

# Policy on IRB Review of Protocol Deviations and Noncompliance for Non-exempt Research

## Background

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Principal investigators (PIs) are responsible for ensuring their research is conducted in accordance with the protocol approved by the Iowa State University Institutional Review Board (IRB) and with applicable University policies and non-University regulatory requirements. Failure to do so can have a negative effect on research participants—deviations from the approved protocol can jeopardize the safety, rights, and welfare of participants. Additionally, these deviations can place the University at risk of federal sanctions, up to and including losing the right to receive federal funding for human subjects research.

The ISU IRB recognizes that deviations from the approved protocol may occur during the course of a research study. All such deviations must be promptly reported to the IRB. This policy outlines the responsibilities for reporting deviations and the process by which these deviations will be reviewed.

## Scope

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This policy is applicable to non-exempt research involving human subjects.

## Definitions

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**Principal investigator (PI):** The individual responsible for the conduct of the research who is named as Principal Investigator on the IRB application. In cases where a co-PI/faculty supervisor is named per the policy on PI eligibility (e.g., student projects), the term “PI” also includes the individual listed as co-PI or Faculty Supervisor.

**Protocol or approved protocol:** The information included in the final approved IRB application, including any attachments, addenda, or appendices. Subsequent modifications and applications for continuing review are included in this definition. A copy of the approved protocol is provided to the PI along with an IRB approval letter when IRB review is complete.

**Protocol deviation:** Any departure from the IRB approved protocol. Protocol deviations may involve changes deemed necessary to eliminate apparent immediate hazards or risks to research subjects. Protocol deviations may be intentional or unintentional/unavoidable. The researcher’s failure to take reasonable steps to prevent protocol deviations may be considered intentional. Examples of intentional protocol deviations include, but are not limited to:

- Enrolling subjects who do not meet the eligibility criteria specified in the IRB approved protocol;
- Exceeding the number of subjects approved for enrollment, except where enrollment is outside of the control of the investigator (see examples of Unintentional/Unavoidable Deviations below);
- Changes to the approved recruitment or informed consent processes (e.g., failing to obtain signed consent, if signed consent was required; changing from an in-person to an online consent process; failing to obtain parental consent prior to enrolling children; etc.)

- Altering the wording in the approved informed consent document (beyond correction of typographical or grammatical errors);
- Changes or additions to survey or interview questions (beyond correction of typographical or grammatical errors);
- Removing survey or interview questions if the questions are designed to assess eligibility or otherwise relate to reducing risk;
- Adding procedures to the approved protocol (e.g., adding a condition, increasing the amount of blood to be drawn, or adding a blood draw, etc.);
- Removing or failing to perform protocol-required procedures when the change adversely affects risk to participants (e.g., failing to assess eligibility, failing to follow confidentiality measures, etc.);
- Changing the timing or order of procedures if timing or order are important for reducing risk to subjects, ensuring adequate time for informed consent, etc.;
- Providing compensation in a manner that differs from that in the approved protocol;
- Engagement of new study personnel in research activities prior to IRB approval of a personnel modification.

Unintentional or unavoidable protocol deviations are those that are largely outside of the reasonable control of the researcher(s). Examples of unintentional/unavoidable protocol deviations include, but are not limited to:

- A subject cannot attend an appointment which results in a change in timing of study procedures (when timing of procedures is part of the approved protocol, and the change does not adversely affect risk to subjects);
- An ineligible subject is enrolled in the study due to misinformation provided to the researcher;
- Exceeding the number of subjects in a study in limited circumstances when enrollment is outside the control of the researcher, (e.g., responses to a recruitment flyer with a link to an online survey exceed the number expected; in this case, the researcher cannot control who sees the flyer, how many individuals choose to respond, etc.).

**Noncompliance:** Failure to adhere to federal regulations or IRB and/or University requirements for human subjects research, including intentional protocol deviations, unless such deviations are necessary to eliminate apparent immediate hazards or risks to research subjects. Noncompliance can be minor, serious, and/or continuing as defined below.

