants is present at the meeting to provide insight and expertise to the committee's discussion and deliberation.

H. Members may be present in person, through virtual media, or audio. Members presenting via virtual media will be noted as such in the minutes. (This notation is required if only specific individuals are not present in person; if the meeting is scheduled as virtual for all members, this will be noted in the minutes.)

2. INITIAL REVIEW BY THE CONVENED IRB

A. On receipt of a complete IRB application in the Prisma Health protocol management system, the IRB Coordinator will complete a preliminary review and assign the submission to the appropriate agenda. The IRB Coordinator will also assign a Primary (Scientific) Reviewer and a Secondary (Consent) Reviewer and engage an expert consultant if required for effective review of the protocol. These assigned reviewers will complete the required reviewer forms, make approval recommendations, and lead discussion of the proposed research at the convened meeting of the IRB.

B. The minutes of the IRB meetings will document separate deliberations, actions, and votes for each protocol undergoing initial review by the convened IRB.

3. USE OF PRIMARY AND SECONDARY REVIEWERS WITH CONVENED REVIEWS

A. In accordance with FDA and OHRP guidance, the Prisma Health IRB utilizes a "primary and secondary reviewer system" to assist in the initial and continuing review of research by the convened IRB and utilization of these roles to have specific focus on the scientific review process and the consent form.

B. When utilized, the Primary and Secondary reviewers are considered the lead reviewers for submissions assigned to them. An IRB member, who is assigned as a primary reviewer, may request that the protocol be assigned to another IRB member if they do not feel that they have the necessary expertise to present the protocol to the committee. These assigned reviewers are responsible for:

   i. Being thoroughly versed in all details of the submission,
   ii. Conducting the review using the provided Prisma Health IRB Reviewer checklist, and
   iii. Seeking clarification, if necessary, from the Principal Investigator as needed prior to the meeting, as well as leading the discussion of the research at the convened meeting.

4. IRB MEMBER INITIAL REVIEW MATERIALS

A. Initial review materials will be provided to all IRB members (including alternate members who will attend the meeting) at least one week prior to the meeting, which will allow the reviewers to conduct a thorough review and analysis for

the purpose of the study, scholarly or scientific rationale, and risks and potential benefits to participants. The following application packet will be provided to the reviewers, and will include the following documents:

i. The Prisma Health application form,
ii. Protocol document,
iii. Investigator Brochure,
iv. The proposed information consent document(s),
v. Any recruitment materials and any public facing documents,
vi. Any Ancillary reviews and/or approvals as required by the protocol,
vii. Principal Investigator and Study Staff credentials and training records, and
viii. Any other information relevant to the conduct of the protocol (e.g., surveys and questionnaires).

B. If either the primary and/or secondary reviewer determine they are unable to be present at the convened meeting, the reviewer should notify the IRB Coordinator as soon as possible so that others may be identified to provide that level of review at the convened meeting.

5. CONTINUING REVIEW

A. For DHHS supported research and for FDA regulated research, the Prisma Health IRB is required to conduct "substantive and meaningful continuing review" of research at intervals appropriate to the degree of risk, but unless otherwise indicated, not less than once per year (45 CFR 46.109(f)(1)). Expiration dates are set at one year minus one day from the approval date.

NOTE: Prisma Health IRB has transitioned all studies approved prior to January 21, 2019, to the standard set forth in the Revised Common Rule.

B. The following regulatory criteria are utilized to determine the continuing review period for Prisma Health IRB reviewed and approved research:

i. The Prisma Health IRB shall conduct a continuing review of all research at intervals appropriate to the degree of risk, not less than once per year.

ii. Annual continuing review of research is not required in the following circumstances:

- Research reviewed and approved after January 21, 2019, by the Prisma Health IRB via expedited review procedures.
- Research reviewed and approved after January 21, 2019, in accordance with the limited IRB review procedures.
- Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB approved study:
  - Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
  - Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

- Studies that have been determined to no longer require continuing review will be assigned a "report due" date 3 years beyond the last reviewed date.
- The IRB will maintain oversight of these studies through administrative reviews at the time the 3 year "approval" period ends. The review will require the submission of the "continuing review" cover sheet in IRBNet.
- The study active period will be extended at 3-year intervals until such time there is notification of study closure. Should the study conclude prior to the end of the approved interval, a study closure notice should be submitted to the IRB to formally close the study.

