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Section 7: Continuing Review of Human Subjects Research Activities

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7.1 Requirement for Continuing Review

Any research activity involving the use of human subjects that has been classified as more than minimal risk by the convened Institutional Review Board (IRB) or, under certain circumstances, warrants additional oversight for a minimal risk project, is subject to continuing review. Time intervals for such reviews shall be made at the discretion of the IRB based on the anticipated risks to subjects.

Effective January 21, 2019, per the revised Common Rule, continuing review is no longer required for studies that qualify for or have been approved through expedited review. Studies reviewed and approved through expedited review prior to the January 21, 2019 date will not undergo additional continuing review unless the IRB determines that additional oversight is required.

Since the research regulations were revised, formal continuing review is no longer required for expedited review protocols. The DU IRB established a Post Approval Monitoring Program designed to periodically and randomly check on the status of studies (See **Section 22: Post Approval Monitoring Program**).

The principal investigator (PI) must seek approval of continuation for studies that the convened board requires **unless** all of the following are true:

1. The research is permanently closed to the enrollment of new subjects.
2. All subjects have completed all research-related interventions.
3. Collection and analysis of private identifiable information and/or identifiable biospecimens has been completed.

As a courtesy, the IRB will send reminders to PIs whose study is required to submit a continuing review before the study expires. **The PI will continue to receive reminders until the study renewal has been formally reviewed and approved**. However, it is ultimately the PI's

responsibility to complete and submit the IRB Continuing Review Form in time for IRB review prior to the study's expiration of approval.

If a protocol requires a continuing review, it must be reviewed and approved at a convened meeting of the IRB. However, if the research initially did not qualify for expedited review, the IRB may designate the protocol as minimal risk and require that the project continue to undergo continuing review or choose to remove the continuing review requirement. This determination can be made at the time of initial review or at a subsequent continuing review.

No research protocol may continue after approval has expired until final approval for continuation is granted by the convened board.

7.2 Submission Requirements

Continuing reviews must be submitted through **IRBNet**, the electronic submission system. Full board review studies and expedited studies under specific circumstances require the following to be submitted for continuing review:

1. Completed IRB continuing review form which includes the following information:
    a. Number of participants accrued.
    b. A summary since the last IRB review of:
        i. Adverse events, untoward events, and adverse outcomes experienced by participants.
        ii. Unanticipated problems involving risks to participants or others.
        iii. Participant withdrawals.
        iv. The reasons for withdrawals.
        v. Complaints about the research.
        vi. Amendments or modifications.
        vii. Any relevant recent literature.
        viii. Any interim or significant findings that might affect participants' willingness to continue.
        ix. Any relevant multi-center trial reports.
        x. The Researcher's current risk-potential benefit assessment based on study results.
2. Consent form, if applicable:
    a. If changes are being made the PI must submit an amendment application as part of the Continuing Review submission. (See **Section 8 Amendment of Human Subjects Research Activities**)
    b. Submit a copy of the consent that highlights changes (i.e. Track Changes) and provide a clean copy of the consent.
3. Other documents relating to the research activities that have not been reviewed by the IRB during initial review or by an amendment to the protocol.
4. Renewal letters from cooperating IRBs as relevant (e.g., site still operational). If the site(s) in question did not have an IRB of record and thus submitted an official letter granting permission for the researcher to conduct the research, then a second letter is not required.
5. Data and Safety Monitoring Plan update if initially requested by the IRB.

If a protocol receives a status of "Deferred - Modifications Required" and the required documents are not submitted within 30 days, or no communication has been received from the PI during that timeframe, the protocol will be administratively closed and receive a permanent status of "Closed - Expired." PIs requesting re-review/re-consideration of their protocols are required to complete the initial submission process.

7.3 Continuing Review of Research Appropriate for Expedited Review

Effective January 21, 2019, the DU IRB no longer requires the submission of continuing reviews

for **expedited projects,** regardless of funding source**.** Protocols that have been approved through the expedited review process may be required to submit continuing review if special circumstances warrant additional oversight.

