Title:	Version Number:	Effective Date:	Page **1** of **10**
Protocol Deviations, Reporting and Documenting	#1	21 MAY 2024	

Revision History		
Version No.	**Effective Date**	**Description**

Purpose

Deviations from the clinical research protocol, Good Clinical Practice (GCP) guidelines, or applicable federal regulations have the potential to place study participants at risk and can undermine the scientific integrity of the study, thus jeopardizing the justification for research. Therefore, deviations should be addressed and corrected where possible, and preventative measures should be established to prevent future occurrences from taking place.

Scope

Deviation reporting procedures outlined in this SOG are designed to ensure compliance with GCP guidelines and IRB policies. These procedures primarily pertain to studies under the oversight of the University of California, San Diego (UCSD) IRB. However, for studies utilizing a central IRB (CIRB) or a different IRB of record, adherence to both deviation reporting requirements (UCSD and Central IRB) is necessary.

The principal investigator (PI) is responsible for conducting clinical research in accordance with the current IRB-approved protocol, GCPs and applicable federal regulations. The PI may not make any changes to the protocol treatment or procedures without prior approval from the IRB except when necessary to protect the safety, rights, or welfare of study participants.

Definitions and Acronyms

Clinical Research: Clinical research includes all research involving human participants. It does not include secondary studies using existing biological specimens or data collected without identifiers or data that are publicly available.

Clinical Trial: Clinical trials are clinical research studies involving human participants assigned to an intervention in which the study is designed to evaluate the effect(s) of the intervention on the participant and the effect being evaluated is a health-related biomedical or behavioral outcome.

Central IRB: Relying IRB and central IRB are often used interchangeably. Both terms refer to an Institutional Review Board (IRB) that provides review and oversight for a research study conducted at multiple sites or institutions. The central or relying IRB is responsible for coordinating the review process, ensuring consistency in protocol evaluation, and facilitating communication among all participating sites (e.g. Advarra, WCGIRB, etc.).

Local IRB: Is an independent committee typically found within academic or research institutions. Its primary responsibility is to review, approve, and oversee research protocols involving human participants to ensure their protection and ethical conduct. The local IRB evaluates the risks and benefits of research studies, assesses participant consent forms, and monitors ongoing studies to ensure compliance with ethical standards and regulations (e.g. UCSD IRB).

CAPA:	Corrective and Preventative Action
CFR:	Code of Federal Regulations
CIRB:	Central IRB
FDA:	United States Food and Drug Administration
GCP:	Good Clinical Practice
ICH:	International Council on Harmonization
IRB:	Institutional Review Board
Kuali IRB:	Electronic Institutional Review Board System

PD: Protocol Deviation(s)

Responsibilities

This policy applies to Principal Investigators (PI), Clinical Research Coordinators (CRC), Regulatory Coordinators (RC) and all study staff directly responsible for completing study related tasks and/or management of regulatory documents.

Procedure

1. Identification of Protocol Deviations

Clinical research investigators and staff should be familiar with the study protocol, GCPs, and applicable federal regulations and strive to ensure that these are followed in the conduct of clinical research.

ICH E3 defines protocol deviations as: …any change, divergence, or departure from the study design or procedures defined in the protocol." This definition is often over-interpreted leading to inclusion of a wide scope of items such as theoretical situations, and situations which are not PDs. For example, discovery that training of a Clinical Research Coordinator (CRC) was delayed needs to be addressed, but it is not a PD. This wide scope of items generates noise and could delay identification of trends or dilute impact of actual PDs.

Protocol deviations can be either major or minor. Protocol deviations can be examples of non-compliance, either non-serious or serious. Repeated failure by an investigator to report protocol deviations may be considered as non-compliance with the federal regulations and the guidelines that govern ethical conduct of research.

