

14. Non-compliance with 45 CFR § 46, HU or CHS Policies/Procedures

The CHS reviews all allegations of non-compliance with federal regulations, University and CHS policies, and CHS determinations (such as approvals and contingencies) relating to research with human participants. Any individual or organization may submit a complaint or allegation of non-compliance to the CHS. The CHS may also initiate a complaint based on information available (e.g., deficiencies noted in CHS files, media or scholarly reports of research activity subject to CHS jurisdiction).

Non-compliance means conducting research in a manner that disregards or violates federal regulations governing human studies research, Harvard University policies, Faculty of Medicine policies, accepted ethical guidelines, CHS policies, and/or CHS requirements and determinations.

14.1. Definitions

- **Research Activity** includes all aspects of the research study, e.g., recruitment methods, consent process, invasive or non-invasive procedures used with the participants, means used to protect privacy and confidentiality (both electronic and traditional), and use of survey or study instruments. In other words, **all** of the information outlined in the study submission and reviewed and approved by the CHS is considered the “research activity.”
- **Non-Compliance** is a failure to follow the regulations or the requirements or determinations of the CHS.
- **Serious Non-Compliance** is non-compliance that adversely affects the rights and welfare of participants or places participants at increased risk of harm.
- **Continuing Non-Compliance** is a pattern of non-compliance that indicates an unwillingness to comply or a lack of knowledge that may lead to an adverse effect on the rights and welfare of participants or may place participants at an increased risk of harm,. Examples of continuing non-compliance include:
 - Repeated instances of allowing a study to expire before it is re-approved;
 - Repeated failure to respond to CHS inquiries or requests for documentation;
 - Repeated failure to respond to and resolve any study contingencies; or
 - Repeated instances of failures to respond to CHS inquiries and contingencies

14.2. Investigator Reports of Protocol Deviations and Non-Compliance

It is the responsibility of the Investigator to ensure proper and prompt reporting of protocol deviations and other non-compliance events to the CHS and to consult with the CHS staff regarding the nature of the deviation and the potential the impact, if any, on study participants.

14.2.1. What to Report to the CHS

Investigators are required to report to the CHS any minor or major protocol deviations or other non-compliance events, and anything they believe to be serious or continuing non-compliance (even if unintended), as outlined above.

Investigators are required to file a Non-Compliance Report Form (Appendix 57) and/or a separate written report to the CHS office including the following information:

- A complete description of the protocol deviation(s);
- The procedures and/or documents involved;
- A timeline of when the deviation began, was discovered and stopped (and if not stopped, a justification for such action);
- The number of participants and/or data affected;
- A reason or justification for not seeking CHS approval prior to implementation of any new procedures or documents;
- A description of any unanticipated problems involving risks to participants or others, or adverse events as a result of the deviations should be fully described;
- A plan for notification to any other sites or Investigators involved (if a multi-site project).

14.2.2. When to Report to the CHS

All deviations and non-compliance events must be reported by the Investigator or his/her staff to the CHS office upon discovery if possible, but in any case not more than 48 hours after discovery. Initial notifications to the CHS office may be provided by phone or email, but must be reported in writing to the CHS office within five working days (unless otherwise specified by CHS staff, depending on the nature of the event). Any study activities or materials not approved by the CHS should be stopped immediately and not re-initiated until the CHS has reviewed and approved the event, activity or material.

14.2.3. Other Allegations or Reports of Non-Compliance

The CHS prefers that Investigators report their own deviations. However, there are times when allegations of non-compliance are reported to the CHS from sources within the research team, the Investigator's department, the CHS office, or by study participants or others with knowledge of a particular situation. Generally, when protocol deviations are reported to the CHS office or discovered by CHS staff, the deviations are treated as allegations of non-compliance. Any allegations of non-compliance may be submitted directly to the CHS office, the Institutional Official's office, or to the Office of Research Compliance. All allegations of non-compliance (including anonymous allegations) will be investigated promptly.