**Minor noncompliance:** Minor noncompliance typically involves administrative oversights, non-substantive changes, etc. Any noncompliance that does, or reasonably may, adversely affect the rights, safety, or welfare of research subjects is **not** minor, even if no actual harm has occurred. Examples of minor noncompliance include, but are not limited to:

- Implementing non-substantive changes to approved procedures without IRB approval, such as:
  - Re-wording survey or interview questions where the meaning and scope of the question does not change;
  - Wording changes in recruitment materials or consent documents that do not change the meaning of the information provided or result in excluding any required element(s) of consent;

- Changing the order in which study conditions are administered, as long as a specific order is not necessary to minimize risk;
  - Enrolling subjects who do not meet the inclusion or exclusion criteria, except in the circumstances described as serious noncompliance below.
- Exceeding the approved number of subjects in a study

**Serious noncompliance:** Noncompliance that compromises the safeguarding of the rights, safety or welfare of human research subjects, or that does or may reasonably adversely affect the rights, safety, or welfare of human research subjects, even if no actual harm occurred. Acts that are determined by the IRB to be a flagrant or intentional violation of IRB requirements may also constitute serious noncompliance. The IRB will consider the circumstances surrounding the case when making a decision related to serious noncompliance. In general, examples of serious noncompliance include, but are not limited to:

- Failure to obtain IRB approval prior to initiating research activities with human subjects;
- Allowing unqualified or untrained individuals to perform research procedures or monitor subject safety;
- Failure to provide participants with all information necessary to constitute meaningful “informed consent” unless a waiver has been granted by the IRB;
- Enrolling a child in a research study without the informed consent of a parent or legal guardian unless parental consent was waived by the IRB;
- Enrolling subjects from a vulnerable population (i.e., children, prisoners, cognitively impaired individuals, etc.) when their inclusion is not described in the IRB-approved protocol and appropriate protections are not in place;
- Enrolling subjects who do not meet the approved eligibility criteria when doing so compromises the safety or well-being of the subjects;
- Failure to follow approved measures for protecting privacy and confidentiality when the failure presents any risk of harm to the research subject (such as harm to their reputation, social or psychological harm, risks of legal or civil liability, embarrassment, harm to workplace or family relationships, etc.);
- Implementation of changes to data collection procedures, without prior IRB approval, that increase risks to participants or adversely affect their rights, safety, or welfare (e.g., adding survey questions that collect sensitive information, substantially increasing the duration or intensity of exercise activities, adding plans to collect data from private records without subject consent, changes to confidentiality protections, etc.);
- Failure to report serious adverse events or unanticipated problems involving risks to subjects or others as required by IRB policy;
- Instructing or knowingly allowing subordinates (e.g., research assistants, employees, etc.) to engage in activities that are contrary to IRB or institutional policies or regulatory requirements;
- Providing false or intentionally misleading information to the IRB;
- Multiple protocol deviations suggesting a lack of oversight, inaction, or negligence such that research subjects’ rights, safety, or welfare could be adversely affected.

**Continuing noncompliance:** Repeated acts of noncompliance in the conduct of human subjects research suggesting a pattern indicative of a lack of understanding or attention to adequate safeguarding of the rights, safety, or welfare of human subjects or of University policies and/or non-University regulatory requirements for the conduct of human subjects research. Continuing noncompliance is characterized by the frequency rather than the magnitude of the noncompliance. Examples of continuing noncompliance include, but are not limited to:

- Repeated failure to obtain IRB approval prior to initiating human subjects research activities;
- Continually late submissions of continuing review applications resulting in repeated lapses in approval;
- Multiple instances of serious or minor noncompliance; this includes multiple incidents within a single project or multiple incidents by a single investigator across more than one project.

## Policy

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All intentional protocol deviations and instances of noncompliance must be promptly reported to the IRB chair(s) or ORR staff. Written reports are preferred, although reports by telephone are acceptable. Instances involving actual or imminent harm to research subjects or others must be reported immediately.

