HRPP Policy 700 Noncompliance, Suspension and Termination

Scope

The policy applies to all University investigators and research personnel who conduct research involving human subjects as well as University designees responsible for the oversight of human research.

This policy defines instances of noncompliance with Institutional Review Board (IRB) review and approval requirements, federal regulation, state law or University policy that must be reported by the investigator or others to the IRB. The policy also defines when and to whom the IRB and the University must report incidents of noncompliance.

Policy Statement

All members of a research team are required to conduct research projects in accordance with the protocol as approved by the IRB, and in accordance with federal regulations, state law, and University policy. Failure to do so constitutes noncompliance in the research endeavor, irrespective of the magnitude or intent of the deviation from the approved protocol. Principal Investigators are responsible for reporting incidents of noncompliance to the IRB along with any proposed corrective action plan to ensure the safety of research participants and others and future compliance with the approved protocol and to prevent reoccurrence.

Other entities responsible for the oversight of human research and University personnel, who believe in good faith that they are aware of an instance of noncompliance, also are required to report such incidents to the IRB office. The University prohibits undue influence, coercion or retaliation for good faith reporting of instances of noncompliance.

The IRB or qualified designee will promptly review and/or investigate reports of noncompliance and take appropriate actions as described herein.

Reason for the Policy

In most instances, changes to research procedures and interventions of IRB approved projects are anticipated by the Principal Investigator, who requests IRB review and approval of the modification prior to its being implemented. The IRB recognizes, however, that deviations from IRB approved protocols may occur during the conduct of research. The IRB also recognizes that noncompliance with established regulations, policies and procedures may also occur during the course of a research study. Therefore, this policy is established to ensure that the Principal Investigator and the IRB assess whether or not 1) an incidence of noncompliance that occurs during the conduct of the research exposes research participants and others to increased risk or reduced benefits, 2) the incident compromises the integrity of the study and 3) identification and implementation of corrective actions are necessary.
It should be noted that unapproved changes to protocols or other failures to comply with University IRB policies may also necessitate review and investigation by other appropriate University officials, which may result in disciplinary actions or sanctions.

Definitions

Noncompliance
Any action or activity associated with the conduct or oversight of research involving human participants that fails to comply with either the research plan as approved by a designated IRB, or federal regulations or institutional policies governing human subject research. Noncompliance may range from minor to serious, be unintentional or willful, and may occur once or several times. Noncompliance includes failure to have protocols reviewed by the IRB as required, protocol deviations in protocols approved by the IRB, including deviations made in the interest of a single participant such as changing a participant’s scheduled study visits. Noncompliance may result from the action of the investigator, research personnel, or a participant, and may or may not impact the rights and welfare of research participants or others or the integrity of the study. Complaints or reports of noncompliance from someone other than the Principal Investigator or study team personnel are handled as allegations of noncompliance until such time that the report is validated or found to be invalidated or dismissed.

Minor Noncompliance: Any behavior, action or omission in the conduct or oversight of research involving human participants that deviates from the approved research plan, federal regulations or institutional policies but, because of its nature, the research project, or subject population, does or did not:
1. harm or pose an increased risk of substantive harm to a research participant;
2. result in a detrimental change to a participant’s clinical or emotional condition or status;
3. have a substantive effect on the value of the data collected; and
4. result from willful or knowing misconduct on the part of the investigator(s) or study staff.

Examples of minor noncompliance may include, but are not limited to, the following:
- Changing study personnel without notifying the IRB;
- Shortening the duration between planned study visits;
- Implementing minor wording changes in study questionnaires without first obtaining IRB approval;
- Routine lab missed at scheduled visit and re-drawn later.

Serious Noncompliance: Any behavior, action or omission in the conduct or oversight of human research that, in the judgment of a convened IRB, has been determined to:
1. adversely affect the rights and welfare of participants;
2. harm or pose an increased risk of substantive harm to a research participant;
3. result in a detrimental change to a participant’s clinical or emotional condition or status;
4. compromise the integrity or validity of the research; or
5. result from willful or knowing misconduct on the part of the investigator(s) or study staff.

