

2.4 IRB Review of Changes in Previously Approved Research

1.0 Purpose

The purpose of this policy is to describe the Organization's requirements for IRB review of changes in previously approved research, including single subject protocol deviations.

2.0 Policy

It is the policy of the Organization that:

- 2.1. Any proposed change in a research activity must be reviewed and approved by the IRB prior to implementation in accordance with 45 CFR 46.108(a)(3)(iii) and/or 21 CFR 56.108(a)(4) except when: 1) a change is necessary to eliminate an apparent immediate hazard to the subject(s), or 2) a subject needs to be advised immediately of significant new information.
 - 2.2. Protocol changes that are minor are eligible for expedited review in accordance with 45 CFR 46.110(b)(1)(ii) and/or 21 CFR 56.110(b)(2), as applicable.
 - 2.3. Single subject protocol deviations (SSPDs) represent a change in protocol for a single subject and must be reviewed by the IRB prior to implementation; single subject protocol deviations that are minor may be eligible for expedited review by the Executive Chair, IRB Chairs, or designee.
 - 2.4. Administrative changes do not require IRB review and can be reviewed and approved by IRB analysts and/or staff, in consultation with the IRB Executive Chair as necessary.
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3.0 Definitions

- 3.1. Major change in protocol is a change that, in general, adversely affects the risk-benefit relationship by appreciably increasing risks, or appreciably decreasing potential benefits, or impacts the process of consent in a manner that might affect a reasonable person's willingness to participate in the research. Examples of specific activities which constitute major changes are listed in the appendix to this policy.
- 3.2. Minor change in protocol is a change that is not characterized as major as above. Examples of specific activities which constitute minor changes are listed in the appendix to this policy.

- 3.3. Single subject protocol deviation is a change in an IRB-approved protocol which is permitted for an individual subject when it is in the best interest of that subject and/or is necessary for research purposes.
 - 3.4. Administrative change is a change which has no impact on the health or welfare of subjects, or on the risk/benefit relationship of the research. Administrative changes include (but are not limited to) correction of typographical errors, clarification or editorial updates to the protocol and/or ICF, administrative changes in the protocol by the sponsor, changes in telephone numbers or other contact information, and addition or deletion of study personnel other than the Principal Investigator.
 - 3.4.1. Changes to studies for which the Organization is relying on another IRB (CIRB studies) are considered administrative changes.
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4.0 Investigator Responsibilities

- 4.1. A Change Request (other than Single Subject Protocol Deviations) must be submitted by the PI thru RSS in accordance with HRPP policy 2.1 (Submission of Items for Review by the IRB).
- 4.2. A Single Subject Protocol Deviation Request must be submitted by the PI thru RSS to the ORA and be approved by either the IRB Executive Chair, IRB Chair or designee or the full IRB prior to the initiation of the deviation.
 - 4.2.1. The PI or designee is responsible for requesting approval for the single subject protocol deviation from the study sponsor (if appropriate) in advance of submission to the ORA.
 - 4.2.2. Initiation of a single subject protocol deviation without IRB approval (unless necessary to eliminate an apparent immediate hazard to the subject, or to provide significant new information as above) represents noncompliance and will be addressed in accordance with HRPP policy 8.4 (Review of Noncompliance Involving the PI and Study Personnel).
- 4.3. Changes required to eliminate an apparent, immediate hazard to the subject(s) may be implemented without prior IRB approval in accordance with 45 CFR 46.108(a)(3)(iii) and/or 21 CFR 56.108(a)(4).
 - 4.3.1. The ORA must be notified of the action as soon as possible, but no later than two business days from the time the change was initiated.
 - 4.3.2. If the change was initiated for all subjects, a Change Request (including a revised IRB application and other required documents) must be submitted in accordance with this policy.
 - 4.3.3. If the change was initiated for a single subject, the Single Subject Protocol Deviation Request must be completed and submitted.
- 4.4. Changes involving immediate disclosure of significant new information (for example, an important new risk) which would likely affect a subject's decision to continue participating in research, may be implemented without prior IRB approval in accordance with 45 CFR 46.108(3)(iii) and/or 21 CFR 56.108(a)(4) and HRPP policy 5.1 (Obtaining Informed Consent from Research Subjects).
 - 4.4.1. The ORA must be notified of the action as soon as possible, but no later than two business days from the time the change was initiated.
 - 4.4.2. No new subjects may be accrued without IRB approval of a revised ICF that includes the relevant information.

5.0 IRB and/or ORA Responsibilities

- 5.1. Change Requests will be processed for review in accordance with HRPP policy 2.1 (Submission of Items for Review by the IRB).
- 5.2. Change Requests (including SSPDs) that are minor may be reviewed and approved thru an expedited process in accordance with HRPP Policy 2.3 (Expedited Review) and 2.5 (Criteria for IRB Approval)
- 5.3. Change Requests (including SSPDs) that are major will be reviewed by the convened IRB (if the protocol was initially reviewed and approved by the convened IRB) or by the expedited process (if the protocol is eligible for expedited review per HRPP 2.3 (Expedited Review) in accordance with HRPP 2.5 (Criteria for IRB Approval).
- 5.4. Administrative changes may be reviewed and processed by an IRB Analyst or ORA staff.
- 5.5. The date of continuing review is not changed based on the date of IRB approval of a Change Request.
- 5.6. Changes in protocol for research classified as exempt per HRPP policy 2.6 (Exempt Research) do not need to be submitted to the ORA provided the changes do not:
 - 5.6.1. Affect the risk-benefit relationship of the research
 - 5.6.2. Pose new risks which are greater than minimal
 - 5.6.3. Constitute a new risk to privacy or confidentiality
 - 5.6.4. Involve sensitive topics (including but not limited to personal aspects of the subject's behavior, life experiences or attitudes)
 - 5.6.5. Involve deception
 - 5.6.6. Target a vulnerable population (as defined in HRPP Policy 4.1 Additional Protections for Vulnerable Populations)
 - 5.6.7. Include prisoners or children
 - 5.6.8. Otherwise suggest loss of the exempt status of the research.