Reports of protocol deviations and/or noncompliance may come from many sources. The PI may self-report such instances and is encouraged to do so. Self-reporting will be looked upon favorably during assignment of corrective actions. In other cases, a research subject may submit a complaint, a member of the research team may report an incident, or an incident may be discovered during IRB review or post-approval monitoring. Research staff who become aware of protocol deviations or noncompliance should notify the PI as soon as possible. In cases where research staff prefer not to notify the PI, reports can be submitted to [IRB@iastate.edu](mailto:IRB@iastate.edu). Alternately, any individual may report concerns to ISU's Compliance and Ethics Hotline.

Instances discovered during IRB review or via post-approval monitoring will be reported by IRB staff to the Director, Office of Research Ethics (DORE), after confirmation that a protocol deviation or noncompliance event has occurred. Immediate reporting is required in cases where evidence suggests human subjects may be at risk.

A PI may also be required to report incidents to his/her department or the study sponsor; PIs are responsible for knowing reporting requirements that may exist beyond those specified by the IRB and for following those requirements.

## IRB Review Process

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Upon receipt of a report of a protocol deviation or noncompliance, IRB staff will forward the information to the DORE and the IRB Co-Chair as needed to ensure that both parties are informed of the incident. In cases involving serious harm to subjects or where immediate action is needed to prevent such harm, other responsible parties should be consulted if the IRB Co-Chair and/or DORE are unavailable. These individuals may include the Associate or Assistant Vice President(s) (AVPR) for Research, the Vice President for Research (VPR) who serves as Institutional Official (IO), and/or the IRB Faculty Chair or Vice-Chair.

### Initial review

The DORE will, in consultation with the IRB Chair and/or Co-Chair, determine the initial course of action. Initial action includes a preliminary evaluation of the allegations/concerns to determine whether the allegations are based in fact. If the DORE, in conjunction with the IRB Chair and/or Co-Chair, deem an allegation/concern unsubstantiated, it may

be decided that no additional action is needed, that further inquiry is necessary, or that the issue should be presented to the convened IRB.

If, upon initial review, the DORE, in consultation with the IRB Chair and/or Co-Chair, determine that the alleged incident is based in fact, a preliminary assessment is made related to whether the issue involves a protocol deviation or noncompliance. When needed, additional information will be gathered at this stage by the DORE, IRB Chair(s), or ORE staff. The VPR or AVPR may be consulted when necessary (e.g., additional resources are needed to adequately complete the investigation, the incident may also involve academic misconduct, etc.). Temporary suspension of IRB approval may be enacted by the parties involved in the initial review if deemed necessary to prevent harm to subjects.

## Sub-committee review

Review of the incident is referred to a subcommittee consisting of the DORE, IRB Chair, Co-Chair, Vice-Chair, and Post-Approval Monitor who review the allegations and related materials during a subcommittee meeting to determine whether an incident constitutes noncompliance. If an incident is determined to constitute minor noncompliance, corrective actions will be imposed to resolve the noncompliance during this initial subcommittee review. Such actions may include, but are not limited to:

- Acknowledgement of the report with no further action needed;
- A warning or reminder to the PI with instructions on how to avoid future incidents, clarifications regarding requirements and rules, etc.;
- Requiring additional training regarding human subjects research;
- Requiring submission of a modification application or report of an adverse event/unanticipated problem;
- Requiring the PI to submit a corrective action plan;
- Directing post-approval monitoring visits or compliance audits.

If the PI complies with these actions, additional review by the convened IRB is not required. A report summarizing these incidents and the outcomes will be provided to the convened IRB but will not require IRB action. If the IRB disagrees with the determination of minor noncompliance, it may request additional information or further review by the convened IRB.

## Committee review

Review of the incident will be referred to the convened IRB review in the following circumstances: (1) if it is determined during the initial review that the incident involves serious or continuing noncompliance; (2) if there is uncertainty or disagreement by the initial reviewers about the level of noncompliance; (3) if the investigator fails to cooperate with the actions required to correct minor noncompliance; or (4) if the IRB disagrees with the determinations made during the initial review.

A report describing the potential noncompliance, along with relevant materials will be shared with the IRB to allow the committee to review and assess the case. The PI will be informed of the committee review and invited to attend the meeting and discuss the report with the IRB. Reasonable efforts will be made to accommodate scheduling needs of the PI. Actions by the IRB will include a formal determination of the type of noncompliance (i.e., serious and/or continuing). If the IRB determines that neither serious nor continuing noncompliance has occurred, the IRB may dismiss the allegations or determine the noncompliance is minor and delegate handling of corrective actions to the DORE.

