

Determining and Reporting Non-Compliance and Protocol Violations

SOP 108
Revised: January 12, 2017

Purpose and Scope

This SOP describes the procedure for managing Non-Compliance that may affect the rights or welfare of human subject participants.

This SOP applies to all HSP staff, IRB members, and Investigators who are involved in the oversight or conduct of research.

Definitions

- **Non-Compliance:** Conducting research involving human participants in a manner that disregards or violates federal regulations and/or the institutional human research protection program policies governing such research.
 - **Continuing Non-Compliance:** a pattern of non-compliance that suggests the likelihood that, without intervention, situations of non-compliance will recur, a repeated unwillingness to comply, or a persistent lack of understanding of how to comply. More specifically:
 - PI or IRB makes same mistake repeatedly, particularly after IRB has informed PI of problem;
 - PI or IRB has multiple problems with non-compliance over a long period (i.e. within 12 months from the time of first report to IRB)
 - PI, IRB, or Institution has a history of problems with multiple projects; and/or
 - Anything the IRB considers to be “continuing”.
 - **Serious Non-Compliance:** non-compliance that adversely affects the rights or welfare of human research participants, specifically:
 - Non-exempt human participant research conducted without IRB approval or without appropriate informed consent, particularly if it is greater than minimal risk;
 - Significant modifications to IRB-approved research without IRB approval; and/or
 - Other instances determined by IRB (e.g., protocol deviation or violation that places participants at risk for significant harm, whether emotional, psychological, or physical; risk in breach of confidentiality or privacy).
- **Protocol Violation:** A type of non-compliance, any deviation or departure from the IRB-approved protocol or proposal that does not have prior approval by the IRB unless the change is necessary to remove an apparent immediate hazard to one or more study participants.

- **Minor Protocol Violation (aka “Protocol Deviation”):** Also known as Protocol Deviation, a protocol violation that does not impact the safety or welfare of study participants, compromise the integrity of study data, or affect participants’ willingness to participate in the study. Examples of protocol deviations include the following (not an all-inclusive list):
 - Use of an outdated version of the consent form if risks to participants described in the form do not differ from those described in the current form;
 - A study procedure conducted out of sequence;
 - A study visit conducted outside the required time period;
 - Failure to perform a required procedure, assessment, or lab test that, in the opinion of the PI, is unlikely to have an adverse impact on participant safety or welfare or the integrity of the data collected; and
 - Enrollment of more than the IRB-approved number of participants.

- **Major Protocol Violation:** A protocol violation that may impact the safety or welfare of study participants, compromises the integrity of study data, or affects participants’ willingness to participate in the study. Examples of major protocol violations include the following:
 - Failure to obtain informed consent, or obtaining informed consent from a participant after initiation of study procedures;
 - Using an outdated version of the consent form when risks to participants described differ from those described in the current consent form;
 - Performing a study procedure not approved by the IRB;
 - Modifying a study without prior IRB approval unless to remove an apparent immediate hazard to one or more study participants;
 - Enrollment of a subject who did not meet any inclusion/exclusion criteria;
 - Failure to perform a required procedure, assessment, or lab test that, in the opinion of the PI, may affect the safety or welfare of one or more participants or the integrity of the data collected;
 - A drug dispensing or dosing error;
 - A study visit conducted outside of the required time period with a potentially adverse effect on the safety or welfare of one or more study participants;
 - Failure to follow applicable federal regulations or IRB policies and procedures, including those for reporting Unanticipated Problems and Adverse Events;
 - Failure to follow an IRB-approved safety monitoring plan.

- **Corrective Action Plan (CAP):** A plan developed in response to a protocol violation that outlines the steps to be taken to: (1) reduce the risk to participants affected by the violation, and (2) prevent a recurrence of the violation.

Procedures

Reporting Protocol Violations PI's Reporting Requirements

Minor Protocol Violations. The Human Studies Program (the HSP) does not require reporting of minor protocol violations to the IRB at the time of each occurrence. If a sponsor requires a PI to report a minor protocol violation to the IRB, the HSP staff will determine if the report will be placed on the agenda of a convened IRB meeting;

If the report is not placed before the convened IRB for review, the HSP will administratively acknowledge receipt of the report in a letter to the PI.