Note: Investigators are encouraged to contact the ORA to discuss whether changes to exempt research requires review by ORA.

- 5.7. Changes to studies for which the Organization is relying on another IRB (CIRB studies) are reviewed administratively.
- 5.8. The convened IRB will be notified of (1) changes in protocol, including SSPDs, approved thru the expedited process, (2) changes implemented without prior IRB approval to eliminate an apparent, immediate hazard to the subject(s), or (3) changes involving immediate disclosure of significant new information, and will take any additional actions necessary to protect human subjects.

Examples of Major and Minor Changes in Protocol or Single Subject Protocol Deviations (per Sections 3.1 and 3.2) Examples of Major Changes:

- Changes in inclusion or exclusion criteria that broaden eligibility (i.e., broadening the range of the inclusion criteria or narrowing the range of the exclusion criteria) when risks to new subjects will be different than to previously eligible subjects
- Addition of a vulnerable population (e.g., children, cognitively impaired, prisoners, socially or educationally disadvantaged, students)
- Increase in target accrual of subjects in studies where UNMC, CN and/or UNO are the only sites
- Increase in study wide accrual of subjects in a multi-institution study
- Increase in subject payment amount that exceeds criteria in HRPP Policy
- Change in study design, where such change might affect risk, potential benefit to subject or scientific value or validity
- Alterations in the dosage or route of administration of an administered drug
- Addition of research activities that carry greater than minimal risk
- Change in research activities where the change might negatively impact the potential benefit of the research (for example, change from one questionnaire to another which is not substantively similar, or to a non-validated questionnaire; change from CT-based staging to clinically based staging of a tumor)
- Modification of research questionnaires or data collection instruments/processes to collect sensitive information (for example, depression, sexuality, illegal activities)
- Addition of an element that may affect subject confidentiality (for example, specimen banking or genetic testing; addition of focus groups or identifiable surveys)
- Extending substantially the duration of exposure to the test material or intervention
- Deletion of laboratory tests, monitoring procedures, or study visits directed at the collection of information for safety evaluations
- Addition of serious adverse events, serious UADEs or other significant risks to the Informed Consent process or form
- Addition of a new (additional) consent form
- Addition of a qualified investigator with a disclosable conflict of interest
- Changes, which, in the opinion of the IRB chairperson or their designee, do not meet the criteria or intent of a minor modification

Note: Multiple minor changes in the protocol, instruments, and/or consent may, together, be considered a major change subject to convened IRB review.

Examples of Minor Changes:

- Changes in inclusion or exclusion criteria that narrow eligibility (that is, narrowing the range of the inclusion criteria or broadening the range of the exclusion criteria).

Note: such changes should not appreciably reduce the likelihood that the research can be completed in a timely manner

- Changes in inclusion or exclusion criteria that broaden eligibility (that is, broadening the range of the inclusion criteria or narrowing the range of the exclusion criteria) when the investigator provides evidence that risks to the new subjects will not be different than to previously eligible subjects
- Increase in local enrollment of subjects in a multi-institution study without a change in the overall study wide enrollment target
- Addition of research activities that constitute no more than minimal risk.

Note: addition of clinically indicated procedures where data will be used for research purposes (that is, where the incremental risk is no more than minimal) are considered a minor change.

- Addition of research activities that would be eligible for expedited IRB review (per §_.110(b)(ii)) under categories 1-7 (unless specifically defined as “major” above)
- Alterations in the dosage form (for example, tablet to capsule or oral liquid) of an administered drug, provided the dose and route of administration are unchanged
- Decrease in the number or volume of biological samples collection, provided that such a change does not affect the collection of information related to safety evaluations
- Decrease in the length of hospitalization or number of study visits, provided such a decrease does not affect the collection of information related to safety evaluations
- Alterations subject payment schedule, provided such payments remain fairly pro-rated
- Increase in subject payment amount provided such amounts are within criteria in HRPP Policy
- Changes to improve the clarity of statements or to correct typographical errors in the protocol, CF or any questionnaire, provided that such a change does not alter the content or intent of the statement
- Changes in recruitment materials and advertising, provided such items continue to satisfy criteria in HRPP Policy
- Revision of subject identification and recruitment strategy to include use of the NM or CN Conditions of Treatment Opt-In database
- Consent form modifications that add or remove information from the consent form so that it is consistent with an already approved IRB requirement
- Updating a consent form using IRB approved boiler plate language

- Addition or deletion of study personnel
 - Change in Principal Investigator, provided the new PI is qualified by education, training, experience and licensure (as applicable) to assume overall responsibility for the safe and proper conduct of the research
 - Addition of study sites that have a valid FWA and Reliance agreement as appropriate; or that serve as performance sites where informed consent will not be obtained; or that serve as performance sites where informed consent will be obtained by a UNMC, CN or UNO investigator.
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DOCUMENT HISTORY:

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? Revised 1/18/2025 – clarified level of review associated with changes in PI and/or research personnel; clarified that changes to CIRB protocols are considered administrative changes; removed references to pre-2018 HHS regulations; stylistic changes {Approved Rusty McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

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