C. Continuing reviews will be conducted by the convened IRB unless the research falls into one or more of the categories appropriate for expedited review. When appropriate, continuing reviews will continue until the study is complete.
D. At least one week prior to the scheduled convened meeting, each IRB member will be provided with the detailed, continuing review materials sufficient to conduct substantive and meaningful reviews. The materials are included in the protocol management system and are available to the reviewer are the Continuing Review cover page, protocol history, participants enrolled/withdrawn, summary of amendments, adverse events, changes to financial disclosure, and notification of any publications or summary reports related to the progress or findings of the study. The provided information will be sufficient to address approval criteria at 45 CFR 46.111 and the relevant FDA regulations.
E. If the IRB determined that continuance of the protocol be conditionally approved or deferred and it is not anticipated that the protocol will be approved by the expiration date, the IRB should consider whether the interventions and interactions with active participants should continue due to over-riding safety or ethical concerns such that it is in their best interest to continue.
F. The committee should also consider any new, significant findings presented with the continuing review, which may affect a participant's willingness to continue participation, and the IRB should require that this information be conveyed to participants.
G. The minutes of IRB meetings will document separate deliberations, actions, and votes for each protocol continuing review conducted by the convened IRB.
H. IRB records must include rationale for conducting continuing review on research that would otherwise not require continuing review.

6. REVIEW MORE OFTEN THAN ANNUALLY

A. The IRB recognizes that protection of the rights and welfare of participants sometimes requires that research be reviewed more often than annually. The IRB may consider the following factors in determining which studies require more frequent review:
    i. The probability and magnitude of anticipated risks to participants,

ii. The likely medical condition of the proposed participants,
iii. The overall qualifications of the principal investigator and other members of the research team,
iv. The specific experience of the principal investigator and other members of the research team in conducting similar research ,
v. The nature and frequency of adverse events observed in similar reach at this and other institutions, and
vi. Any other factors that the IRB deems relevant.

B. In specifying an approval period of less than one year, the IRB may define the period with either a timed interval or a participant enrollment target.

7. INDEPENDENT VERIFICATION FROM SOURCES OTHER THAN THE INVESTIGATOR

A. The Prisma Health IRB recognizes that protecting the rights and welfare of participants at times will require the IRB to seek independent verification of issues/practices related to the protection of human subjects in research. This independent verification will establish on behalf of the IRB that there are no material changes, issues of non-compliance, or other problematic events, to have occurred during the IRB designated approval period.

B. The IRB may consider the following factors in determining which studies/activities require such independent verification:
   i. The probability and magnitude of anticipated risks to participants,
   ii. The likely medical condition of the proposed participants,
   iii. The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed,
   iv. Prior experience with the principal investigator and research team, and
   v. Any other factors that the IRB deems relevant.

C. In making determinations about the independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period or may retrospectively require such verification at the time of continuing review.

8. REVIEW OF MINOR CHANGES IN PREVIOUSLY APPROVED RESEARCH

The IRB may utilize expedited procedures to review a proposed change to previously approved research if it represents a minor change. Minor changes are those which are not greater than minimal risk and do not substantially alter the aims, design, or conduct of the research. Minor changes include, but are not limited to:

- Adding or removing study personnel (not to include the PI)
- Adding or removing an investigative site
- Adding monitoring procedures aimed at enhancing participant safety
- Changes to the consent document that seek to correct grammatical errors or offer clarification.

9. EXPEDITED REVIEW OF RESEARCH

A. DHHS regulations, the Federal Policy (Common Rule), and the FDA regulations permit the IRB to review research through expedited procedures if:
    i. Some or all the research may be reviewed by the IRB through an expedited review procedure, unless the reviewer determines that the study involves more than minimal risk.
    ii. Minor changes in previously reviewed research during the period for which approval is authorized, or
    iii. Research for which limited IRB review is a condition of exemption under 45 CFR 46.104(d)(2)(iii), (d)(7) and (8).
B. The IRB Chair and/or HRPP Director determine which IRB members have the experience and expertise to conduct expedited reviews on behalf of the IRB. This designation will be noted in the committee members profile in IRBNet.
C. Under the expedited review procedure, the designated reviewer may review and approve the research on behalf of the IRB, request additional information, or forward to the fully convened IRB for review and approval determination.
D. The IRB member may also request that the protocol be assigned to another IRB member if they feel they do not have the required expertise to review.
E. When the convened IRB requests substantive clarifications or modifications that are directly relevant to the determinations required by the IRB, the protocol must return to the convened IRB and not approved by expedited procedure.
F. The expedited reviewer may not disapprove any research activity. The research activity may be disapproved only after review by the fully convened Prisma Health IRB.
G. For initial reviews conducted through expedited review procedures, the IRB reviewer shall review all relevant documentation and ensure that the research undergoing initial review meets all applicable expedited review criteria.
H. For modifications, the IRB reviewer should receive all the documentation to include the protocol and related materials, consent document(s) if required by the nature of the protocol, and any participant facing documents, such as surveys, questionnaires, and/or recruitment materials.
I. Reviewer evaluation of expedited studies will include a determination that:
    i. The research involves no more than minimal risk, if the reviewer finds that research is greater than minimal risk, the reviewer must document the rationale for this determination and the rationale for review by the convened IRB.
    ii. The research represents one or more approvable, expedited review categories.
    iii. The research does not include activities where identification of the participants or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so