The PI should provide to the IRB a summary of minor or major protocol violations that occurred during the prior IRB approval period at the time of *continuing review*.

Timeframe of Reporting Major Violations. The PI must notify the IRB of major protocol violations no later than 24 hours after the P.I. becomes aware of the event by phone or email, and report the event to the IRB no later than 10 business days after discovery of the violation using the protocol violation report form by a member of the study team.

Changes to Remove a Hazard. If a protocol change has been initiated to remove an apparent immediate hazard to one or more study participants, the PI will report this change under SOP 115, **Submitting Modification Requests to the IRB.** The PI must submit the report no later than *five business days* after initiation of the change.

The Content of the Report.

Reports of major protocol violations should include the following elements:

- Date of report, study title, and CHS protocol number;
- PI's name, title, affiliation, phone number, and email address;
- The study's enrollment status (open or closed) and number of locally enrolled participants;
- Description of the protocol violation, including dates and other details;
- Description of the factors that led to the protocol violation;
- Description of any compromises to patient safety or welfare or to the integrity of the study data;
- A statement addressing whether, in the opinion of the PI, the violation is likely to affect subjects' willingness to continue participation in the study;
- As applicable, a description of corrective actions already taken, dates of implementation, and whether and how participants were informed of the violation, and outcomes.
- The current version of the IRB-approved consent form.
- A **Corrective Action Plan (CAP)**. Corrective action plans may include one or more of the following (not an all-inclusive list):
 - Drafting new or revised standard operating procedures,
 - Developing new or revised study monitoring plan or tools (e.g., checklists),
 - Notifying participants of risks associated with the violation (e.g., a confidentiality breach),
 - Training staff, or independent review by a combination of the following two: HSP staff, IRB member, and/or HSP Director
 - Hiring additional staff or modifying staff roles, or
 - Applying sanctions.
- **Signature.** The PI or designee will sign the protocol violation report.

Submission.

Protocol violation reports can be submitted through the eProtocol system using the Protocol Violation Form.

Reporting Non-Compliance In General

Non-compliance of a particular research protocol or proposal can be reported by other individuals (may be done anonymously) via telephone, email or letter to the Human Studies Program office.

Reports of non-compliance, not self-reported, are recorded by the HSP staff on the **WKSH 317 Allegation Report Form**.

Review of Protocol Violations

- **Review of Major Violations.** Reports of major protocol violations will be placed on the agenda of the next scheduled IRB meeting.
- **IRB Decisions**
 - The IRB can vote to accept the protocol violation report as submitted or request further information or actions.
 - The IRB may determine that the protocol violation is an “Unanticipated Problem” or “Serious or Continuing Non-Compliance” that requires reporting to the Office for Human Research Protections (OHRP), Food and Drug Administration (FDA), the sponsor, and/or UH leadership.
 - IRB determinations and requirements will be documented in the IRB meeting minutes.
 - IRB determinations and requirements will be provided to the PI in a letter.

Review of Allegations or Findings of Non-Compliance

- a. All reports of non-compliance are initially evaluated by the HSP staff. A report will either be designated as not requiring further action, or will be escalated for review by the HSP Director or their delegate.
- b. The HSP Director or their delegate ensures that immediate action is taken as necessary to prevent unacceptable risk to research participants. For non-compliance that is potentially serious or continuing (in the opinion of the HSP Director), the HSP Director reports within five business days to the Institutional Official and subsequently provides updates on any fact-finding and IRB review process.
- c. A report requires no further action if the non-compliance is:
 - i. A factual assertion of non-compliance (generally self-reported by the investigators);
 - ii. Neither serious nor continuing; and
 - iii. Addressed by the investigator through a corrective action plan to remedy the problem.
 - iv. If a report of non-compliance does not require further action, the incident and corrective action plan will be documented in writing and stored in appropriate files. Findings of possible serious or continuing non-compliance are referred to the IRB for review. (See below.)
 - v. If a report is an allegation, the HSP Director or the Director’s designee will review the report.

