Title:	**Cross-Network Protocol Deviation Reporting Guide**		
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Revision History:

Revision History	Section	Description
v2.0 01 November 2022 – 05-Jun-2023	1.0	Added section 1.0 Purpose and Scope.
	1.1	Updated definitions for major and critical protocol deviations to clarify differences between classifications. Removed minor protocol deviation classification. Added the timelines for reporting critical and major protocol deviations.
	1.5	Added additional examples of protocol deviations, updated existing examples for clarity.
	1.6	Added section 1.6 Abbreviations and Acronyms.
	-	Removed placeholders for protocol numbers and eCRF IDs. Acronyms spelled out on first use. Added document ID to footer. Renamed document to clarify purpose and scope.
v1.0 25 April 2022	-	Initial release

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1.0 Purpose and Scope

The purpose of the Cross-Network Protocol Deviation Reporting Guide (reporting guide) is to establish standard definitions and classifications for protocol deviations. In addition, the reporting guide describes the process for reporting protocol deviations via the Cross-Network Protocol Deviation Electronic Case Report Form (PD eCRF).

This reporting guide is to be utilized by the National Institute of Allergy and Infectious Diseases (NIAID) HIV/AIDS Clinical Trials Networks. The Division of AIDS (DAIDS) and the HIV/AIDS Clinical Trials Network Leadership and Operations Centers have the authority to review and update this reporting guide. The Office of HIV/AIDS Network Coordination (HANC) is responsible for the maintenance and control of the Cross-Network Protocol Deviation Reporting Guide.

Note that all protocol deviations must also be recorded in the participant's research record. See the Source Documentation Requirements section of the DAIDS Site Clinical Operations and Research Essentials Manual (SCORE) for further guidance.

1.1 Definitions

Protocol deviation: A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the DAIDS approved, Good Clinical Practice (GCP) compliant protocol (ICH E3). Non-compliance may be on the part of the participant, the investigator, the study staff, or a combination of these groups.

The term "protocol deviation" is often used interchangeably with "protocol violation." "Protocol deviation" is the term preferred by the International Council for Harmonisation (ICH).

Protocol deviations classified as Reportable or Not Reportable. Reportable PDs require submission of a PD eCRF by the Investigator of Record (IoR) or designee, as described in Sections 1.2–1.5. Definitions for Reportable and Not Reportable protocol deviations are as follows:

- **Reportable PDs**: *"Reportable protocol deviations* are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of **key** study data or that may significantly affect a participant's rights, safety, or well-being.

For example, reportable protocol deviations may include enrolling participants in violation of eligibility criteria or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial."

- **Not Reportable PDs**: Any PD that does not meet the definition of reportable PD

Participant non-compliance (e.g., missed visits, missed doses of study drug) is considered a protocol deviation but is not typically considered a reportable protocol deviation. Participant non-compliance should be documented and reported per usual site procedures and any applicable protocol requirements but should not be reported using the PD eCRF.

Protocol deviations may escalate in classification if the scope is broader, the number of participants impacted is greater, or the deviation is more significant in the context of the protocol requirements.

1.2 Identification of Protocol Deviations:

Protocol deviations may be detected by the protocol team, site staff (e.g., PI, study coordinator/study nurse, internal monitor, site data manager), or identified through routine monitoring visits or audits of the clinical research records.

When a deviation has occurred, it is expected that the site staff will verify the impact of the PD against the study protocol, MOP, applicable regulations or relevant GCP principles and will report it accordingly via the PD eCRF. The final decision on whether a protocol deviation is Reportable will be determined by the Sponsor.

1.3 Reporting Timelines

Reportable PDs: Sites are expected to report these protocol deviations via the PD eCRF within 5- reporting days of awareness.

Reporting Days: "Reporting days" are those that count towards the timeline provided for reporting of protocol deviations (PD) to DAIDS via the eCRF. The criteria used to determine reporting days are as follows:

- A reporting day starts at 12:00 AM (midnight) and ends at 11:59 PM local time.

- A day is counted as a reporting day regardless of the time of day that awareness occurred.
- The day a site indicates that site personnel became aware of a PD that meets reporting criteria shall count as day 1 if that day occurs on a reporting day (i.e., Monday through Friday).
- If that day occurs on a non-reporting day (i.e., Saturday or Sunday), then the next reporting day shall count as day 1.
- Monday through Friday count as reporting days.
- Saturday and Sunday are not considered reporting days.
- Any holiday (U.S. or in-country/local) that occurs on a Monday through Friday counts as a reporting day.