In cases where the IRB determines that serious and/or continuing noncompliance has occurred, the IRB will recommend corrective actions to be considered for implementation by the Institutional Official. When appropriate, a reasonable timeframe for implementation of these actions should also be established. Such actions may include, but are not limited to:

- A warning or reminder to the PI with instructions on how to avoid future incidents, clarifications regarding requirements and rules, etc.
- Requiring additional training regarding human subjects research
- Requiring the investigator to submit a corrective action plan
- Disallowing use of the data collected as a result of the non-compliant actions
- Directing post-approval monitoring visits or compliance audits
- Restrictions on serving as an investigator on human subjects protocols (e.g., requiring a supervising co-PI, barring future eligibility as PI, etc.)
- Notification of study participants
- Requirement that participants re-consent to participation

The IRB may also require modifications to the protocol or informed consent process, more frequent review, or that all future submissions be reviewed by the convened IRB. The IRB may also suspend or terminate approval of protocols found to be noncompliant if deemed necessary to protect human subjects. The welfare of currently enrolled subjects will be taken into account when considering suspension or termination of approval.

The IRB may refer the issue to other organizational entities, such as legal counsel, risk management, the Research Integrity Officer, etc., in lieu of or in addition to the recommended corrective actions.

Principal investigators are encouraged to play an active role in the noncompliance review process. The PI will be provided with an opportunity to review and comment on reports provided to the IRB for consideration. Such comments must be received by the deadline established by the DORE. The PI will be invited to address the IRB during the meeting where the noncompliance review occurs. A report summarizing the IRB's determinations and recommended corrective actions will be provided to the PI for review and comment prior to submission to the Institutional Official for consideration of corrective actions. Comments must be provided by the deadline established by the DORE. The PI's comments will be forwarded to the IRB for reconsideration if the comments reveal new factual information or other circumstances that are reasonably likely to effect the IRB's determinations or recommendations.

## Institutional Official review

In cases of serious or continuing noncompliance, the Institutional Official will receive a final report documenting the noncompliance review process, the IRB's recommendations, and any response to these recommendations by the PI. The Institutional Official may accept, revise, add to, or reject any or all of the IRB's recommended corrective actions but may not change the IRB's determinations related to the level of noncompliance or overturn the IRB's decision to suspend or terminate IRB approval, to require modifications to the approved protocol, or to require more frequent or higher level IRB review. The final report documenting the Institutional Official's actions will be provided to the PI, the PI's department chair/head, supervising faculty (if applicable), the IRB Chair(s), and for the IRB file. Other internal and external reporting requirements are outlined below.

## Other review

There may be instances where noncompliance rises to the level of academic misconduct. Academic misconduct charges are processed in accordance with ISU policy.

## Follow-Up

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Investigators are responsible for ensuring the corrective actions outlined in the final noncompliance report are implemented by the timeframes established in the report. The Post-Approval Monitor (PAM) will oversee the progress of implementation with the assistance of the DORE and IRB Co-Chair as needed. Failure to meet the conditions established in the report will result in additional review by the IRB and possibly termination or suspension of IRB approval.

## Internal reporting

The PI's department chair will be provided with a copy of the finalized report in cases determined to be serious or continuing noncompliance. Other ISU offices will be informed of the IRB's noncompliance review as necessary to conduct the review or meet reporting requirements. For example, the Office of Sponsored Programs may be contacted for advice on requirements for sponsored research related to reporting noncompliance.

## External reporting

When applicable, incidents of serious or continuing noncompliance must be reported to the Office of Human Research Protections per the requirements set forth in 45 CFR 46.103(b)(5) and the funding agency or sponsor in accordance with their requirements. Similarly, reports of serious or continuing noncompliance must be provided to the Food and Drug Administration for FDA-regulated research in accordance with 21 CFR 56.108(b), 21 CFR 56.113, 21 CFR 812.150. When appropriate, preliminary reports may be filed pending final resolution of the case.

### Document History

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