IRB Protocol Deviations

I. Policy Statement:

A Principal Investigator will not implement any changes to the protocol without sponsor approval and prior documented IRB review and approval, except when necessary to eliminate apparent immediate hazards to human subjects (21 CFR 312.66 and/or 21 CFR 812.150(a)(4)).

Investigators (or designated study team members) are responsible for appropriately recognizing, classifying, recording, and reporting protocol deviations and/or violations.

This policy applies to research conducted at any Trinity Health West Region ministry.

II. Definitions:

Protocol Deviation: defined as any change, divergence, or departure from the study design or procedures defined in the approved protocol without prior sponsor and IRB approval. Protocol deviations may include unplanned instances of protocol noncompliance. For example, situations in which the clinical investigator failed to perform tests or examinations as required by the protocol or failures on the part of subjects to complete scheduled visits as required by the protocol, would be considered protocol deviations. (e.g., study visit outside protocol window, blood work drawn outside protocol window, etc.). Depending on the details, protocol deviations may be determined to be non-compliance (serious, continuing, or otherwise). Deviations may be either minor or major in nature and may or may not have a direct effect on individual subjects.

Minor Deviation: a deviation that does not impact participant safety, compromise the integrity of study data, and/or affect the participant's willingness to participate in the research. Minor deviations do not need to be reported to the IRB. Examples may include, but are not limited to:

- Implementation of unapproved recruitment procedures that would have been approved by IRB-HSR if submitted according to the recruitment procedures.
- Missing signed and dated consent form, however, there is source documentation the subject willingly consented to the study.
- Missing pages of executed consent form and subject was later re-consented with a complete consent.
- Inappropriate documentation of informed consent, such as: an omitted subject or parental signature where related source documents indicate the subject/parent voluntarily agreed to participate in the study and understood the risks , copy not given to the person signing the form, someone other than the subject dated the consent form, or the individual obtaining informed consent/study procedures not listed on IRB approved study personnel list
- Use of invalid consent form, i.e., consent form without IRB-HSR approval, or outdated/expired consent form (unless there was a change in the study procedure that increased risk to subjects, subject requirements, cost to subjects, or risks of the study as described in the consent form).

- Failure to follow the approved study procedure that **does not** affect subject safety or data integrity such as when: a study procedure was conducted out of sequence, an approved portion of the protocol was omitted, a lab requirement was missed and/or lab results not noted in research record, or a study visit occurred out of the defined visit window AND there is no increased potential risk to the participant.
- Subject visit/procedure falls outside of the window of time indicated by the protocol and there is no increased potential for risk to the subject or any damage to the integrity or completeness of the data.
- Minor dosing errors where the potential risk to the subject is not increased or the increased risk is felt to be minor.
- Procedures not completed at a participant's request.

Minor deviations should be reported to the IRB at the time of continuing review. The IRB recommends that a record or log and/or narrative note be maintained to document the minor deviation(s) and describe the circumstances surrounding the event. If you or your sponsor determines it is necessary to submit a minor deviation to the IRB prior to the time of continuing review, this may be done and the IRB will provide an acknowledgement of receipt of the submission.

Major Deviations: Protocol deviations must be reported if any of the following criteria are met:

- Event represents a **serious** failure on the part of the study team to comply with the protocol, standard operating procedures, GCPS, federal, state, or local regulations.
- Event represents a **continuing** failure on the part of the study team to comply with the protocol, standard operating procedures, GCPS, federal, state, or local regulations.
- Event results in significant negative impact to subject safety or alters risks to subjects. The deviation/noncompliance may or may not result in actual harm to the subjects. Risk or actual harm may be clinical, emotional, social, financial, etc. The risk/potential risk to the subject present by this deviation is deemed to be greater than minimal risk.
- The event significantly damages the completeness, accuracy and reliability of the data collected for the study.

Examples of major deviations include, but are not limited to:

- Evidence of willful or knowing misconduct on the part of the investigator(s), or study team
- Implementation of non-exempt human subject research prior to IRB approval.
- Inadequate documentation of consent or failure to obtain informed consent prior to initiating study procedures. (i.e., there is no documentation of informed consent, or informed consent is obtained after initiation of study procedures) where a source document is not present to describe the details of the consent process.
- Use of unapproved or expired consent form where there is a change in the study procedure(s) that increased risk to subjects, altered subject requirements, changed the cost to subject, or modified the risks of the study when compared to a prior version used for the participant.
- Enrollment of a subject who did not meet all inclusion/exclusion criteria.
- Implementing a modification prior to IRB approval, except in certain specific cases where modifications must be implemented to protect subject safety.
- Failure to report serious unanticipated problems/adverse events to all parties in accordance with established policy, guidance, and regulations.

