PROTOCOL DEVIATIONS STANDARD OPERATING PROCESS

PROCESS:

Investigators are responsible for conducting human-subjects research in accordance with all applicable federal and state regulations, CHRISTUS Health Institutional Review Board (IRB) policies, guidance, and procedures. In the event that CHRISTUS Health IRB is not the IRB of record the specific requirements of the IRB that reviewed the research study must be followed as well. During the conduct of the study, changes to the protocol may be proposed or unintentional changes may be discovered. Changes to the IRB-approved protocol, planned or otherwise, are governed by federal regulations and CHRISTUS IRB policies and procedures.

The federal regulations specifically require the IRB to review proposed changes in a research activity, and to ensure that such changes in approved research are not initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject [45CFR46.103(b)(4)(iii) and **21CFR56.108(a)(4)].** Research activity includes all aspects of the conduct of the research study, all of the information outlined in the protocol submission and reviewed and approved by the IRB. Examples include recruitment methods, informed consent process, and procedures used to protect privacy and confidentiality. Non-compliance with these regulations, CHRISTUS Health IRB policies, guidance, procedures, and requirements during the conduct of a research study results in a protocol violation, and as such must be reported to the IRB.

OVERVIEW:

The CHRISTUS health IRB requires reporting of protocol deviations in order to monitor for Serious or Continuing Noncompliance.

Any deviation from the IRB approved protocol must be submitted to the CHRISTUS Health IRB as a protocol deviation as outlined below.

Planned changes to the IRB approved protocol or study related documents must be submitted to the CHRISTUS Health IRB prior to implementation by the study site. The protocol and study related documents include, but are not limited to, the detailed protocol, protocol summary, informed consent form, recruitment materials, questionnaires, and any other information relating to the research study.

DEFINITIONS: The following definitions apply throughout this guidance document:

PROTOCOL DEVIATION: Any unapproved change, divergence, or departure from the IRB-approved study design and study related documents and may or may not affect the subject's safety, rights, or welfare and/or the completeness, accuracy, and integrity of the study data.

CORRECTIVE ACTION: The action that was taken by the researcher or research staff to correct a protocol deviation that has already occurred.

PREVENTATIVE ACTION: Any action to prevent a protocol deviation from occurring in the future.

SPONSOR OR CONTRACT RESEARCH ORGANIZATION (CRO) APPROVED DEVIATION: Any deviation from the IRB-approved study design and study related documents that has been pre-approved by the study sponsor or study CRO.

SERIOUS OR CONTINUING NONCOMPLIANCE: Noncompliance is a failure to comply with the IRB-approved study design or study related documents (see above definition of protocol deviation). Any failure to comply with the IRB-approved study design may be found as serious noncompliance by the CHRISTUS Health IRB. Continued failure to comply with the IRB-approved study design may be determined as continuing noncompliance by the CHRISTUS Health IRB. If the CHRISTUS Health IRB determines that a serious noncompliance issue has occurred or that continuing noncompliance is

occurring the CHRISTUS Health IRB may suspend or terminate the approval of the research project. In the event that any of the above occur the CHRISTUS Health IRB will process the noncompliance report according to the CHRISTUS Health IRB guidance *IRB Reporting to Institutional Officials and External Agencies.*

REPORTING REQUIREMENTS AND PROCESS

The Principal Investigator (PI) must report all protocol deviations to the CHRISTUS Health IRB within ten (10) working days of discovery (awareness) using the Protocol Deviation Form within iRIS (https://christus.imedris.net).

- In the event that a protocol deviation was not reported within ten (10) days of awareness the protocol deviation should be reported as soon as possible after the oversite is noticed and an explanation of late reporting should be included in the Protocol Deviation submission within iRIS.
- Protocol deviations that occur or awareness occurs within ten (10) business days of continuing review can be reported within the continuing review submission.
- Reporting of protocol deviations to sponsors and CROs should be completed per the sponsor/CROs reporting requirements.

