2.4 IRB Review of Changes in Previously Approved Research

1.0 Purpose

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

2.0 Policy

- **2.1.** It is the policy of the Organization that any proposed change in a research activity must be reviewed and approved by the IRB prior to implementation in accordance with the requirements of 45 CFR 46.103(b)(4) (rev 45 CFR 46.108(3)(iii)); 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. Administrative changes do not require IRB review and can, accordingly, be approved by ORA.
- **2.2.** It is the policy of the Organization that protocol changes that are minor are eligible for expedited review under the provisions of HHS regulations at 45 CFR 46.110(b)(2) (rev 45 CFR 46.110(b)(1)(ii)) and FDA regulations at 21 CFR 56.110(b)(2), as applicable.
- **2.3.** It is the policy of the Organization that single subject protocol deviations 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 under HHS or FDA regulations as above.

3.0 Definitions

- **3.1.** ***Major change in protocol*** is a change that, in general, adversely affects the risk-benefit relationship by adding appreciably increasing risks, or appreciably decreasing potential benefits, or impacts the process of consent in a manner that might effect a reasonable person's willingness to participate in the research. 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 per 3.1 above. Specific activities which constitute major 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 (e.g., data completion).
- **3.4.** ***Administrative change*** is a change where one of the following criteria must be met: 1) the proposed change has no impact on human subject protection, or 2) the proposed change is necessary to clarify or provide only editorial updates to the protocol and/or ICF. These changes can be reviewed and approved by IRB administrators/staff in consultation with the IRB Executive Chair as necessary.
  Examples of administrative changes include: changes in telephone numbers, deletion of study personnel, correction of typographical errors, or minor administrative changes in the protocol by the sponsor.

4.0 Procedures for Change Request in Protocol (other than Single Subject Protocol Deviation)

- **4.1.** The PI must submit a Change Request in accordance with HRPP policy 2.1 (Submission of Items for Review by the IRB).
- **4.2.** The Change Request will be processed for review in accordance with HRPP policy 2.1 (Submission of Items for Review by the IRB).
- **4.3.** Administrative changes are reviewed and processed by an IRB Administrator or ORA staff.
- **4.4.** The procedure for review via full IRB review or expedited review is in accordance with HRPP policies 2.2 (Full IRB Review) and 2.3 (Expedited Review), respectively.
- **4.5.** The criteria for approval via full IRB review or expedited review is in accordance with HRPP policies 2.2 Section 3.9 (Full IRB Review) and 2.3, Section 5.4 (Expedited Review), respectively.
- **4.6.** The date of continuing review is not changed based on the date of IRB approval of a Change Request.
- **4.7.** 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:
  - **4.7.1.** Affect the risk-benefit relationship of the research
  - **4.7.2.** Pose new risks which are greater than minimal
  - **4.7.3.** Constitute a new risk to privacy or confidentiality
  - **4.7.4.** Involve sensitive topics (including but not limited to personal aspects of the subject's behavior, life experiences or attitudes)
  - **4.7.5.** Involve deception
  - **4.7.6.** Target a vulnerable population (as defined in HRPP Policy 4.1; Additional Protections for Vulnerable Populations)
  - **4.7.7.** Include prisoners or children
  - **4.7.8.** 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.

5.0 Procedure for Single Subject Protocol Deviation*

- **5.1.** A Single Subject Protocol Deviation Request must be submitted 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.
- **5.2.** The PI/authorized study personnel should request approval for the single subject protocol deviation from the study sponsor (if appropriate) in advance of submission to the ORA.
- **5.3.** The IRB Executive Chair, IRB Chair or designee will obtain any additional information required for the review.
- **5.4.** Single subject protocol deviation requests that are more than minor cannot be approved by the IRB Executive Chair, IRB Chair, or designee and will be referred to the full IRB by the designated IRB Administrator for review and approval.
- **5.5.** Single subject protocol deviation requests that are minor will be reviewed and approved by the IRB Executive chair, IRB Chair, or designee.
- **5.6.** All minor single subject protocol deviation requests approved by IRB Executive Chair, IRB Chair, or designee will be submitted to the IRB for their notification.
- **5.7.** Initiation of a single subject protocol deviation without IRB approval represents noncompliance and addressed in accordance with HRPP policy 8.4 (Review of Noncompliance Involving the PI and Study Personnel).

6.0 Changes in a research activity requiring immediate implementation

- **6.1.** If the change is required to eliminate an apparent, immediate hazard to the subject(s), the PI may implement the change without prior IRB approval in accordance with 45 CFR 46.103(b)(4) (rev 45 CFR 46.108(3)(iii)); 21 CFR 56.108(a)(4).
- **6.2.** The ORA must be notified as soon as possible, but no later than two business days from the time the change was initiated.
  - **6.2.1.** If the change was initiated for all subjects, a Change Request, the revised IRB application and other required documents must be submitted in accordance with this policy.
  - **6.2.2.** If the change was initiated for a single subject, the Single Subject Protocol Deviation Request must be completed and submitted.
- **6.3.** The full IRB will be notified of all changes implemented without prior IRB approval and will take any additional actions necessary to protect human subjects.

7.0 Provision of new information to subjects which requires immediate implementation

- **7.1.** If a change involves immediate disclosure of significant new information (e.g., an important new risk) which is essential to a subject's decision to continue participating in research, the investigator is authorized to implement the change without IRB approval in accordance with 45 CFR 46.103(b)(4) (rev 45 CFR 46.108(3)(iii)); 21 CFR 56.108(a)(4) and HRPP policy 5.1 (Obtaining Informed Consent from Research Subjects).
- **7.2.** The ORA must be notified as soon as possible, but no later than two business days from the time the change was initiated. No new subjects can be accrued without IRB

approval of a revised ICF that includes the relevant information.

- **7.3.** If a Change Request is submitted to the ORA which includes a revised ICF or an addendum ICF containing significant new information involving risk which is germane to a subject's decision to continue participating in the research and the change is not eligible for expedited review, the ORA will submit the RFC for review at the earliest possible full Board meeting.
- **7.4.** The full IRB will be notified of all changes implemented without prior IRB approval and will take any additional actions necessary to protect human subjects.

Appendix to HRPP Policy 2.4 (Changes in Previously Approved Research)

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. CHMC 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 (e.g., 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 (e.g., depression, sexuality, illegal activities)

? Addition of an element that may affect subject confidentiality (e.g., 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 his/her 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 (i.e., 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 (i.e., 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 (i.e., 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 (e.g., 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

? Alternations 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 Nebraska Medicine 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 qualified investigators or personnel

? 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, CHMC or UNO investigator.

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