that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

iv. Does not involve classified research.

v. When research involves vulnerable populations, additional safeguards have been included in the study to protect the rights and welfare of these participants.

J. Expedited review categories for DHHS regulated or FDA regulated research are as follows:

Category 1: Clinical studies of drugs and medical devices only when one of the following conditions are met:

i. Reseach on drugs for which an investigational new drug application (21CFR Part 312) is not required. [Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.]

ii. Research on medical devices for which:
   - An investigational device exemption application (21 CFR 812) is not required, or
   - The medical device is cleared/approved for marketing and the medical device is being used in accordance with its approved labeling.

Category 2: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

i. From healthy, non-pregnant adults who weigh at least 110 pounds. For these participants, the amount drawn may not exceed 550 ml in an eight-week period and collection may not occur more frequently than two times per week, or

ii. From other adults and children, considering the age, weight and health of the participant, as well as the collection procedures and the amount of blood to be collected. For these participants, the amount drawn may not exceed (the lesser) of 50ml or 3 ml/KG in an eight-week period and collection may not occur more frequently than two times per week.

Category 3: Prospective collection of biological specimens for research purposes by noninvasive means. Examples:

i. Hair and nail clippings in a non-disfiguring manner,

ii. Deciduous teeth at time of exfoliation or if routine patient care indicates the needs for extraction,

iii. Permanent teeth if routine patient indicates a need to extraction,

iv. Excreta and external secretions,

v. Uncannulated saliva collected within an unstimulated fashion or by chewing gum or wax or by applying a diluted citric solution to the tongue,
vi. Placenta removal at delivery,
vii. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor,
viii. Supra-and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques,
ix. Mucosal and skin cells collected by buccal scraping or sway, skin swab, or mouth washings, or
x. Sputum collected after saline mist nebulization.

Category 4: Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of medical devices are not generally eligible for expedited review, including studies for cleared medical devices for new indications.) Examples:

i. Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the participant or an invasion of the participants privacy.
ii. Weighing or testing sensor acuity.
iii. Magnetic resonance imaging.
iv. Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiograph.
v. Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

Category 5: Research involving materials (data, documents, records, or specimens) that:

i. Have been collected for non-research purposes (such as medical treatment or diagnosis), or
ii. Will be collected solely for non-research purposes (such as medical treatment or diagnosis).

(*NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects.)*

Category 6: Collection of data from voice, video, digital, or image recordings made for research purposes.

Category 7: Research on individual or group characteristics or behaviors including, but not limited to: research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior, or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Category 8: Continuing review of research previously approved by the convened IRB as follows:

i. The research is permanently closed to enrollment of new participants
ii. All participants have completed all research-related interventions, and the research remains active only for long-term follow-up of participants; or
iii. Where no participants have been enrolled and no additional risks have been identified or the remaining research activities are limited to data analysis.

Category 9: Continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories two (2) through (8) do not apply but the IRB has determined and documented that the research involves no greater than minimal risk and no additional risks have been identified.

10. PROTOCOL REVISIONS, MODIFICATIONS, AND AMENDMENTS

The IRB may utilize expedited procedures for the initial or continuing review of research that is not greater than minimal risk and falls within the FDA and DHHS specified expedited review categories #1-9, as noted above. (These categories DO NOT apply to research involving prisoners.)

A. Revisions, modifications, and amendments to a previously approved protocol will be presented with appropriate tracked changes and copies of all revised documents so that reviewers may clearly determine changes requested, Documents should be clearly noted with revisions dates and version number.
B. Tracked changes versions should also be provided of other documents impacted by requested change, to include but not limited to consent form(s) and investigator brochures.
C. All revisions, modifications, and amendments must be prospectively reviewed and approved by the IRB prior to implementation, except as necessary to mitigate identified safety risks to participants. Should this be the case, the IRB will be notified via a written communication explaining the circumstances under which the changes were applied prior to IRB approval. This information will be provided to the reviewing IRB with the full board submission.
D. The review of revisions, modifications, and amendments will be conducted by the convened IRB unless the change is minor, as previously noted, or the

research falls into one or more of the categories appropriate for expedited review.