1.1 Principles for identifying actual PDs

- An event occurred (e.g. not theoretical)
- The events is related to the study protocol or documents referenced in the protocol (e.g. laboratory manual)

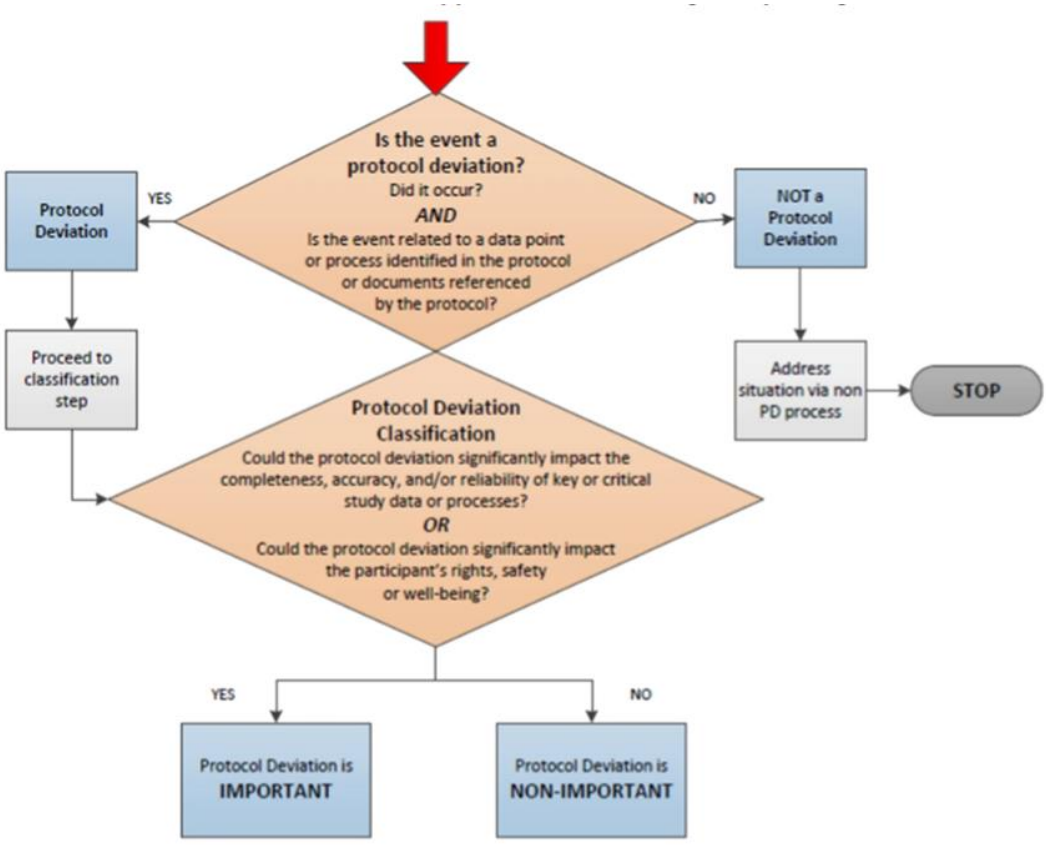
There are events or situations that are not PDs that may require follow up through other processes.

1.2 Categorizing significance of PD:

Once a PD is identified, then it is important to categorize the PD as either major or minor. Guidance on defining major PDs is provided in ICH GCP E6 R2.

- Major PDs: important PDs that impact on data quality or patient safety or lead to participant death and repeated serious or non-serious compliance
- Minor PD: PDs that have no impact or minor impact on data quality or patient safety

"Important (major) 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 subject's rights, safety, or well-being". Examples include enrolling subjects in violation of key eligibility criteria or failing to collect data necessary to interpret primary endpoints, which could may compromise the trial's scientific value.



Protocol deviation decision tree.

Performing procedures or processes not included in the Sponsor- and IRB-approved protocol, even with sponsor approval (e.g., by email, phone call, or protocol administrative letter), is considered a protocol deviation by federal, state and institutional authorities. The sponsor must provide an amended protocol or protocol administrative letter (or equivalent) that includes the alternate procedure(s) and/or process(s). The amended protocol or administrative letter must be submitted to and approved by the IRB of record through an amendment prior to changes being implemented. The requirement for prior IRB-approval does not apply to deviations made for participant safety.