Examples of serious noncompliance may include, but are not limited to, the following:
- Conducting non-exempt research that requires direct interaction or interventions with human participants without first obtaining IRB approval;
- Enrolling participants who fail to meet the inclusion or exclusion criteria in a protocol that involves greater than minimal risk and that in the opinion of the IRB Chair, designee, or convened IRB, places the participant(s) at greater risk;
- Failing to submit a continuing review application to the IRB before study expiration for an ongoing study;
- Failing to obtain and/or document a participant’s informed consent provided the IRB has not granted a waiver of consent;
- Failing to retain copies of signed informed consent forms;
• Performing a study procedure not approved by the IRB; or failing to perform a required study visit or procedure that, in either case, may affect subject safety or data integrity;
• Failing to follow the safety monitoring plan;
• Enrolling study subjects after the IRB-approval of a study has expired; or
• Failing to report serious adverse events and/or unanticipated problems to the IRB in accordance with IRB Policy 710 Reporting Adverse Events and Unanticipated Problems.

Continuing Noncompliance: A pattern of noncompliance that, in the judgment of a convened IRB:
1. indicates a lack of understanding or disregard for the regulations or institutional requirements that protect the rights and welfare of participants;
2. compromises the scientific integrity of a study such that important conclusions can no longer be reached;
3. suggests a likelihood that noncompliance will continue without intervention; or
4. involves frequent instances of minor noncompliance, for example, repetitive protocol deviations.

Examples of continuing noncompliance may include, but are not limited to, the following:
• Repeated failure to respond to requests from the IRB to resolve an episode of noncompliance or a pattern of minor noncompliance, such as repetitive protocol deviations; or
• Consistently late submissions of continuing review applications or other items that require prompt reporting to the IRB.

Protocol Deviation: Any alteration/modification to an IRB-approved protocol made without prior IRB approval.

Note: Whether a protocol deviation qualifies as minor or serious noncompliance depends heavily on the specific facts of the situation. The examples of minor or serious noncompliance provided above are not intended to be an exhaustive list. The key to whether a protocol deviation will qualify as “minor” or “serious” depends upon whether, under the specific circumstances, it may adversely affect the rights and welfare of participants, harm or pose an increased risk of substantive harm to a research participant, have a substantive effect on the value of the data collected, or result from willful or knowing misconduct on the part of the investigator(s) or study staff.

Deviations from the study design and/or procedures that are due to a study participant’s non-adherence do not need to be reported to the IRB (e.g., study participant did not return for a scheduled study visit or participant refused to have blood drawn) unless they impact the participant’s safety or well-being, or if a pattern of protocol deviations indicate a need for changes in the protocol and/or informed consent document(s).

Suspension
A temporary cessation of one or more aspects of an IRB-approved study while the research is considered active. The activities to be suspended are determined by the specific concerns raised and the potential risks to participants of continuing or not continuing study procedures and must be either determined by or endorsed by the IRB. Suspensions may apply to some or all protocol activities such as stopping further enrollment of new participants or stopping all protocol-related activities. (45 CFR §46.113 and 21 CFR §56.113)

Termination
Withdrawal of IRB approval of a study. Following a determination to terminate a study, no study procedures may occur other than those identified by the IRB as necessary for the orderly closing of the study. (45 CFR §46.113 and 21 CFR §56.113)
Policy Sections

700.1 Reporting Noncompliance
Investigators, research personnel, or other individuals who believe that an instance of serious or continuing noncompliance has occurred must report it to the IRB within five (5) working days of becoming aware of the noncompliance. Upon the complainant’s request, his or her anonymity will be preserved to the extent practicable.

Principal Investigators are responsible for reporting instances of serious or continuing noncompliance that occur at Yale’s research site(s) to the IRB within five (5) working days of discovery. Principal investigators are also required to report results of audits or inspections conducted by sponsors, other external entities such as the Food and Drug Administration (FDA), or internal oversight committees, which indicate noncompliance. Investigators are not required to report instances of noncompliance that occur at other sites unless a Yale investigator serves as the lead Principal Investigator or managing investigator acting as the lead coordinating center for a multi-center study.

All instances of minor noncompliance should be summarized for the IRB at the time of continuing review. Alternatively, when appropriate, the summary may be a simple brief statement that there have been no protocol deviations or other instances of noncompliance.

Retaliation, coercion or undue influence against an individual for having made in good faith an allegation of noncompliance with human research regulations or policy is a violation of University policy and a offense subject to University disciplinary procedures. Concerns about possible retaliation or harassment must be reported to the IRB.

Reporting of instances of noncompliance by Yale or its IRBs are further defined in Section 700.4 below.