7.3.1 Review of Protocol

Continuing reviews for expedited studies may be required, and this will be determined during the initial review or in response to an unanticipated event that may have occurred during the course of the study. Only under special circumstances, as requested by the convened board, will these expedited studies be initially reviewed by the IRB Compliance Analyst or other designee for completeness and congruence with the currently approved protocol, and it may be referred to the convened IRB for review and continuation.

7.3.2 Review of Materials

The materials that will be reviewed as part of an expedited continuing review application include, but are not limited to the materials listed in **Section 7.2**.

7.3.3 Reviewer Considerations

1. The research falls into one or more of the categories of research eligible for review using the expedited procedure and meets applicable criteria for expedited review:
    a. The research procedures present no more than minimal risk to subjects. For continuing review, this applies to current and future procedures and does not include procedures no longer being performed. These criteria do not apply to Category 8(b).
    b. The identification of subjects or their responses will not reasonably place them at risk of criminal or civil liability or be damaging to their financial standing, employability, insurability, reputation, or be stigmatizing unless reasonable and appropriate protections will be implemented so that the risks related to invasion of privacy and breach of confidentiality are not greater than minimal For continuing review, this applies to current and future procedures and does not include procedures no longer being performed. These criteria do not apply to Category 8(b).
    c. The research is not classified.
2. The regulatory requirements for approval are met. (refer to **Section 7.2**)

7.3.4 Possible IRB Protocol Determinations

Either the IRB Chair or a designated review will render one of the following determinations for each expedited protocol:

1. **Approved**: It is approved as written with no explicit conditions.
2. **Modifications Required:** The protocol requires minor changes. These modifications and clarifications will be communicated to the PI and must be completed and documented prior to continuing the research.
3. **Refer to Full Board:** The information in the submitted documents has deficiencies that the reviewer is unable to approve. Per regulations, the designated review is not allowed to render a decision of disapproval. Protocol disapprovals may only be rendered by the IRB at a convened meeting. A notification will be sent to the PI regarding the action to refer their continuing review report to the full board.

7.3.5 Length of Review Period

If an expedited protocol is referred to the full board for continuing review, the interval for continuing review will be determined at the convened meeting. Expedited protocols that are issued an expiration date may also be issued a Next Report Due date that is established less than the established review period timeframe.

7.3.6 Notification of the IRB of Expedited Review

A list of expedited protocols required for continuation through full board review will be posted on the IRB agenda and in the meeting minutes.

7.4 Continuing Review at an IRB Convened Meeting

7.4.1 Assignment of Primary and Secondary Reviewers

Upon receipt, each protocol will have a reviewer(s) from the IRB roster who will review the protocol in detail and act as a liaison between the IRB and the PI. Primary and secondary reviewers are assigned, as closely as possible, according to their expertise with the research being proposed and/or the subject population(s) being enrolled, and their appropriate scientific or scholarly expertise to review the protocol. Protocols are not assigned to reviewers who have a conflict of interest or have academic appointments in the same administrative unit as the PI. The primary and secondary reviewers may contact the investigator, co-investigators, other IRB members, or outside sources as necessary to ensure a thorough evaluation of risks and benefits of the proposed research.

At times, the IRB may not have the appropriate expertise to review the study for scientific or scholarly validity. In those cases, the IRB Chair will consider who in the University faculty or community has the appropriate scientific expertise to serve as an expert consultant to perform an in-depth review of the study. Consultants will disclose any conflict of interest (COI) prior to performing the review, and those with a COI will not be used for protocol review.

7.4.2 Distribution of Submitted Documents

The following continuing review documents are provided to all IRB members (including alternate members, if attending) and consultants for review:

1. IRB Continuing Review Application (Status report) containing the following information:
    a. The number of participants accrued;
    b. Adverse events and outcomes experienced by participants;
    c. Unanticipated problems involving risks to participants and others;
    d. Participant withdrawals and reasons for withdrawal;
    e. Complaints about the research;
    f. Amendments or modifications;
    g. Any relevant recent literature;
    h. Any interim findings;
    i. Any relevant multi-center trial reports, if applicable;
    j. The researcher’s current risk-potential benefit assessment based on study results
2. Research protocol.
3. New informed consent form.
4. Data and Safety Monitoring Plan (if applicable).