Study teams are required to request an amended version of the protocol from the sponsor that includes all changes proposed in the protocol administrative letter (or equivalent). Requests should be documented clearly (via email, or other method which provides clear documentation of the request) and filed in the regulatory binder.

Deviations may be identified through routine reviews of clinical research records. Verify these deviations as mentioned above and present them to the PI for timely assessment and IRB reporting if necessary.

The following scenarios provide examples (not exhaustive) to guide the determination of major vs minor PDs.

PD Category	Major (important) PD	Minor(non-important) PD	Not a PD
Informed Consent	*Study assessments conducted prior to obtaining initial informed consent *New clinical study assessment performed before the participating was re-consented *Re-consent containing new safety or risk information not signed	*If required by LIRB or CIRB, participant did not initial all pages on ICF	*Administrative issues such as: participant did not date the ICF with the format required by the sponsor (i.e. MM/DD/YYYY vs DD/MM/YYYY)
Inclusion/Exclusion Criteria	*Participant was enrolled in the study without meeting all entry criteria		
Investigational Product	*Incorrect research treatment or intervention given to the participant *Participant received the wrong arm of study treatment (i.e. 50 mg BID vs 50 mg TID)	*Participant was dispensed study drug that underwent a temperature excursion, but was not taken *Participant missed study drug intake for an entire day	*Study drug underwent a temperature excursion, but was never dispensed to the participant
Prohibited Concomitant Medication	*Participant took specific class of medication before a specific procedure (i.e. drug may affect results of PK for example).	*Participant took a prohibited medication on a couple of occasions (repeated use may be considered significant)	
Study Assessments	*A serious accidental or unintentional change to the IRB approved protocol that alters the level of risk *Study procedures not approved by the study protocol *Missed safety or efficacy assessments related to primary or key secondary endpoints *Personnel not listed in the Delegation of Authority Log performed study assessments *Use of un-calibrated equipment to collect data for key safety or efficacy endpoints	participant safety *Missed assessments that have no impact on reliability of study results (i.e. exploratory analysis) *Missed laboratory measurements that are not key or critical safety or efficacy endpoints *Non critical assessments performed out of a specified window	*Training of study personnel on study related assessments
Participant Discontinuation	*Participant met withdrawal criteria for study or study drug during participation, but was not withdrawn		
Adverse Events or Unanticipated Problems (UPs)	*failure to report serious unanticipated problems/adverse events involving risks to subjects or others to the IRB		

2. Documentation of Deviations

Deviations, whether major or minor and regardless of severity or outcome that are identified by the PI or research staff member should be collected, documented, processed and reported as they occur. Deviations can be documented

electronically on (e.g. Microsoft Excel), or written on a paper form (e.g. Protocol Deviation Log).

The deviation report should include adequate attribution, including:

- Date of event (deviation)
- Date the deviation was identified
- Description of event
- PI's assessment of the event (e.g., risk to subject)
- Person completing the report
- Protocol assessment/procedure that was not followed
- Protocol number
- Subject ID
- CAPA: for serious PDs that pose significant operational problems threatening data integrity or participant rights, welfare and/or safety of participants, a CAPA plan is essential. In such cases, the PI must promptly implement corrective actions - without first obtaining IRB approval - to ensure participant well-being. This is followed by conducting a root cause analysis and developing the CAPA plan.
  GENERAL RULE: If study operations (or an oversight in operations) results in a reportable event or new information, it likely requires a CAPA Plan. For detailed instructions on completing one, refer to the CAPA SOG.

3. Reporting of Study Deviations

3.1 Reporting to PI

All Deviations will be reviewed and assessed by the PI. Deviations noted by study staff or monitors will be communicated to the PI in a timely manner.