700.2 Investigation of Reports of Possible Noncompliance
All allegations or reports of possible noncompliance submitted to the IRB office will be reviewed and resolved according to Procedure 700 PR.3: Review and Investigation of Reports of Noncompliance

700.3 Consequences of Noncompliance
The IRB has the authority to take whatever action it deems appropriate, up to and including suspending or terminating approval of research that is not being conducted in accordance with IRB policies or with state and federal law, or that involves allegations of misconduct (see the Yale Policies and Procedures for Dealing with Allegations of Academic Misconduct at http://provost.yale.edu/node/732/attachment), or has been associated with unexpected serious harm to participants and others (e.g., unanticipated problems involving risks to participants or others). Except in cases of imminent harm to research participants or others, the IRB will not fully suspend approval of research studies until the investigator has had an opportunity to respond to the initial allegation(s) of noncompliance.

If participants are at immediate risk of harm and may be placed at further risk while awaiting the outcome of a convened IRB meeting, the IRB Chair(s) or designee has the authority to place one or all aspects of a study on-hold pending the decision of the fully-convened IRB.

700.4 Record Keeping and Further Reporting Requirements
Whenever an allegation or complaint of noncompliance warrants inquiry and further action as described in Procedure 700 PR.3: Review and Investigation of Reports of Noncompliance, notice of the allegation(s) will be provided to the investigator at the start of the investigation. Throughout the investigation, the investigator will be provided the opportunity to respond. In instances of
noncompliance, an investigative report and any appropriate corrective action taken with the investigator or research personnel (such as retraining or modification to research procedure) will be documented in the study file. The investigator will be provided written notification of the outcome of the investigation.

Allegations which are determined to not actually constitute noncompliance will nonetheless be documented in an IRB compliance file and an explanation of this determination may be provided to the complainant when the reviewer deems it appropriate.

When an incident is considered potentially serious or continuing noncompliance, the matter will be reported by either the HRPP Compliance Manager, IRB Chair or designee to the fully-convened IRB for deliberation regarding appropriate corrective actions including whether or not further information for or protection of research subjects and others is required.

For all incidents determined by the fully-convened IRB to be serious or continuing noncompliance, or when the fully-convened IRB makes a decision to suspend or terminate approval of any research study for any reason, the IRB will notify the following individuals within five (5) working days: the PI and where applicable, the Faculty Advisor, and the Department Chair involved in the research, and the Institutional Signatory Official. Where applicable, the IRB will also notify within thirty (30) days, the Office of Research Administration, the Office of Sponsored Projects, the U.S. Office for Human Research Protections (OHRP); the U.S. Food and Drug Administration (FDA); the funding agency and for other institutions participating in the research, the HRPP Administrator(s) and the IRB Chair(s) of those institutions. IRB suspension of any federally-funded studies must be reported to the appropriate federal department or agency.

Related Information

IRB Policy 710: Reporting Adverse Events and Unanticipated Problems

100 FR.6: Request for Approval of Amendment

700 PR.1: Reporting Noncompliance and Protocol Deviations to the IRB

700 PR.2: Soliciting and Responding to Research Participant Feedback and Concerns

700 PR.3: Review and Investigation of Reports of Noncompliance

700 PR.4 Suspension and Termination of Human Research

Federal Regulations: 45 CFR §46.103(b)(5); 45 CFR §46.113; 21 CFR §56.108(b); and 21 CFR §56.113
Contacts

<table>
<thead>
<tr>
<th>Subject</th>
<th>Contact</th>
<th>Phone</th>
</tr>
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<tbody>
<tr>
<td>Reporting Noncompliance</td>
<td>Human Investigation Committee</td>
<td>(203) 785-4688</td>
</tr>
<tr>
<td></td>
<td>Human Subjects Committee</td>
<td><a href="mailto:hrpp@yale.edu">hrpp@yale.edu</a></td>
</tr>
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<td></td>
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<td><a href="mailto:human.subjects@yale.edu">human.subjects@yale.edu</a></td>
</tr>
<tr>
<td>Oversight of Reports of Noncompliance</td>
<td>Institutional Signatory Official</td>
<td>(203) 785-3012</td>
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Roles and Responsibilities

**Human Investigation Committee (HIC)**

The HIC I, HIC II, HIC III and HIC IV serve as the four Institutional Review Boards or IRBs for biomedical human subjects research conducted at Yale University.

**Human Subjects Committee (HSC)**

The HSC serves as the Institutional Review Board for social, behavioral and educational research involving human subjects conducted at Yale University.

**Institutional Signatory Official**

The Associate Vice President for Research Administration serves as Institutional Signatory Official for Yale University. As such, the Institutional Signatory Official is responsible for ensuring that Yale fulfills the obligations and responsibilities promised in the terms of its Assurance.

Revision History