CAPA Reporting:

The CAPA information is not captured on the eCRF and is not required to be completed within the initial (5-day) reporting timeline.

1.4 Cross-Network Protocol Deviation eCRF (PD eCRF)

The PD eCRF should only be completed for reportable deviations as defined in Section 1.1 of the reporting guide. Additional information on how to complete the questions on the eCRF can be found below. Refer to your study eCRF completion guidelines for additional information.

0a. Date of site awareness: Enter the date the site became aware of the deviation.

0b. Deviation start date: Enter the date the deviation started.

0c: Deviation stop date: Enter the date the deviation stopped. The stop date may be the same as the start date.

1. Has this deviation been reported, or will it be reported to the IRB/EC? Indicate if the deviation has been or will be reported to the local IRB/EC.

2. Is this deviation related to (significant disruptive event): Indicate if the deviation is related to a local, national, regional, or global disruptive event (e.g., COVID-19 pandemic, natural disaster, geopolitical conflict).

3. Deviation category: Select the deviation category that best fits the scenario. The categories are defined below in Table 1.

Table 1: Reportable Deviation Categories

Category	**Description**
Informed assent/consent process deviation	Informed assent/consent not collected, incorrect version used, or mishandled such that participant risk/benefit analysis is impacted.
Did not meet eligibility criteria	Inclusion or exclusion criteria not properly assessed before starting intervention.
Failure to follow trial randomization or blinding procedures	Enrollment/randomization or blinding procedures not properly followed.
Conduct of non-protocol procedure	A clinical or administrative procedure was performed that was not specified in the protocol and was not covered under local standard of care practice.
**Visit completed outside of window*	Study visit completed outside of protocol-defined visit window.
**Blood volume maximum exceeded*	Blood sample collection for research purposes exceeds blood drawing limits as defined in the protocol and informed consents.
Study product management	Participant-specific study product not prepared or stored as directed in the protocol.
Study product dispensing	Participant-specific study product not dispensed as directed in the protocol.
Study product administration	Participant-specific study product not administered by study staff as directed in the protocol.

AE/SAE/EAE reporting	Adverse events (AEs)/Serious Adverse Events (SAEs)/Expedited Adverse Events (EAEs) not managed or reported as per protocol.
Physical assessment	Physical assessment(s) missed for which endpoints/critical study assessments are required per the protocol.
Lab assessment	Laboratory assessment(s) missed for which endpoints/critical study assessments are required per the protocol.
Specimen handling	Specimen(s) not prepared, collected, processed, stored, or transported as per protocol.
**Behavioral intervention*	Behavioral intervention(s) missed for which endpoints/critical study assessments are required per the protocol.
Breach of confidentiality	Participant's confidentiality potentially compromised.
Staff performing duties that they are not qualified or delegated to perform	Staff performing duties that they are not qualified, trained, or delegated to perform per documented agreements.
Use of non-IRB/EC-approved materials	Use of any study-related material or provision of study documents to participants that have not been approved by the IRB/EC or do not have a current approval from IRB/EC.
IRB, ethics, or regulatory review	Continuing IRB/EC review(s) of study documents is/are not maintained or obtained in a timely manner.
Other	Deviation does not fit into categories listed.

Note: Descriptions in Table 1 are intended as a guide. Consult with protocol team members as needed. Categories marked with an asterisk (*) may not be included on the eCRF and removed from the protocol-specific version of the PD eCRF based on protocol requirements.

4a-4c. If deviation category is "Did not meet eligibility criteria" indicate the category not met: The site should indicate the criteria category (inclusion or exclusion), which protocol version the participant was enrolled under at the time of the deviation, and the criterion not met.

5a. Please provide a full description of the deviation [1900]:
Provide a full description of the deviation, including visit week(s), and reason for the deviation. For example, “At visit week 4, the participant’s medical records received after the entry visit revealed that they had received a COVID-19 vaccine 3 weeks prior to study entry. The entry criteria stated that no vaccines were allowed within 8 weeks prior to study entry.”

5b. [For ACTG and IMPAACT only] Please provide a brief summary of the deviation [200]:
Provide a brief (<200 character) description of the deviation. For example, “Participant received vaccination within 8 weeks prior to enrollment which was an entry criteria violation.”

