University of California, San Diego
Human Research Protections Program
Institutional Review Board
Standard Operating Policies and Procedures

Section 3.14
Protocol and Regulatory Violations and Exceptions

Policy

Federal regulations require that any modification to an approved protocol must be reviewed and approved by the IRB prior to implementing the change except when necessary to eliminate apparent immediate hazards/risks to subjects. Conducting research procedures without IRB approval can negatively impact the rights, welfare, and safety of human subjects who participate in research. Research activities include all aspects associated with the conduct of the research including activities related to recruitment, consent, protection of privacy and confidentiality and all information outlined in the IRB reviewed and approved application/protocol.

Protocol/Regulatory Violations

Investigators are required to conduct their research according to the plans reviewed and approved by the IRB. Instances where this does not occur, either inadvertently due to circumstances beyond the investigator's control, or due to errors of omission or commission by research project staff, are considered violations and must be reported to the IRB in a timely fashion. Minor violations may be reported to the IRB at the time of continuing review. *Major violations must be reported to the IRB within 10 working days of awareness of the violation.*

Major violations include instances that impact participant safety, substantially alter risks to participants, are non-compliant with applicable UCSD HRPP, federal, state and institutional policies and regulations, or any instance determined by the IRB Chair, HRPP Director or HRPP Associate Director to require review by a convened IRB.

Examples of major violations include but are not limited to any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject; an event or incident that meets the criteria for an unanticipated problem involving risk to participants or others; a serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk; failure to obtain legally effective informed consent; study procedures that are done that are not approved by the IRB; incorrect research treatment or intervention given to the subject; failure to report serious unanticipated problems/adverse events involving risks to subjects or others to the IRB; failure to perform a required lab test or perform a study visit/study labs during the required time frame, that, in the opinion of the PI, may affect subject safety or data integrity; and loss of adequate resources that affects the protection of the rights and welfare of participants.

Minor protocol violations include instances that do not impact participant safety or substantially alter risks to participants.

Examples of minor violations include but are not limited to failure to perform a required lab test or perform a study visit/study labs during the required time frame, that, in the opinion of the PI, does not affect subject safety or data integrity; over enrollment; and missing lab results.

The IRB shall investigate allegations concerning possible regulatory non-compliance with UCSD HRPP policies and all applicable federal, state, and institutional polices and regulations.

During such investigations, confidentiality will be maintained concerning the source of the report to the extent allowed by law.

Action taken will include presentation of the allegation to the person(s) involved with a request for a response; review of the problem by the IRB and communication of its recommendations to the investigator; and presentation to the IRB by the investigator at a full committee meeting, if appropriate.

Any instance of serious or continuing investigator non-compliance with federal, state, or UCSD regulations or policies will be reported promptly to the UCSD Institutional Official; the Dean, UCSD School of Medicine; the Office of Human Research Protections (OHRP) and the US FDA (for FDA-regulated test articles), as appropriate.

Serious noncompliance includes noncompliance a) that results in substantive harm or damage (or risk of substantive harm or damage) to the safety, rights, or welfare of human subjects, research staff, or others; or b) substantively compromises the integrity or effectiveness of the research.

Ongoing noncompliance includes a pattern of noncompliance that indicates a deficiency likely to result in further noncompliance (e.g., a pattern that indicates a lack of attention to or knowledge or understanding about regulations or ethics) or a circumstance in which an investigator fails to cooperate with investigating or correcting noncompliance.

For a more detailed description of policies and procedures associated with review of regulatory violations, see SOPP, section 5.2, Communications, Sanctions, Appeals, and Disciplinary Actions.

<u>Protocol Exception to Enroll an Individual Subject</u>
A protocol exception to enroll an individual subject is to allow a one-time enrollment of a single individual who does not meet the inclusion/exclusion criteria of an approved protocol or emergency use criteria (emergency use criteria can be found in SOPP, section 3.5, Emergency Use and Informed Consent). Protocol Exception to Enroll requests should be rare and clearly determined to be in the best interest of the patient.