14.2.4. Initial Inquiry

Whenever an allegation or complaint of non-compliance is received, the ORSP Director and CHS Administrator will review the allegation/complaint with the project file. The Director or Administrator may re-contact the person filing the allegation or complaint (if known, as some reports may be anonymous), if necessary. Depending on the nature and seriousness of the allegations, the Administrator or Director may contact the Investigator and may find it necessary to assess the validity of the report. Depending on the nature and seriousness of the allegation or

complaint, it may be necessary to meet with the Investigator at his/her study site in order to assess the validity of the report, or to review the Investigator's files. It may also be necessary to meet with the person bringing the allegation or complaint to the attention of the CHS. No allegations or complaints will be dismissed until the validity of the report/complaint is determined by the CHS office.

Upon confirmation of a valid allegation or complaint, the Administrator or Director will forward the allegation to the Chair. The Chair may consult with a member of the CHS with expertise in the area of study or a member who is familiar with the reviews of the particular study, or may refer the allegation back to the appropriate CHS staff with a request to provide or obtain more information. Thereafter, the following actions ordinarily will take place:

- i. The CHS Chair or staff (as directed by the Chair) will send written notice of the allegations to the Investigator and request a response specifically addressing the allegations.
- ii. The Chair and/or designee will review the allegation/complaint, the response from the Investigator and any other relevant information (such as the initial or continuing review application and related materials, copies of amendment requests, unanticipated/adverse event/DSMB reports, consent forms, communications with the Investigator and any other pertinent information) in order to determine whether the allegation is serious or continuing, and if so, provide a recommendation to the CHS concerning appropriate action. If the non-compliance is not serious or continuing the Chair may determine the following corrective actions, which will be forwarded to the Investigator by the Chair, or the CHS staff (if so requested by the Chair):
 - Resolution through corrective or educational measures.
 - Require changes to the protocol, consent form or process, or study procedures or processes to avoid future incidents of non-compliance.
 - Referral to a convened CHS meeting to review and recommend appropriate actions.
 - Referral to other organizational entities (e.g., Office for Research Issues for allegations of research misconduct (for example fabrication, falsification, or plagiarism).
 - In some situations, especially those involving allegations of continuing non-compliance, the CHS may require verification from someone other than a researcher (for example, a Department Head, Department Administrator, CHS member or staff) that changes to documents or procedures, required by the CHS, have been made. Although not typical, this external verification may be required by the CHS if it has made more than one unsuccessful attempt to receive documentation of changes from the researcher, or if it has received a report from study personnel, study participants, or others, that the changes required by the CHS were not implemented.
- iii. All incidents determined by the Chair to be serious or continuing non-compliance are reviewed by the convened CHS. The Chair acts as the primary reviewer, and all of the documents the Chair reviewed in order to make the determination of serious or continuing (see ii., above) will be sent to the CHS members who will be present at the convened meeting via the same procedures outlined in Section 4.10.3 .
- iv. The allegation of serious or continuing non-compliance (including all of the materials reviewed by the Chair in (ii), above) is reviewed at a convened CHS meeting where one of the following determinations will be made:

- Modification of the protocol.
- Modification of the information disclosed during the consent process.
- Providing additional information to past participants.
- Notification to current participants when such information might relate to participants' willingness to continue to take part in the research.
- Requiring current participants to re-consent to participation.
- Modification of the continuing review schedule.
- Monitoring of the research.
- Monitoring of the consent.
- Suspension of the research.
- Termination of the research.
- Referral to other organizational entities.

At any time during the inquiry process, the Investigator may request a meeting with the CHS staff, chair, or time at a convened CHS meeting to discuss the report/allegation.

14.3. Further Investigation by the CHS

Where the Initial Inquiry has resulted in a decision by the CHS that an investigation is warranted, a sub-committee of the CHS ordinarily will be formed for this purpose. The subcommittee will conduct an appropriate investigation, which may include, for example:

- Meeting with the Investigator;
- Visiting the study site;
- Consulting with appropriate experts;
- Reviewing the study files;
- Meeting with members of the research team, the Investigator's Department Head, study participants, or others;
- Consulting with the Institutional Official and/or other University and Faculty of Medicine officials.

Ordinarily, the sub-committee investigation will result in a report detailing their findings and recommendations, which is sent to the CHS Chair and Administrator, ORSP Director and Institutional Official upon completion, and reviewed at the next convened CHS meeting for further determination of actions.

14.4. Confidentiality

The CHS shares information relating to an open inquiry or investigation only with others at the University who have a need to know, those who are involved in or necessary to the investigative process, and with federal agencies as required.