- Failure to perform study procedures outlined in the protocol where subject safety or data integrity may be significantly and negatively impacted.
- A disclosure, access, or use of PHI that is unauthorized, including the loss of identifiable health information, including consent forms / HIPAA Authorization forms.
- Drug/study medication dispensing or dosing error where the subject is negatively affected/potentially negatively affected.
- Subject visit/procedure is not done per protocol resulting in **significant** increased potential for risk to the subject or significant damage to the integrity or completeness of the data.
- Missing safety labs where the study team ordered the correct tests but for some reason the test was not performed, **OR** there was a lab processing error **AND** subject safety was significantly and negatively affected.

All major protocol deviations must be reported to the IRB immediately upon discovering them, and no later than five (5) calendar days from the time the study team receives knowledge of the event**.**

Protocol Violation: defined as an accidental or unintentional change to, or non-compliance with the IRB-approved protocol without prior sponsor and IRB approval. Violations generally result in increased risk or decreased benefit, affect the subject's rights, safety, or welfare, or the integrity of the data. Examples of protocol violations:

- Failure to obtain valid informed consent (e.g., obtained informed consent on a non-date stamped form)
- Loss of laptop computer that contained identifiable, private information about subjects.
- Accidental distribution of incorrect study medication or dose
- Not following inclusion/exclusion criteria

Protocol Exceptions: Exceptions are circumstances in which the investigator wishes to deviate from eligibility criteria or one or more of the specific procedures called for in a research plan. Unlike modifications that apply to all subsequent subjects in the research, a protocol/research plan exception only applies to a specific subject or group of subjects. Exceptions are planned, and the investigator gets approval from the sponsor, the IRB, and the FDA (for medical devices) ahead of time, unless the change is necessary to eliminate apparent immediate hazards to the human subjects, or to protect the life or physical well-being of the subject.

III. Equipment: None

IV. Procedure:

During the conduct of a study, unintentional events, or deviations from standard operating procedures and/or the protocol may occur or subsequently be discovered upon periodic reviews and must be reported to the IRB when the event meets the criteria for a major deviation.

A. Investigator Responsibilities

The principal investigator (PI) is responsible for ensuring human subjects research is conducted in accordance with all applicable federal and state regulations, institutional policies and procedures and the study protocol. In addition to complying with the IRB's deviation reporting requirements, the PI is also responsible for complying with the sponsor's reporting requirements. While a deviation may or may not increase risk to participants, it is particularly important that the IRB be notified immediately when the deviation could potentially cause increased harm to participants or others or may alter the outcome of a study.

The PI must report to the IRB major deviations within five (5) business days and minor deviations at continuing review or periodically at the discretion of the PI or sponsor. Major deviations should be reported through IRB Manager, using the Protocol Deviation Form. When reporting the major deviation, the following information must be included:

- Date of occurrence and date discovered.
- How and who discovered.
- Effects it may have on current or future participants.
- Action taken to mitigate the event AND to avoid recurrence of the deviation.

The investigator and the study team should review the current protocol thoroughly before the trial opens at the investigational site. All study site staff should attend the site initiation visit to ensure appropriate protocol training and completion of protocol-specific procedure education.

B. IRB Responsibilities

The IRB Chairperson or designee will review deviations to determine whether the risk/benefit ratio has increased and assess if participant harm resulted from the deviation. After this initial assessment, the report will be sent to the next convened full board IRB meeting for review and consideration of further actions that may need to be taken.

The range of actions may include:

- revisions to the protocol,
- audit/review of the conduct of the study,
- change in frequency of continuing review reports, or
- additional protective procedures requested by the IRB (i.e., observation of the informed consent process).

If the IRB is in receipt of an excessive number of protocol deviations arising from a single study and/or investigator, it is within the authority of the IRB to conduct an inspection to ensure integrity and compliance. Protocol deviations reported to the IRB will be reviewed and documented on the IRB agenda and meeting minutes. PIs will receive a written correspondence regarding protocol deviation(s) determinations/approval.

V. Ministry Specific Related Addendums, Procedures, and/or Policies:

A. Saint Agnes Medical Center: None

B. Saint Alphonsus Health System: None

VI. Additional Approval: Not applicable.

VII. Related Policies:

THWR IRB Policy: Trinity Health West Region IRB: Research Noncompliance

THWR IRB Policy: Misconduct in Research