E. No less than one week prior to the convened meeting, each IRB member will be provided with access to the amendment application form and related documents and protocol history. A primary reviewer will be assigned and if significant consent form changes proposed, a secondary reviewer will also be assigned.
F. The IRB may require changes to any of the documents submitted based on the information provided in the amendment submission, or if there are any significant new findings.

11. EXEMPT RESEARCH

The identification of individuals permitted to determine exempt status for research studies is determined by the HRPP Director and/or IRB Chair. Investigators are not allowed to make this determination for their submitted protocols. Trained IRB coordinators are typically the personnel to be assigned these reviews.

A. It is required that the study be submitted through the "exempt" workflow in IRBNet with the protocol and any additional relevant supplemental materials.
B. The exempt reviewer will review submitted materials to determine the exempt status and assure that there is compliance with ethical standards to include:

   i. The research holds no more than minimal risk to participants.
   ii. Selection of participants is equitable.
   iii. If there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of data.
   iv. If there are interactions with participants, someone with appropriate qualifications and expertise should determine whether there should be a consent process that will disclose such information as:
      a. That the activity involved research,
      b. A description of the procedures,
      c. That participation is voluntary, and
      d. Provide the name and contact information for the investigator(s).
   v. There are adequate provisions to maintain the privacy interests of participants.
   vi. All exempt determinations are communicated to the investigator through a formal determination letter within the IRBNet notification workflow.
   vii. Specific consideration of exempt status will be applied for study participants that meet the criteria identified in Subpart B [45CFR 46 104 (b)(1)], Subpart C [45 CFR 46.104(b)(2) *no exemptions may be applied to this subpart], and Subpart D [45 CFR 46.104(b)(3) * limited exemptions may be applied to this subpart].

C. Except as described within this section, the following categories of human subjects research are exempt from this policy:

Exemption 1. Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. The effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Exemption 2. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

i. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
ii. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
iii. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

Exemption 3. Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

i. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or indirectly linked to the subjects;
ii. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
iii. information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be

ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

Exemption 4. Secondary research for which consent is not required. Use of identifiable information or identifiable biospecimens that have been or will be collected for some other "primary" or "initial" activity, if ONE of the following criteria are met:

i. The identifiable private information or identifiable biospecimens are publicly available;
ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;
iii. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or
iv. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for non-research activities.

Exemption 5. Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs

Exemption 6. Taste and food quality evaluation and consumer acceptance studies [not applicable at this site].

Exemption 7. Storage or maintenance for secondary research for which broad consent is required. Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §46.111(a)(8).

Exemption 8. Secondary research for which broad consent is required. Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:

i. Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §46.116(a)(1) through (4), (a)(6), and (d);
ii. Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §46.117;
iii. An IRB conducts a limited IRB review and makes the determination required by §46.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and
iv. The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

12. INVESTIGATORS' DUTY TO REPORT TO THE IRB

A. DHHS regulations at 45 CFR 46.108(a)(4)(i) and FDA regulations at 21 CFR 56.108 require that investigators report promptly to the Prisma Health IRB:
    i. any unanticipated problems in research involving risks to subjects or others; and
    ii. any serious or continuing non–compliance with the human subjects regulations or the determination of the IRB.
B. These same regulations require that the Institutional Official report promptly to OHRP, to any Federal Agency supporting the research, and/or to the FDA:
    i. any unanticipated problems in research involving risks to subject or others;
    ii. any serious or continuing non-compliance with human subjects regulations or the determinations of the IRB; and
    iii. any suspension or termination of IRB approval of research.
C. FDA regulations at 21 CFR 812.150 require that investigators report unanticipated device effects to the IRB and require that investigators report adverse drug effects to the IRB.
D. Investigators Duty to Report Unanticipated Problems.

Investigators are required to report to the IRB any unanticipated problems involving risks to subjects or others that occur in research conducted under the auspices of Prisma Health. These reports must be submitted in the Prisma Health protocol management system using the appropriate cover sheet, including a complete description of the problem along with any other relevant documentation.