Investigation

The HSP Director or delegate reviews the report and chooses one of the following courses of action in investigating the allegation:

- a. Conducts the review alone
- b. Conducts the initial review in co-ordination with the IRB Chair
- c. Delegates some of the review to IRB staff
- d. Delegates all of the review to IRB staff

- e. Empanels a reviewing subcommittee of the IRB
- f. Requests that legal counsel provide advice and conduct the review,
- g. Requests assistance from others at UH (e.g., Office of General Counsel, a non-involved UH physician as an expert, or outside consultants)
- h. The individual(s) or subcommittee conducting the investigation may take any of the following actions necessary to determine whether allegations are true, and to determine the seriousness or number of occurrences of the actions:
 - a. Reviewing written materials
 - b. Interviewing knowledgeable sources
 - c. Collecting relevant documentation.
- i. During the fact-finding process, the HSP Director or delegate communicates as appropriate with the PI or representative about the progress of the review and investigation. A factual and objective written record of findings and evidence is made by the HSP and stored in the appropriate files.
- j. Allegations which, in the opinion of the HSP Director or delegate and the IRB Chair, are supported by the preponderance of evidence are determined to be findings of non-compliance.
- k. Findings of non-compliance are assessed by the HSP Director or delegate and the IRB Chair as to whether they are either serious or continuing.
- l. If the non-compliance is neither serious nor continuing, the HSP Director or delegate, alone or with the IRB Chair, examines whether the PI understands the non-compliance and has an adequate corrective action plan. If so, the decision and corrective action plan are documented and filed, otherwise the report is referred to the IRB (the convened IRB, the IRB Chair, or their delegate) for review.

Serious or Continuing Non-Compliance Referred to the IRB

Non-compliance that is believed to be serious or continuing is referred for review by the convened IRB. The IRB Chair (or designee) is assigned as primary reviewer for all serious and continuing non-compliance cases. The report, along with pertinent materials, is made available to all IRB members of the reviewing committee prior to the convened meeting.

Upon convened IRB review, the following actions may be taken:

- i. The IRB determines that additional information is needed and requests that such information be obtained before further action is taken.
- ii. The IRB determines that non-compliance did not occur or that non-compliance occurred but was neither serious nor continuing, and either takes no action or requires or recommends an appropriate corrective action plan.
- iii. The IRB determines that non-compliance occurred and that it was serious or continuing. The IRB:
 - a) Takes action appropriate to the situation (see possible actions below)
 1. Follows the required internal reporting procedure concerning determinations of serious or continuing non-compliance.
 2. For concerns not within the IRB's purview, the IRB refers the matter to the appropriate official at UH.
 3. IRB determinations and actions are recorded, and communicated as appropriate to the relevant, involved individual(s), normally including the PI. IRB determinations of serious or continuing non-compliance must be reported internally and externally, if applicable, to:
 - a. Institutional Official

- b. Department Dean or Director
- c. Office for Human Research Protections (OHRP)
- d. Food & Drug Administration (FDA)
- e. The sponsor (via the Office of Research Services)

Post-Review Reporting Procedures

Possible IRB Actions for Serious or Continuing Non-Compliance

1. In considering actions for serious or continuing non-compliance, the IRB seeks to:
 - a. Correct the non-compliance
 - b. Deter it from occurring again (e.g., hold the relevant individuals accountable for their actions and provide education on how to comply), and
 - c. Attempt to mitigate any adverse effects on participants.

2. The IRB must consider:
 - a. Suspension or termination of the protocol (**see SOP 109 Termination or Suspension of Research**)
 - b. Notification of current participants (required when such information may relate to participants' willingness to continue to take part in the research)
 - c. Other possible IRB actions include but are not limited to the following:
 - i. Monitoring of the research, including reviewing the protocol more often than annually. This may include providing the IRB additional periodic status reports, as prescribed by the IRB, during the review period.
 - ii. Monitoring of the consent process
 - iii. Referral to other organizational entities (e.g., legal counsel, risk management, institutional official)
 - iv. Modification of the research protocol
 - v. Modification of the information disclosed during the consent process
 - vi. Provision of additional information to past participants
 - vii. Requiring re-consent of current participants to continued participation
 - viii. Modification of the continuing review schedule
 - ix. Participation by research team members in additional training or education
 - x. When appropriate, applying any corrective action to all similar protocols.