In order to enroll such a subject, a request must be submitted to the IRB for review and approval. The subject *may not be enrolled* until approval has been granted from a convened IRB. The request must include the following information:

1. Why it is appropriate to enroll this subject is this protocol.
2. What specific study criteria are not satisfied by the subject.
3. Justification of potential risk to the subject.
4. Have other protocol exception(s) been done on this study. If so, provide a brief description of each.
5. Documentation of approval by the study sponsor to provide the exception, as appropriate.
6. Clarification as to whether data collected on this subject will be provided to the study sponsor.
7. Clarification as to whether an amendment to the protocol's inclusion/exclusion criteria will be done. If yes, the timeframe for submitting the amendment to the IRB. If no, justification for not submitting such an amendment including why modifying the inclusion/exclusion criteria are appropriate for this subject and not all potential subjects.

Procedures

1. Submission of Major Protocol Violation and Regulatory Violation Reports to the IRB
    a) The PI submits a report to the IRB outlining any and all Major Protocol Violations and any and all Regulatory Violations to the IRB immediately upon becoming aware of the event but no later than 10 working days. The report should include subject ID; description of event, date of event; any costs (if known); who paid the costs (if known); and the PI's assessment of the event (e.g., risk to subject(s)) as well as what procedures will be done in the future to prevent a similar violation and provide revised study documents, as appropriate.
    b) The PI reports the violations to the sponsor, if applicable, following the sponsor's requirements.
2. Submission of Minor Protocol Violations to the IRB
    a) The PI provides information regarding minor protocol violations at the time of continuing review or study closure on the "Narrative Summary Of Progress To Date" or Narrative Summary of Progress to Date at Study Closure" (as appropriate) form including subject ID; description of event, date of event; any costs (if known); who paid the costs (if known); and the PI's assessment of the event (e.g., risk to subject(s)) as well as what procedures will be done in the future to prevent a similar violation and provide revised study documents, as appropriate.
3. Submission of Protocol Exception requests to the IRB
    a) The PI provides requested information for a protocol exception request to the IRB as soon as possible upon determination that enrollment of subject is in the best interest of the potential subject.
4. Review of Violation Reports submitted to the IRB
    a) Reports regarding protocol/regulatory violations will be reviewed by the IRB Chair, HRPP Director or Associate Director. If the violation is determined to be major or regulatory in nature or appropriate for review by a convened IRB, the report will be placed on a meeting agenda to be reviewed by the IRB at the next appropriate IRB meeting. If the report is determined to be a minor violation, the report may be reviewed using expedited procedures.

b) Reports provided at the time of continuing review will be placed on a meeting agenda to be reviewed by the IRB at the next appropriate IRB meeting as part of the continuing review.
c) Reports provided at time of study closure will be reviewed by the IRB Chair, HRPP Director Associate Director. If the violation is determined to be major or regulatory in nature or appropriate for review by a convened IRB, the report will be placed on a meeting agenda to be reviewed by the IRB at the next appropriate IRB meeting. If the report is determined to be a minor violation, the report may be reviewed using expedited procedures.

5. Review of Protocol Exception Requests
   a) Protocol Exception Requests will be reviewed by the IRB Chair, HRPP Director or Associate Director and will be placed on the agenda of the next appropriate IRB meeting for review by a convened IRB.
6. Review outcomes
   a) The IRB may approve, approve pending, or defer a violation report/protocol exception request.
   b) For Regulatory Violations, the IRB will follow policies and procedures as outlined in SOPP, section 5.2, Communications, Sanctions, Appeals, and Disciplinary Actions.
   c) The IRB will, as appropriate, determine whether the violation constitutes "serious" or "continuing" non-compliance or an "unanticipated problem involving risks to subjects or others." Violation(s) found to describe serious and/or continuing non-compliance or an unanticipated problem involving risks to subjects or others will be reported to various entities as outlined in SOPP, section 5.2 and SOPP, section 3.13, Reporting Adverse Events and Unanticipated Problems, respectively.

Applicable Regulations, SOPPs, and Forms

21 CRR 56.108(a)(4)

45 CFR 46.112

45 CFR 46.113

UCSD SOPP, section 3.5

UCSD SOPP, section 3.13

UCSD SOPP, section 5.2

UCSD Narrative Summary of Progress to Date for Biomedical Studies

UCSD Narrative Summary of Progress to Date for Social and Behavioral Studies

UCSD Narrative Summary of Progress to Date at Study Closure for Biomedical Studies

UCSD Narrative Summary of Progress to Date at Study Closure for Social and Behavioral Studies