An Unanticipated Problem is defined as:

- **Unexpected** (in terms of nature, severity, or frequency) given:
  - The research procedures that are described in the protocol- related documents, such as the IRB approved research protocol and informed consent documents, and
  - The characteristics of the subject population being studied.
- **Related or possibly related to participation in the research**, meaning there is a reasonable possibility that the incident, experience, or outcome may have been caused by the research.
  - Suggests that **the research places subjects or others at a greater risk of harm than was previously know or recognized** including physical, psychological, economic, or social harm defined as a new or increased risk for which the reviewer or convened IRB requires some action such as, modifying the consent form, modification of protocol procedures or addition of risk mitigation or safety monitoring.

E. Investigators' Duty to Report Serious Adverse Events

i. Investigators are required to report to the IRB any serious adverse event that occurs in research conducted at Prisma Health and is considered reportable per the Prisma Health Reportable Event Timing Guidance. These reports must be submitted to the IRB via the protocol management system utilizing the appropriate forms with required supporting documentation.

ii. A serious adverse event is defined as any adverse event occurring results in any of the following outcomes: death, a life- threatening experience, in-patient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability, incapacity, a congenital anomaly, or birth defect. [21 CFR 312.32(a) and 21 CFR 812.3(s)]

F. Investigator's Duty to Report All Protocol Violations

Investigators are required to report all violations for approved protocols. This includes any change from the protocol that was implemented by the investigator to respond to immediate safety concerns. These reports must be submitted to the Prisma Health IRB. This report should be submitted utilizing the appropriate "Reportable Event" form available in the protocol management system.

G. Investigator's Duty to Report all Protocol Deviations

Investigators are required to request IRB review of all reported/identified protocol deviations. Deviations that do not impact participant safety or indicate issues of significant non-compliance may be reported in aggregate at the time of continuing review.

H. Investigator's Duty to Forward Correspondence or Reports of External Monitoring or Auditing

Investigators are required to forward reports or correspondence concerning the monitoring or auditing of their research activities or research sites by sponsors, cooperative research groups, federal agencies, or other external entities to the Prisma Health IRB within five working days of receipt, only if the findings require the submission of a corrective action plan. This is submitted utilizing the appropriate reporting form available in the Prisma Health protocol management system for administrative and committee review, if required.

I. Investigator's Duty to Forward Sponsor or Cooperative Group Safety Reports

Investigators are required to forward safety reports (or other information concerning adverse events e.g., NCI Action Letters) issued by sponsors or cooperative groups to the Prisma Health IRB within ten working days of receipt. These forms should be submitted along with associated protocol/consent form amendments as required by the nature of the report.

J. Investigator's Duty to Forward Data and Safety Monitoring Board (DSMB) Reports

Investigators are required to forward DSMB reports to the IRB at the time of the annual continuing review submission. The IRB conducting continuing review of research may rely on a current statement from the DSMB indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research.

K. Investigator's Duty to Notify the IRB of Non-Compliance

Investigators are required to report issues of non-compliance as soon as possible and if resulting in any unexpected risk or injury to participants, reporting is required within 3 days of identification of the event. Whether involved in the research or not, all Prisma Health employees are required to notify the Prisma Health IRB via email: ***IRB @prismahealth.org*** or phone message***, 864-455- 8997*** by or the ***Prisma Health Compliance Hot Line*** ***https://www.complianceresource.com/hotline/*** if they become aware of any non-compliance with human subject regulatory requirements or with the determinations of the IRB.

13. REVIEW OF REPORTS OF UNANTICIPATED PROBLEMS, ADVERSE EVENTS, PROTOCOL DEVIATIONS AND VIOLATIONS

A. All materials, including the most recently approved informed consent document(s) and protocol, along with submitted reports described above are reviewed by the IRB Chair or a qualified member of the Prisma Health IRB.
B. If the situation or event is determined not to meet the definition of an unanticipated problem involving risks to subject or others, the reviewer will document this determination in the reviewed comments section of the submission.
C. In the instance of a protocol change implemented without prospective IRB approval to eliminate apparent immediate hazards to participant(s), the IRB at a convened meeting, will determine whether the change was consistent with ensuring the participants' continued welfare.
D. Reviewers will determine whether any events reported are unanticipated problems involving risks to subjects or others.
E. Submitted materials and/or reports of documentation of the reviewer's determination, and investigator notification is placed in the protocol record in the Prisma Health protocol management system.
F. The event and determination are reported in the list of expedited actions provided to the IRB committee at the next convened meeting.
G. When a newly discovered risk is reported to the Prisma Health IRB, it will be reviewed in accordance with Prisma Health IRB policies and procedures. For the review of unanticipated problems involving risk to participants, which are determined to be of no more than minimal risk, any required determinations may be made using expedited procedures.