7.4.3 Presentation and Discussion of Protocols

Protocols undergoing continuing review are presented individually to the IRB by the assigned Primary Reviewer. IRB staff will assure that appropriate scientific expertise, local knowledge, and other expertise specific to the protocol(s) is present at the IRB meeting and at least one member who is knowledgeable about or experienced in working with such subjects, when research involving subjects who are vulnerable to coercion are reviewed, will be present at the IRB meeting. If a member with the appropriate expertise, knowledge, or experience in working with the specific vulnerable population cannot be present, the IRB staff will notify the IRB Chair to obtain a consultant if needed. To be properly presented and discussed, a quorum of the members must be present for the presentation, discussion, and deliberations of the protocol. Members not present for a substantial part of the discussion and deliberations should abstain from voting. For those protocols undergoing continuing review, the following are discussed in detail (list is not all-inclusive):

1. The regulatory criteria for approval at 45 CFR 46.111 are met.
2. The new consent form to be used for the next approval period and the adequacy of the consent process.
3. Demographics of recruited/enrolled subjects.
4. Reports of protocol deviations, unanticipated problems, amendments, multi-center/ Data and Safety Monitoring Board reports, and audits reports.

7.4.4 Possible IRB Determinations

After presentation by the primary and secondary reviewers and complete discussion by the IRB, each protocol is voted upon for one of four possible dispositions:

1. **Approved**: It is approved as written with no explicit conditions.
2. **Approved with Modifications Required**: Approval with conditions is not a final approval. The protocol was approved with minor changes or simple concurrence of the PI. These will be identified to the PI and must be completed and documented prior to beginning the research. For these conditions, the IRB Chair's designated reviewer, (IRB member, IRB Compliance Administrator) upon reviewing the PI's response(s) to the conditions, may approve the research on behalf of the IRB. PI responses to conditions deemed to be significant or that are directly relevant to regulatory criteria must be reviewed at a convened meeting.
3. **Deferred:** The information in the submitted documents has deficiencies that prevent accurate determination of risks and benefits or requires significant clarifications, modifications, or conditions that, when met or addressed, require full IRB review and approval of the PI's responses and revisions. The deficiencies will be specified to the PI, who must address all IRB concerns in a written response. On occasion the PI is asked to attend the full board meeting in order to clarify the points in question. PIs may respond to a "deferred" decision with a written request. The IRB will review the appeal and invite the PI to the IRB meeting if the IRB has additional questions. The IRB will reconsider its original decision in light of new information presented by the PI. The second decision is final.
4. **Disapproved:** The submitted materials describe events or situations that indicate that research risks now outweigh potential benefits. PIs may appeal a determination for disapproval in writing or by attending an IRB meeting and presenting reasons for reconsideration. Upon appeal, the IRB will reconsider its original decision in light of new information presented by the PI. The second decision is final.

Researchers may be invited to attend the meetings to address specific concerns regarding research protocols, but will be asked to leave the meeting during all deliberations and votes.

7.4.5 Length of Approval Period

The IRB will determine the interval for the continuing review of the research, appropriate to the degree of risks that will be experienced by subjects. The interval for continuing review will be at least once per year (not to exceed 365 days; 366 days during a leap year) but may be shorter. When the IRB grants approval for one year at the time of continuing review and performs the continuing review and re-approval (with or without explicit conditions) of the research within 30 days prior to the IRB approval period expiration, the IRB will retain the anniversary of the expiration date of the initial IRB approval as the expiration date of the subsequent one-year approval period. Protocols that have not undergone continuing review will expire at midnight on the expiration date. Research activities may not continue after midnight of the expiration date.

The IRB may require certain protocols be reviewed more than once a year. Reasons for the IRB to require more than annual review include but are not limited to the following:

1. Increase in risks over what was originally anticipated.
2. Noncompliance history.

7.4.6 Third Party Observation

The IRB has the authority to observe or appoint a third-party to observe research conduct, including consent procedures. It may also consider whether a study requires independent verification from sources other than the PI to ensure that no material changes have occurred since the last IRB approval. The IRB will require verification of the information provided for continuing review when:

1. Continuing review materials appear inconsistent or inaccurate compared to prior applications or records and discrepancies cannot be resolved via communication with the PI; or
2. The IRB determines that such actions are useful as part of a corrective action plan for any unanticipated problem or event.