All protocol deviation forms submitted to the CHRISTUS Health IRB via iRIS should include the following information:

- Subject ID
- Subject initials
- Date of deviation
- Date of discovery (awareness)
- Date reported to the CHRISTUS Health IRB
    - If the deviation is reported later than ten (10) days of discovery (awareness) an explanation of late reporting is required.
- Brief description of the protocol deviation
- Corrective action (measures that were taken to correct the deviation)
- Preventative measures (measures put into place to prevent the deviation from reoccurring)
- IF changes to the protocol or informed consent are required in response to the deviation

EXAMPLES OF THE TYPES OF DEVIATIONS THAT SHOULD BE REPORTED

Examples (the list of examples is intended as a guide and is not all-inclusive):

- Failure to obtain informed consent, i.e., there is no documentation of informed consent; informed consent obtained after initiation of study procedures, not using the IRB approved informed consent form to consent subjects, or not using the most current IRB approved stamped informed consent form to consent subjects.
- Informed consent obtained by someone other than individuals authorized by IRB to obtain consent, e.g. someone other than a licensed physician investigator, someone not listed on the delegation of authority log as being delegated to obtain informed consent
- Enrollment of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the IRB

- Failure to report serious adverse events to the IRB and/or sponsor
- Failure to perform a required lab test
- Drug/study medication dispensing or dosing error
- Study visit conducted outside of required timeframe
- Failure to follow safety monitoring plan
- Implementation of unapproved recruitment procedures
- Missing original signed and dated consent form (only a photocopy available)
- Missing pages of signed informed consent form
- Inappropriate documentation of informed consent, including:
    - missing subject signature
    - missing investigator signature
    - missing documentation of a copy not given to the person signing the form
    - someone other than the subject dated or signed the informed consent form
- Use of invalid consent form, i.e. consent form without IRB approval stamp, or outdated/expired consent form
- Failure to follow the approved study procedure
    - Study procedure conducted out of sequence
    - Omitting an approved portion of the protocol
    - Failure to perform a required lab test
    - Missing lab results
    - Enrollment of ineligible subject (e.g., subject's age was 6 months above age limit)
    - Study visit conducted outside of required timeframe
- Failure of subject to return study medication
- Over-enrollment
- Enrollment of subjects after IRB-approval for the study has expired
- Failure to submit continuing review application to the IRB before study expiration

CHRISTUS HEALTH IRB DEVIATION REVIEW PROCESS: Upon receipt of the Protocol Deviation submitted to iRIS, a CHRISTUS Health IRB Coordinator will review the submission for completeness. If clarifications or corrections are required the coordinator will send the submission back to the study team as a stipulation. The stipulation will need to be met prior to continuing review by the CHRISTUS Health IRB. Once the coordinator has verified that the submission is complete and all clarifications (if any) have been received, the coordinator will send the submission for review by the CHRISTUS Health IRB Chair, Vice-Chair, Compliance Officer, Director, or designated CHRISTUS Health IRB member. The protocol deviation reviewer may request further information in order to complete the review of the reported protocol deviation. All protocol deviations are reviewed at the next fully convened CHRISTUS Health IRB Board meeting after submission. After review the CHRISTUS Health IRB Board may take one or more of the following actions prior to indicating in writing the determination of the Board to the protocol deviation. The investigator should receive notification in writing of the CHRISTUS Health IRB Board determination within ten (10) days of the fully convened CHRISTUS Health IRB Board meeting.

IRB ACTIONS:

- No further action is required
- The event constitutes an unanticipated problem and/or a serious or continuing noncompliance issue
- Accept and approve the investigator's corrective action plan

- Require modifications to the informed consent form
- Require modifications to the protocol when permissible
- Require the investigator to re-consent enrolled subjects
- Notification of previously enrolled and/or currently enrolled subjects of new information
- Increase monitoring of subjects by the CHRISTUS Health IRB and CHRISTUS Health Compliance Officer
- Increase frequency of continuing review reporting
- Observation or monitoring of the research by the CHRISTUS Health IRB or CHRISTUS Health Compliance Officer
- Educational of study staff interventions
- Suspension of all or parts of the research
- Termination of CHRISTUS Health IRB approval of the research
- Refer to the appropriate institutional entity