- Major Deviations: Notify the PI of significant deviations affecting subject safety as soon as possible or within 48 hours, whenever feasible and write CAPA plan once the problem is identified.
- Minor Deviations: Less severity may be communicated to the PI in a regular study team meeting following discovery of PD.

3.2 Reporting to the IRB

Reliance Considerations:

If using an External IRB (such as Advarra, WCGIRB, Sterling IRB) under UCSD's SOG IRB Reliance (Single IRB review), the PI must adhere to the relying IRB's protocol deviation reporting criteria, including CAPA plans. Additionally, it's crucial for the PI and study team to ensure compliance with the post-approval responsibilities of using a relying IRB (central IRB). These responsibilities are not duplicative and include reporting protocol deviations to UCSD IRB when the reviewing IRB determines protocol deviations are significant/major or findings of continuing or serious non-compliance. The relying IRB's determination letter must be submitted to UCSD IRB via the Kuali system.

If the University of California, San Diego IRB is the IRB of record for a study, the PI must report any event meeting UCSD's protocol deviation reporting criteria via the Kuali system. The PI is responsible for ensuring detailed and accurate reporting and developing a corrective and preventive action plan (CAPA) appropriate and actionable within the local context.

IRB Protocol Deviation Reporting Criteria: The PI will determine whether the deviation meets one or more of the following IRB reporting requirements:

- Immediate hazard elimination, such as changing the dose of a medication due to toxicity.
- Possible harm to participants or others, such as breach of confidentiality, participant enrolled without meeting eligibility criteria.
- Possible serious or continued non-compliance
    - Serious non-compliance are deviations that result in significant harm (physical, psychological, safety, or privacy) or significantly increase the possibility or likelihood of harm to the health, rights or welfare of study participants.
    - Continuing non-compliance is a pattern of repeated actions or omissions to act (either serious or non-serious in nature) that suggests a future likelihood of recurrence and that indicates a deficiency in the ability or willingness to comply with the protocol, GCPs or regulations.

The logs with PD assessments for IRB reporting should be documented and signed or initialed and dated by the investigator.

Reportable deviations are submitted in the Kuali system via the "reportable event" link.

The PD report should describe the plan to prevent the deviation from occurring again. Corrective and preventative action plans (CAPA) should be carefully developed, so that when implemented, they address the root cause of the problem and prevent further occurrences. If the CAPA involves re-training, this training should be documented. See CAPA SOG for instructions on how to complete CAPA and for template.

- Minor deviations (non-important): Report via Kuali IRB system during continuing review for studies under UCSD IRB oversight.
- Major (important) deviations: Report via the Kuali IRB system within 10 working days from awareness of deviation.
- For relying IRBs, report major deviations or as require by the monitors/sponsors. Follow the relying IRB submission instructions.

If the report of a major deviation is not submitted to the local IRB within 10 working days, a written explanation for its tardiness must accompany the report. Late reports may be assessed by the IRB as additional non-compliance.

IRB will evaluate deviation reports for their impact on participant safety, rights, welfare, or scientific data integrity. After review, the PI will be notified of the outcome, which may require additional corrective actions.

IRB deviation reports and supporting documents should be retained with the study records in the regulatory binder.

Materials Required

- IRB-approved protocol and informed consent form
- Protocol Deviation Log, or other department-specific or study-specific deviation documentation form, or electronic data capture system
- Access to Kuali (IRB electronic application and document system)

References

- GCP 45 CFR Part 46.103(b)(5) (iii)
- GCP 21 CFR 56.108 (a) (4).
- ICH GCP Guidance for Industry E6(R2): Good Clinical Practice, Section 4.5
- ICG E3
- UCSD IRB SOG Section 3.14 Protocol and Regulation Violations and Exceptions

Title:	Version Number:	Effective Date:	Page **10** of **10**
Protocol Deviations, Reporting and Documenting	#1	21 MAY 2024	

Document Approval

- Name and Title of Approver
- Date in the format (MM/DD/YYYY)
- Insert Name and Title below Signature

Approved By: Date:

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Insert Name and Title

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