Protocol Deviations and Violations

VCU/VCU Health CLINICAL RESEARCH STANDARD OPERATING PROCEDURES

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1. PURPOSE

This Standard Operating Procedure defines the procedures relating to protocol compliance and the prevention and reporting of protocol deviations/violations by the investigator in the conduct of a clinical trial.

2. REQUIREMENTS

The Principal Investigator will not implement any changes to the protocol without sponsor approval and prior review and documented approval from the IRB, 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.

3. DEFINITIONS

Note: Different IRBs have differing definitions and reporting requirements. Ensure the applicable definitions from the study IRB of record are utilized.

Protocol Deviation- A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the approved protocol. 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. In the case of deviations which are planned exceptions to the protocol, such deviations should be reviewed and approved the the IRB, the sponsor, and by the FDA for medical devices, prior to implementation, 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.

Protocol Violation- Accidental or unintentional change to, or non-compliance with the IRB-approved protocol without prior sponsor and IRB approval. Violations generally *increase risk or decrease 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

4. PROCESS

A. Prevention of protocol deviations and violations:

- Per 21 CFR 312.23 (a)(6)(ii): A phase 2 or 3 investigation should be designed in such a way that if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset.
- The investigator and the team should review the current protocol thoroughly before the trial starts.
- All investigators and study site staff should attend the site initiation visit in which the sponsor or sponsor's delegates would provide training on the protocol and the protocol-specific procedures to the investigators and the team.

B. Reporting of protocol deviations/violations to the sponsor

- Depending on the nature and extent of the protocol departure, the investigator may be required to document and promptly report any protocol deviations/violations to the sponsor according to defined reporting requirements and timelines in the protocol. The study team should also be familiar with these requirements and follow reporting procedures.
- Should serious and continued protocol deviations and/or violations occur, the sponsor may terminate the study and report to the FDA, as applicable.
- A protocol deviation or violation may be implemented without sponsor and IRB approval if it is deemed necessary to eliminate an immediate hazard(s) to subjects.
- As soon as possible after such an emergency has occurred, documentation and reporting of the deviation or violation must be submitted to the sponsor and IRB(s) according to the process below. This should include a description of the implemented change and the reasons for the change. The IRB of record's policies and the sponsor protocol should be consulted to determine timelines for reporting to the IRB and the sponsor.

C. Reporting of protocol deviations/violations to the IRB
- The investigator (or designee) should document and report protocol deviations/violations to the IRB of record in accordance with their policy on protocol deviations/violations.

D. Reporting of protocol deviations/violations to other parties
- The investigator (or designee) should follow the applicable requirements of documenting and reporting protocol deviations/violations to any other local, state, or federal regulatory body(ies) and institution(s) involved.

5. REFERENCES

A. Code of Federal Regulations
- 21 CFR 312.66 – Assurance of IRB reviews
- 21 CFR 812.140 (a)(4) – Records
- 21 CFR 812.150 (a)(4) – Reports: Deviations from the investigational plan

B. Good Clinical Practice
- ICH E6 (R3): Harmonized Tripartite Guideline for GCP
    - Section 1 - Institutional Review Board/Independent Ethics Committee (IRB/IEC)
        - Section 1.4.7 - Procedures
    - Section 2 – Investigator
        - Section 2.5.2 – Compliance with protocol

C. VCU HRPP Policies and Guidance - HRPP Toolkit
- HRP–103 - Investigator Manual

Review/Revision History CR-RE-340

Version No.	Effective Date	Description
CR-RE-340.3	03-14-2025	● Updated protocol deviation definition ● Aligned with HRPP toolkit ● Biennial review performed ● Minor formatting edits ● Reference links updated ● Updated to ICH E6(R3)
CR-RE-340.2a	07-01-2020	● Links Updated

CR-RE-340.2	07-01-2020	● Biennial review performed ● Minor formatting edits ● Reference links updated
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