14. REFERRAL FOR CONVENED IRB REVIEW

A. If, in the judgement of the IRB reviewer, the event constitutes an unanticipated problem involving risks to participants or others, the reviewer will refer the situation or event to the convened IRB for review. The IRB Chair may require modification or suspension of research activities as deemed necessary to eliminate apparent immediate harm to participants.
B. No less that one week prior to the convened meeting, the information related to the reported event will be assigned to a committee reviewer and related documents will provided through the meeting agenda to all committee members for review prior to the meeting.
C. The convened IRB committee will review the reported problem and will render a determination related to the actual or potential risks to participants or others. The IRB committee may require actions to mitigate and manage future similar/related risks and whether any information related to this risk must be communicated to all participants. The committee will also determine if a consent form revision is required and to what extent re-consenting of current participants is warranted.
D. The IRB will also consider whether the event or problem should be referred to other institutional officials or committees for review or action. Responses to the required actions will be forwarded to the convened IRB unless the action

is a minor modification, in which case the review of the response may be eligible for expedited review.

15. NOTICE OF IRB DETERMINATION(S)

Regardless of the type or types of review (expedited or convened), the investigator is notified in writing of the determinations, even if no further action is necessary on the part of the investigator.

It is the responsibility of the IRB Chair, in coordination with the HRPP Director, to provide prompt written notification to the Institutional Official, Legal Counsel, Prisma Health Compliance, or other relevant Prisma Health Administrative Officials of:

i. Any unanticipated problem in research involving serious risks to participants or others and of the resolution of those problems or issues,
ii. Any serious or continuing non-compliance with human subjects regulatory requirements or with the determinations of the IRB and of the resolution of non-compliance, and
iii. Suspension or termination of IRB approval of the research.

16. REVIEW OF NON-COMPLIANCE

A. Non-compliance is defined as a failure to follow the IRB approved protocol or other requirements and determinations of the IRB, institutional policies or procedures, or relevant State or Federal laws. The Prisma Health IRB policy requires the reporting of all such non-compliance to the Prisma Health IRB. This includes reporting deviations/violations and non-compliance for review.
B. Serious non-compliance is defined as non-compliance that involves greater than minimal risk of harm or discomfort to subjects, breach of confidentiality or privacy, or other as involved in the research.
C. Continuing non-compliance is defined as on-going or repetitive incidents that impact the previously assessed risk-benefit determination.
D. Non-serious and non-continuing non-compliance involves isolated incidents, such as mistakes, oversights, and incidents that are not serious or continuing in nature.
E. As a general matter, serious non-compliance would include situations involving risks to participants or significant problems impacting the integrity of the protocol and participants' safety. Continuing non-compliance may include failure to comply with protocol, IRB requirements, or institutional procedures, or Federal or State laws as described above, but not in a manner that impacts the safety of participants.

17. INITIAL REVIEW OF REPORTS OF NON-COMPLIANCE

A. IRB coordinators will provide administrative review of all reports of non-compliance and make a determination as to whether the reports are eligible for expedited review or review by the convened IRB is necessary.

B. Generally, non-serious, non-continuing non-compliance will be eligible for expedited review. Any IRB member or IRB staff may refer the issue to the IRB Chair of full board for review for any matter that is more than minor and/or any matter that warrants review by a full IRB.

18. OPTIONS FOR REVIEW OF NON-COMPLIANCE

When reviewed by an IRB member the member may:

A. Conduct an initial review in coordination with the IRB Chair,
B. Review any materials relevant to the issue under review including, but not limited to, investigator research records, relevant patient medical records, IRB records, available audit reports, etc.,
C. Interview relevant, knowledgeable individuals and collect relevant documentation,
D. Request a convened IRB Review,
E. Request review and recommendation or advice from Prisma Health Legal Counsel or Compliance,
F. Recommend an interim suspension of the research to the IRB Chair and the HRPP Director pending review by a convened IRB Committee, and
G. Request that the HRPP Director communicate with the Principal Investigator or study team for additional information or provide follow up on, or status of the review.

19. CONVENED IRB REVIEW OF NON-COMPLIANCE

A. A written report of the findings of any investigation is distributed to all members of the reviewing IRB, along with relevant documentation and documents summarizing findings.
B. The convened IRB will consider and determine if reported issues of serious non-compliance and or continuing non-compliance are to be reported to any government agencies with oversight of the research. All findings and determinations will be documented in meeting minutes with determinations as follows:
    - **Deferred:** The IRB determines a lack of sufficient information related to the reported events to proceed with its review. The IRB may request the HRPP Director to obtain additional information for presentation and review at a future meeting.
    - **No Further Action Required**: The convened IRB determines that no further corrective action need be taken.
    - **Corrective Action as Proposed by the Investigator must be Implemented**: The IRB may determine that the issue was appropriately referred for review and that the corrective actions proposed by the investigator are appropriate and should be implemented.

