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Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual: Protocol Compliance

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COMPLIANCE WITH PROTOCOL

Clinical Research Sites (CRSs) are required to adhere to Institutional Review Board (IRB)/Ethics Committee (EC) and/or, as applicable, Regulatory Entity (RE)/Regulatory Authority (RA) approved protocols and have established processes to avoid protocol deviations to the extent possible. They must explain, document, and report any protocol deviations per the applicable DAIDS Clinical Trials Network, protocol, and/or IRB/EC/RE/RA requirements.

DAIDS does NOT permit planned deviations, and sites are not permitted to implement a planned deviation unless necessary and acceptable to protect participant rights, safety, and well-being or would shield a participant from an immediate hazard.

International Council for Harmonisation (ICH) Good Clinical Practice (GCP) (“ICH E6”), Section 4.5 “Compliance with Protocol” states: “The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/EC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).”

Examples of protocol deviations include enrolling an ineligible participant, performing protocol-specific procedures before obtaining informed consent, failing to comply with study randomization and blinding procedures, a participant missing a required study visit, failing to follow protocol-specified procedures, breaching participant confidentiality, or not consistently performing a protocol-specific assessment.

CRSs should implement processes that use tools, checklists, Network's Manuals of Procedures/Operations (MOPs), and/or study-specific procedures (SSP) in conjunction with the protocol to avoid any departure from approved protocols. Such processes will help safeguard participants' rights, safety, and well-being and generate high-quality, reliable data.

Identifying and Reporting Protocol Non-compliance

Non-compliance (deviation) from the approved protocol is usually identified:

- By the monitoring contractor during monitoring visits
- By CRS staff during the completion of activities described in their CRS Clinical Quality Management Plan (CQMP)
- By programmed database checks and during data cleaning processes performed by the Data Management Centers

Each protocol and/or applicable DAIDS Clinical Trials Network MOP/SSP will outline CRS requirements for reporting deviations. CRSs must also be aware of the IRB/EC requirements and timelines for reporting non-compliance with the protocol. Depending on local requirements, periodic and/or expedited reporting may also be required (i.e., central IRB, local IRBs, EC, and REs/RAs).

SUSPECTED RESEARCH MISCONDUCT

Research misconduct is defined as fabricating or falsifying data when proposing, designing, performing, recording, supervising, or reviewing clinical research. This deviation does not include honest errors or differences of opinion. The National Institute of Allergy and Infectious Diseases (NIAID) [Allegations of Research Misconduct Standard Operating Procedure](#) (SOP) describes three misconduct categories:

Fabrication: making up data or results and recording or reporting them.

Falsification: manipulating research materials, equipment, or processes, or changing or omitting data or results, such that the research is not accurately represented in the research record.

Plagiarism: appropriating another individual's ideas, processes, results, or words without giving appropriate credit.

Examples of research misconduct include:

Reporting data for a participant who does not exist.

Altering or omitting exam results to make a participant meet eligibility criteria.

Reporting Suspected Research Misconduct

CRS staff must notify the Principal Investigator (PI)/Investigator of Record (IoR) and/or designee (e.g., CRS Leader) of any suspected research misconduct. The PI/IoR and/or designee must then provide all applicable facts about the allegation to the appropriate individual within the institution, the IRB/EC, and the appropriate DAIDS staff member. The involved parties determine if the CRS must suspend some (e.g., new participant enrollment) or all clinical trial activities while the allegation is investigated.

If CRS staff cannot notify the PI/IoR and/or designee (e.g., fear of retribution; PI/IoR/designee is the individual suspected of perpetrating misconduct) they must notify DAIDS and an appropriate individual within their institution (e.g., institution's Research Integrity Officer).

REFERENCES

1. [United States \(U.S.\) Code of Federal Regulations, Title 21, Parts 11, 50, 54, 56, 312 and 812](#)
2. [U.S. Code of Federal Regulations, Title 45, Part 46 and Subparts](#)
3. [International Council for Harmonisation Good Clinical Practice \(ICH E6\)](#)
4. [FDA Guidance: Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects \[Oct 2009\]](#)
5. [Office for Human Research Protections \(OHRP\)](#)
6. [OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events](#)
7. [Guideline for Industry Structure and Content of Clinical Study Reports](#)
8. [ICH E3 Guideline: Structure and Content of Clinical Study Reports \(R1\)](#)
9. [ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions &Answers \(R1\)](#)
10. [NIAID SOP Research Misconduct Cases](#)

REVISION SUMMARY

Version / Revision	Summary of Changes
V1.0	Original Version and became effective on 1/19/2021.
01	The document number and format were updated to meet current requirements.