If the findings of such investigations during the continuing review process warrant corrective actions, the IRB may suspend or terminate a research project to ensure the quality of research and protection of research subjects.

7.5 Criteria for IRB Approval of Research Continuation

In order to approve research for continuation, the IRB must consider the PI's continuing review report and assure that the requirements 45 CFR 46.111 remain satisfied as follows:

1. Risks to subjects are minimized:
    a. By using procedures that are consistent with sound research design and which do not unnecessarily expose subjects to risk; and
    b. Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
2. Risks to subjects continue to be reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result from the research. In evaluating risks and benefits, the IRB will consider only those risks and benefits that may result from the research, as distinguished from risks and benefits of therapy the subjects would receive even if not participating in the research.
3. Selection of subjects is equitable and takes into account the purpose of the research and the setting in which the research will be conducted. Special attention is paid to problems of research involving vulnerable populations such as children, prisoners, pregnant women, fetuses, and decisionally impaired adults.
4. Unless waived by the IRB, informed consent will be appropriately sought from each prospective subject or the subject's legally authorized representative in accordance with and to the extent required by appropriate local, state, and federal laws or regulations. The IRB is responsible for the review and approval of the informed consent form submitted by the PI.
5. Informed consent will be appropriately documented according to local, state, and federal laws or regulations.
6. Where appropriate, there are adequate provisions to protect the privacy of the subjects and to maintain the confidentiality of their identifiable data.
7. When appropriate, the research plan continues to make adequate provision for monitoring the data collected to ensure the safety of subjects.
8. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study and in the IRB review process, to protect the rights and welfare of the subjects.

7.6 Notification of IRB Determinations

Within five (5) working days after the IRB meeting at which the protocol was reviewed for continuation, the PI will be notified of the IRB determination for their protocol. Approved protocols require no further action. Protocols that are approved with modifications required will have a list of conditions provided, and PIs are notified that final approval will not be granted until all conditions have been met. For protocols reviewed at a convened meeting, the IRB will determine, at the convened meeting, whether the PI's responses to modifications must be reviewed by the entire

IRB or may be reviewed for appropriateness and completeness by the Chair or the Chair's designee. Responses to clarifications that are directly relevant to regulatory criteria must be reviewed by the convened IRB. When the PI has responded appropriately and completely to all conditions, via IRBNet, a final approval is granted. The PI will be issued an approval letter stating that research can resume and when the protocol will require continuing review.

For deferred protocols, the PI will be notified by letter posted in IRBNet of the reasons the protocol was deferred. The entire submission, with all required documents, will need to be resubmitted after revision for IRB review.

For protocols that are disapproved for continuation, the PI will receive a letter that delineates the reasons for disapproval. PIs may appeal the determination in writing to the IRB Chair.

7.7 Failure to Comply with Continuing Review Requirements – Lapsed Protocols

IRB approval can be for no longer than a one year period of time and there is no grace period beyond the expiration date of IRB approval. Extensions of approval beyond the expiration date cannot be granted. Failure to submit the required documents and receive IRB approval for the protocol before the end of the approval period will result in a status of "Closed - Expired." This will occur even if the PI has provided the required documents, but IRB review and approval is not completed before the expiration date. If a protocol is placed in this status, the PI will be notified that they must cease all research activities (recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection and analysis of private identifiable information) until the required documents are submitted, reviewed, and approved by the IRB.

During the "Closed - Expired" period, subjects who are currently enrolled and for which continuation would be in the best interest of their health or well-being may continue to participate if the PI requests and justifies, in writing, the need for continuation. The request will be considered by the IRB Chair. If the IRB Chair is of the opinion that stopping participation could result in increased risk or potential injury or hardship to subjects, the IRB Chair may approve continued participation for a reasonable time beyond the expiration date. Therefore, to prevent expiration of IRB approval and stopping research, it is of vital importance to ensure timely completion and submission of the continuing review documents to allow sufficient time for IRB review prior to the expiration date. No research protocol may continue activities after the expiration date of the protocol until final approval for continuation is granted.