- **Action Required:** The IRB determines that further information or further corrective actions are required. Reponses to the required actions will be provided to the convened IRB for review unless the action is a minor modification, in which case the review of the response may be eligible for expedited review. The IRB will determine if a report of serious or continuing non-compliance is required or whether additional information must be obtained for further review.

C. **Forward to Other Officials for Further Action**. The IRB determines that the issues of concern are not within the purview of the IRB and refer relevant matters to the appropriate official. Other appropriate officials may include Legal Counsel, Risk Management, Compliance, or clinical departments.

D. Any IRB discussion, determinations and vote are recorded in the convened meeting minutes. All determinations are communication to the principal investigator and other involved individuals.

20. ACTIONS CONSIDERED BY THE IRB FOR SERIOUS OR CONTINUING NON-COMPLIANCE

A. In considering actions for serious or continuing non-compliance, the IRB will:
   i. Seek to correct the non-compliance,
   ii. Deter it from happening again,
   iii. Hold relevant individual(s) accountable for their actions and provide guidance to ongoing compliance,
   iv. Consider the impact of institutional systems and embedded processes that might affect ongoing research and assist in the communication of these issues to relevant administrative leaders who can affect change in these areas, and
   v. If recommended actions impact enrolled participants, the IRB must consider the impact on the participants willingness to continue in the research.

B. Possible IRB action may include, but are not limited to, the following:
   i. Modification of the research protocol or information disclosed to participants,
   ii. Notification or reconsenting of participants,
   iii. Modification to the continuing review schedule, requiring reviews more frequent than annually,
   iv. Additional training or education for participating research team members,
   v. Suspension or termination of the protocol,
   vi. Disqualification of an investigator from a particular research project, requiring remediation and/or training prior to re-engaging in research activity,
   vii. Disqualification of one or more research sites,
   viii. Disqualification of certain study staff,

ix. Additional education and training in the ethics and regulations of human subjects research,
x. Application of action to other protocols, and
xi. Any other reasonable measure deemed appropriate to protect the rights and welfare of research participants on this protocol or other protocols that may be impacted by issues contributing to the event(s) reviewed.

C. Outcomes of IRB Review

i. The Prisma Health IRB will notify investigators in writing of its determinations. All IRB actions must be communicated in writing.

ii. Prisma Health IRB actions for initial and continuing review of research, as well as the review of revisions, modifications, and amendments include the following:

- **Approved with no required changes** (or no additional changes). The research may proceed once Institutional approval and all other Prisma Health signatures required for activation have been obtained.
- **Approved with Non-Substantive Modifications**. Such changes will be clearly delineated in IRB communication to the investigator. The investigator may concur with the IRB's stipulations and/or make requested changes to the materials/information as requested. The follow up review of the submitted changes, if aligned with requested changes may be reviewed through expedited procedures. If required changes have not been made or if the changes are beyond those requested by the IRB and are more than minor, the changes must be forwarded for review by the convened IRB.
- **Approved with Substantive Modifications**. If the IRB determines that the submission lacks sufficient information about the research or requires significant (substantive changes) to the submitted information, the IRB will provide to the investigator a summary of the requests changes required to secure approval. The research may not proceed until the convened IRB has approved a revised application incorporating all necessary/requested information.
- **Disapproved**. The IRB determines that the research cannot be conducted at Prisma Health or by its employees. Written information related to this determination will be provided to the Investigator and maintained in the protocol submission record in the Prisma Health protocol management system.

iii. The communication to the investigator will include at a minimum the following information when appropriate:

- Investigator's name
- Title of the study
- Prisma Health IRB protocol record number

- Level of Risk as determined by the IRB
- Approval date (if issued)
- Summary of actions and determinations
- Changes needed to secure approval with re-submission with required information or changes

21. EXPIRATION OF APPROVAL PERIOD

The IRB is required to conduct substantive and meaningful continuing review of the research not less than once per year. The IRB approval period for research may extend more than 365 days after the convened meeting at which the research was last approved.