1.5 Review

DAIDS will review all deviations periodically. Required protocol team review may be included in the protocol and other implementation materials; if not specified in the protocol or other implementation materials, deviations may also be reviewed periodically by the protocol team. Based on this review, queries may be sent to re-classify the deviation or add greater detail to the deviation description. In addition, DAIDS, Network groups, and/or protocol teams may request sites send the full details of the corrective/preventative action plan.

1.6 Examples of Protocol Deviations

Table 2: Examples of Protocol Deviations

Deviation Category	Example of Protocol Deviation	**Deviation Classification
Informed assent/ consent process deviation	One page of informed consent form (ICF) was not initialed or confirmation missing that participant was provided with a copy of the ICF	N/A (only document in study files)
	Incorrect version of ICF signed	Reportable
	Failure to obtain informed consent or assent from the participant, legal guardian, or other legally authorized representative prior to performing protocol-specific procedures	Reportable

Did not meet eligibility criteria	Participant enrolled in research for which they did not meet eligibility criteria *without* possible serious health-related consequences because of participation	Reportable
	Participant enrolled in research for which they did not meet eligibility criteria *with* possible serious health-related consequences because of participation (e.g., use of an undisclosed prohibited concomitant medication that resulted in virologic rebound, such as an over-the-counter antacid interfering with absorption of an antiretroviral medication)	Reportable
Conduct of non-protocol procedure	Performing physical exam not required by the IRB/EC-approved protocol	N/A
	Performing breast, gynecological, or rectal exam that could cause psychological harm to the participant when participant was made aware that exam should not have been done as part of study procedures	Reportable
	Performing lumbar puncture that is not specified in the IRB/EC-approved protocol and not otherwise clinically indicated for the participant based on local standards of care	Reportable
Study product error	Participant was instructed to store study product in provided container but did not (for products not affected by minor temperature excursions)	N/A
	Study product not available to be dispensed	Reportable
	Participant dispensed and received wrong study agent (regardless of any subsequent adverse effects)	Reportable
AE/SAE/EAE reporting deviation	EAE was reported within 4 days, rather than within the 3 required days	N/A
	SAE reported well beyond the required timeframe (e.g., participant hospitalized due to head injury from a car accident, reported 6 days after site awareness)	Reportable
	Suspected Unexpected Serious Adverse Reaction (SUSAR) reported well beyond the required timeframe (e.g., participant hospitalized due to stroke that is unexpected and suspected to be related to study product, reported 6 days after site awareness)	Reportable

Breach of confidentiality	Materials containing participant's personally identifiable information are shared with unauthorized individuals	Reportable
	Loss of a computer that contains participants' private identifiable information	Reportable
Use of non-IRB/EC-approved materials	Site use of obsolete or non-IRB/EC-approved participant informational materials	Reportable
IRB, ethics, or regulatory review deviation	A lapse in IRB/EC approval	Reportable
Other	Research misconduct – fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results	Reportable

** The list of examples shown above is not all-inclusive and **Deviation Classification is intended as a guide. Examples classified as "N/A" represent protocol deviations that do not meet the definition for reportable and do not need to be reported via the PD eCRF but should be documented in the site's study files.

Note: A site IoR can determine that a deviation is reportable, even if the deviation does not fit into one of the pre-defined examples listed above. A repeated not-reportable deviation may be considered, as a series of events, to be a reportable deviation. A site IoR can also determine that any deviation is reportable, even if the deviation does not fulfill one of the pre-defined examples listed above.

1.7 Abbreviations and Acronyms

Abbreviation/ Acronym	**Term**
ACTG	AIDS Clinical Trials Group
AE/SAE/EAE	Adverse Event/Serious Adverse Event/Expedited Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
DAIDS	Division of AIDS
DMC	Data Management Center
GCLP	Good Clinical Laboratory Practice
GCP	Good Clinical Practice

HANC	Office of HIV/AIDS Network Coordination
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
HVTN	HIV Vaccine Trials Network
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMPAACT	International Material Pediatric Adolescent AIDS Clinical Trials Network
IRB/EC	Institutional Review Board/Ethics Committee
IoR	Investigator of Record
NIAID	National Institute of Allergy and Infectious Diseases
OCSO	DAIDS Office of Clinical Site Oversight
PD eCRF	Cross-Network Protocol Deviation Electronic Case Report Form
SUSAR	Suspected Unexpected Serious Adverse Reaction