3. If the IRB action will affect participants in the protocol (e.g., requires withdrawal of participants), the IRB utilizes a process that takes into account the impact on their health and safety.

4. Reports to OHRP and/or FDA on serious or continuing compliance should be submitted to the following locations/ contacts:

Office for Human Research Protections
 U.S. Department of Health and Human Services
 200 Independence Avenue S. W.
 Washington, D. C. 20201

For Drug Products (FDA):

Ms. Dana Walters

Dana.Walters@fda.hhs.gov

Division of Scientific Investigations (HFD-45)

Office of Compliance

Center for Drug Evaluation and Research

White Oak Campus

10903 New Hampshire Ave.

BLDG 51, Rm. 5341

Silver Spring, MD 20993

Phone: (301) 796-3150

Fax: (301) 847-8748

For Biologic Products (FDA):

Ms. Patricia Holobaugh

Patricia.Holobaugh@fda.hhs.gov

Bioresearch Monitoring Branch (HFM-664)

Division of Inspections and Surveillance

Office of Compliance and Biologics Quality

Center for Biologics Evaluation and Research/FDA

10903 New Hampshire Ave.

Building 71, Room 5133

Silver Spring, MD 20993

Phone: (240) 402-8955

Fax: (301) 595-1304

For Medical Devices (FDA):

Phone (301) 796-5490

Fax: (301) 847-8136

Email: bimo@cdrh.fda.gov

Reporting Timeframe for Serious or Continuing Non-compliance

The maximum time allowed between the recognition of a reportable, serious or continuing non-compliance event and fulfilling its reporting requirements should not exceed more than thirty (30) working days.

IRB-related Non-Compliance Involving an IRB Chair, IRB Member or HSP Staff

IRB Chairs, IRB Members or HSP Director

The Assistant Vice Chancellor of Research Compliance (AVCRC) is primarily responsible for investigating and reviewing IRB-related non-compliance involving an IRB Chair, IRB member or the HSP Director. If a fact-finding review of an allegation is necessary to assess the evidence, it could include the AVCRC acting alone, delegating some or all of the review to IRB staff, empanelling a review committee, requesting that legal counsel provide advice and conduct the review, or requesting assistance

from others. If the ACVRC makes a finding of serious or continuing non-compliance, the report is referred to the IRB for review.

HSP Staff

The HSP Director is primarily responsible for reviewing non-compliance involving HSP staff, and determining if allegations are supported by a preponderance of evidence. The HSP Director may delegate the initial review or fact-finding to others. If the non-compliance is deemed to have merit the HSP Director is ultimately responsible for determining the action.

Possible IRB Actions for Non-Compliance Involving an IRB Chair, IRB Member or Staff

Possible actions include but are not limited to the following:

1. As appropriate: Evaluation of the IRB Chair's or member's ability to serve on the IRB, or evaluation of the staff member's ability to support the IRB
2. Retraining individuals, as appropriate.
3. Terminating or suspending individual from reviewing protocols or serving on the committee (for IRB members) or serving as Chair.

Materials

- APP 06 Status Report Form
- APP 10 Protocol Violation Report Form
- WKSH 315 Protocol Violation Reviewer Worksheet
- WKSH 317 Allegation Report Form
- TMP 434 Letter Accepting Protocol Violation Report
- TMP 470: Reporting Letter – FDA Notification of Suspension or Termination of Research Involving a Biologic
- TMP 471: Reporting Letter – FDA Notification of Suspension or Termination of Research Involving a Drug
- TMP 472: Reporting Letter – OHRP Notification of Non-Compliance
- GUIDE 614 Events and Information that Require Prompt Reporting to the IRB

References

- The University of Hawaii (UH) has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board, as appropriate. **(AAHRPP Element I.1.D)**
- The University of Hawaii has and follows written policies and procedures for addressing allegations and findings of non-compliance with Human Research Protection Program requirements, and works with the Institutional Review Board, when appropriate, to ensure that participants are protected when non-compliance occurs. Such policies and procedures include reporting these actions, when appropriate. **(AAHRPP Element I.5.D)**