Research that continues after the approval period expires is research conducted without IRB approval. Consequently, the IRB will automatically suspend the enrollment of new participants in any ongoing research that does not receive continuing review and approval prior to the end of the stipulated approval period. Previously enrolled participants may continue their involvement in suspended research only where the IRB determines that continued involvement is in the best interest of the participants.

The IRB office will notify the investigator of any determinations in this regard.

22. SUSPENSION OR TERMINATIONS OF IRB APPROVAL

The Prisma Health IRB may determine that a Suspension or Termination action is required in response to notification or identification that research is not being conducted in accordance with IRB or regulatory requirements or has been associated with serious unexpected problems or serious harm to participants.

A. Suspension means a temporary withdrawal of IRB approval of some components of or the permanent withdrawal of IRB approval of part of a protocol. Continuing review of a suspended protocol is still required.

B. Termination is a permanent withdrawal of IRB approval of a previously approved protocol. With the termination of IRB approval, continuing review is required until all study activities are completed, and a study close out is completed.

C. When issuing a suspension or termination of approval, the IRB shall also determine whether suspension of enrollment or continued participation of previously enrolled participants should cease and if enrolled participations should be notified of the suspension and subsequent outcomes.
D. If the IRB determines that suspension of continued participation of previously enrolled participant is required for safety, continuity of care is required. If participant withdrawal is required, the IRB will also determine whether the plan for withdrawal adequately protects participants' rights and welfare.

E. The IRB Chair or HRPP Director may independently determine that termination or suspension action is required to protect the rights and welfare of participants. An immediate, temporary suspension of enrollment of new participants or of continued participation of previously enrolled participants may be issued pending review of the situation by the convened IRB.

23. NOTIFICATION OF DETERMINATION TO THE INVESTIGATOR

The Prisma Health IRB will notify the Principal Investigator in writing of such suspensions or terminations and will include a statement of reasons for the IRB's actions. The Prisma Health IRB will also advise the investigator of any requirements for notifying currently enrolled participants. The investigator will be provided with an opportunity to respond in person to the committee or in writing. The suspension or termination action along with all associated decisions (i.e., suspension of enrollment) is immediate until adequate information is provided to the committee to address or clarify issues and the committee conducts a follow-up review.

24. NOTIFICATION OF DETERMINATIONS TO PRISMA HEALTH OFFICIALS AND FEDERAL AGENCIES

It is the responsibility of the IRB Chair, in collaboration with the HRPP Director to provide prompt (within fifteen business days) written notification of any for-cause suspensions or terminations of IRB approval to the Institutional Official, Legal Counsel and other relevant organizational leaders, as well as relevant Federal agencies including OHRP (for DHHS research) and FDA (for FDA regulated research).

25. PRISMA HEALTH REPORTING REQUIREMENTS TO FEDERAL AGENCIES

A. DHHS regulations at 45 CFR 46.103(b)(5) and FDA regulations at 21 CFR 56.108(b) require that the Institutional Officials or the HRPP Director as IO designee, report the following events as determined by the IRB or IO promptly (within 30 days) and in writing to OHRP, to any Federal Agency supporting the research and/or to the FDA:
   i. Any unanticipated problems in research involving greater than minimal risks to subjects or other (except where the IRB has determined and documented in writing that the problem was not related to the research in any way),
   ii. Any serious or continuing non-compliance with federal human subjects protection regulations or requirements, or with the determination of the IRB, and
   iii. Any suspension or termination of IRB approval of research.

B. In developing and forwarding such reports, the HRPP Director will consult as appropriate with the Institutional Official, Legal Counsel, the IRB Chair, Prisma

Health Oversight committees including Audit and Clinical Leadership. The HRPP Director will review and approve any report before it is forwarded to any Federal Agency.

C. In preparation of such reports, consideration should be given to notification of any funding agency and industry sponsors when the report is a serious allegation of non-compliance or other problems that warrant investigation.

26. RESEARCH ACTIVITIES IN EMERGENCY SITUATIONS

DHHS regulations do not permit research activities to be started in an emergency without prior IRB review and approval. When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any reports of a prospectively conceived research activity, except as required under FDA regulations.

The IRB must be notified in writing within five days of any activities involving the Emergency Use of a Test Article under an FDA Exemption or Exception. The IRB will acknowledge such notification in writing; however, in accordance with FDA guidance, the IRB will not issue any "approval" of the activity.

DHHS regulations at 45 CFR 46.101(i) and FDA regulations at 21 CFR 50,24 include special provisions for IRB review and approval of planned emergency research with waiver of the usual informed consent requirements. See Chapter 11 for specific requirements of these provisions.