14.5. Coordination with Other Investigative Process

As appropriate, the CHS will cooperate with other Harvard offices or committees, or with federal agencies such as OHRP or the FDA, which may be conducting an inquiry, investigation, review or audit involving a researcher about whom the CHS has knowledge or documentation. Where

the CHS and another University committee are conducting inquiries, investigations, reviews or audits involving the same or related allegations, the CHS will work to coordinate with the other committee to avoid duplication of effort.

14.6. Action Prior to Decision

At any time during an inquiry or investigation, the CHS may determine that it is necessary to suspend accrual of research participants or to suspend approval of research project(s) to ensure the protection of research participants, to preserve the integrity of the study, or to preserve the integrity of the Faculty of Medicine's human research protection program. Ordinarily, the CHS will not suspend approval of research studies until the Investigator has had an opportunity to respond to the allegation of non-compliance, but such opportunity may occur after the suspension where there is an immediate risk to participants.

14.7. Decision (including suspension or termination of approval)

The CHS will review all reports from the sub-committee's investigation and any information provided by the Investigator before reaching its final decision. Actions the CHS may take with respect to the investigation include, but are not limited to:

- Dismissal of the complaint;
- Imposition of remedial education for the Investigator and/or other personnel working on the study;
- Monitoring of research activities;
- Increased reporting to the CHS by the Investigator of his/her human studies activities;
- Restrictions on research practice, such as limiting the Investigator to conducting studies with only minimal risk or conducting research under supervision;
- Suspension of approval for one or more of the Investigator's studies;
- Termination of approval for one or more of the Investigator's studies;
- Referral to other Harvard officials or committees for possible further review.

14.8. Notification of CHS Determinations to Investigator, Institutional Officials, and Regulatory Agencies

The CHS Administrator or ORSP Director will notify the Investigator in writing of CHS determinations or actions and the reasons for the determinations and actions, ordinarily within two working days of the CHS meeting, although notification may be sooner depending on the severity of the event or the specifics of the CHS determination. However,

- If the CHS determines that a study needs to be suspended or terminated immediately, the Investigator will be notified by phone or email immediately after the meeting.
- In cases where enrollment in the study had been temporarily suspended and the suspension has been lifted, the Investigator will be notified immediately after the meeting by phone or email. Email messages will be sent with a "receipt confirmation" affixed to the message so that the CHS staff will know that the Investigator received the message.

The CHS is required to report to OHRP “any serious or continuing noncompliance with this policy [45 CFR § 46 and its subparts B, C and D] or the requirements or determinations of the IRB”, and thus the ORSP Director will forward decisions of the CHS within five working days to the Director of Compliance at OHRP and to the following other agencies or institutional officials, as appropriate:

- The Investigator’s Faculty of Medicine Department Head (and any additional Department Heads where the Investigator holds multiple professional appointments)
- The Faculty of Medicine Institutional Official. The IO will contact any additional institutional authorities, such as the Dean of the Faculty of Medicine, the President of the University, the Associate Provost for Research, the representative from the Office of the General Council, and Risk Management and Audit Services;
- The Sponsored Research Administration representative (where grants are supporting the research), and the Office of Technology Development (where corporate/company contracts are supporting the research). SPA or OTD will notify the study sponsor.
- Any additional University departments involved in the conduct of the research;
- Any additional IRBs and institutions involved in the research (for multi-site studies, subcontracts, IRBs and institutions relying on CHS review);
- The FDA, when the research is FDA-regulated; and
- Any additional federal agencies involved when the research is subject to those agencies.

Suspensions and terminations of research will be handled and managed as outlined in Section 15 of this policy document.

14.9. Retaliation

The CHS will inform Investigators that, in accordance with University policy and the law, they are prohibited from engaging in any kind of retaliatory action following allegations of research non-compliance or misconduct.

15. Suspension or Termination of Research

The CHS is authorized to suspend or terminate the approval of research that:

1. Is not being conducted in accordance with the CHS’s requirements; and
2. Has been associated with unexpected or serious harm to participants.

Suspension of research approval means a halt in all research activities until the CHS determines whether the research may commence (with or without modifications to the research), or whether it shall be terminated.

Termination of research approval means a permanent stop to the research and all related activities.

Suspensions or terminations of approval of research are determined at a convened CHS meeting. When the CHS votes to suspend or terminate the CHS approval of a research study based on a