

CARILION CLINIC INSTITUTIONAL REVIEW BOARD

Standard Operating Guidelines

Title: 2.7: Review of Research: CONTINUING REVIEW and CHECK-IN	
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Primary Sponsor: Human Research Protections Office	Approved By: Director of the Human Research Protections Office

Objective:

To provide researchers with the process for applying for continuing review with the Carilion Institutional Review Board (IRB).

General Description:

Federal regulations mandate that a research protocol must be reviewed by the IRB at intervals appropriate to the degree of risk, but not less than at least once every 12 months for the duration of the study. Continuing review must be substantive and meaningful, and it must address any new information or changes that relate to risk/discomfort, benefits, safeguards for participants, and informed consent to assure that all criteria for approval specified under 45 CFR 46.111 and/or 21 CFR 56.111 are satisfied. The IRB will determine which studies need verification from sources other than the investigator and assure that no material changes in the research have occurred since the previous IRB review. It will ensure that changes in approved research are promptly reported, and approved by, the IRB, and that any suspensions or terminations of approval of research are being conducted in accordance with IRB requirements. It is the responsibility of the principal investigator to provide the IRB with a report summarizing the status of the project-at the time of continuing review or check-in.

Procedure:

It is the responsibility of the principal investigator (PI) to provide in a timely manner the information needed by the IRB to perform its continuing review functions. As a courtesy, the IRB staff will send a reminder email to the PI before the expiration of a protocol for studies that were originally reviewed by the convened IRB. All submissions will receive notifications from the PRISM system for their reminder of the need for continuing review or annual check-in. The PI will be reminded to submit a continuing review application and other documents necessary for ongoing review of the research. For research requiring review at a convened meeting, conducted via Microsoft Teams, submissions will be timed, when at all possible, so that they go to the IRB Committee that originally approved the study.

Unless the research qualifies for review under an expedited review procedure, continuing review must take place at a convened meeting. When continuing review of research is conducted under an expedited review procedure, the review must be conducted by the IRB chairperson or one or more experienced reviewers designated by the IRB chairperson from among the IRB members. At Carilion, the Human Protections Administrator or designee, who are alternate members of all IRB committees, are permitted to conduct continuing reviews. The IRB chairperson or designated IRB members may approve or require modification in (to secure approval of) research; however, may not disapprove research using expedited procedures.

Disapproval of a research project at the time of continuing review can only occur after review by the IRB at a convened meeting, not by the expedited review process. All IRB members will be advised of research that has been approved under an expedited review procedure in a summary list which is part of the minutes distributed to the IRB committees.

Investigators will submit the following documents for IRB Continuing Review in the Carilion IRB electronic submission system PRIS3M:

- A continuing review application that includes the following:
 - The number of subjects accrued
 - A brief summary of any amendments to the research approved by the IRB since the IRB's initial review or the last continuing review;
 - Any new and relevant information, published or unpublished, since the last IRB review, especially information about risks associated with the research
 - Information about any unanticipated problems and available information regarding adverse events
 - A summary of any withdrawal of subjects from the research since the last IRB review, and the reasons for withdrawal, if known; and
 - A summary of any complaints about the research from subjects or others since the last IRB review;
 - Any other significant information related to subject risk, such as the most recent report according to the Data Safety Monitoring Plan if available; and
 - Email 1 copy of the most recently signed consent form to irb@carilionclinic.org with the PRIS3M study number in the subject line.

The project summary, informed consent document(s) and continuing review application information will be distributed to all IRB members in advance of the convened meeting if the Continuing Review requires review and approval at a convened IRB Meeting. The primary reviewer(s) will access all currently approved study documents in PRIS3M, as well as any additional documents submitted by the investigator with the continuing review submission. In addition, the primary reviewer(s) will have access to the complete relevant IRB minutes prior to or during the convened IRB meeting. The complete IRB file will be made available upon request to any IRB member prior to the meeting at which the research is to be reviewed and will be accessible during the meeting to allow members to resolve any questions that may arise during the IRB's deliberations.

IRB Review and Approval

If the Continuing Review is to be reviewed by the Full Board, at a convened IRB meeting the reviewer(s) will give a summary of the research activity since the last review. The IRB members are given the opportunity to comment on the study or ask questions relevant to any new information that may have been received in the past year. In addition, the IRB will ensure that the currently approved or proposed consent document is accurate and complete. Once all discussion has taken place, a vote will be taken.

The board may issue approval of a research project contingent upon conditions being met by the investigator. The IRB will only issue a contingent approval when it is able to specifically stipulate in its motion the action requested before approval will be granted. If any of these conditions require substantive modifications or clarifications that are directly relevant to the determinations made by the IRB to satisfy federal regulations, then once the changes have been made, the research will again be brought before the convened IRB. Any approval of the proposed research will be deferred pending subsequent review by the convened IRB. If the required changes do not involve substantive modifications or clarifications that are directly

relevant to the determinations made by the IRB to satisfy federal regulations, then once the changes have been made and reviewed by the IRB chair or designee, an approval can be granted.

The vote will include the IRB's decision for the frequency of continuing review required to ensure the continued protection of the rights and welfare of research subjects. The principal investigator will be contacted in writing of the IRB's decision to either allow the research to continue, to require modifications to the research, or to discontinue the research. Once the study is approved for continuance the consent form will be stamped with a new expiration date and mailed back to the principal investigator along with an approval letter for continuance.

Criteria for Approval

Generally, the continuing review requires the same level of review as the initial review. Criteria that must be satisfied for the IRB to approve research include:

- The science and procedures of the study are understood
- Risks to subjects are minimized (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes;
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
- Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.20.
- Informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27.
- Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects
- Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects

When conducting continuing review and evaluating whether research continues to satisfy the criteria for IRB approval of research, IRBs should pay particular attention to the following four aspects of the research:

- Risk assessment and monitoring;
The IRB will consider whether there is any new information provided by the investigator, or otherwise available to the IRB, that would alter the IRB's previous conclusion that (1) the risks to subjects are minimized, and (2) the risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result. The IRB will consider relevant information received since the date of the last IRB review and approval of the research project from the investigator, any monitoring entity (e.g., the research sponsor, a coordinating or statistical center, an independent medical monitor, a data and safety monitoring board (DSMB), or a data monitoring committee (DMC)), or any other source. Information regarding any unanticipated problems that have occurred since the previous IRB review also will be considered.
- Adequacy of the process for obtaining informed consent
The IRB will review a copy of the informed consent document submitted by the investigator to verify that the investigator is using the most recently approved version and that the document contains the most accurate, up-to-date information about the research. If the IRB waived the requirement for the investigator to obtain a signed consent form for some or all subjects, it will assess the accuracy of the content of the information being provided to subjects orally and of any written statement regarding the research that is being provided to subjects. The IRB will assess whether the currently approved consent document adequately addresses the elements of informed consent required under DHHS and FDA regulations.
- Investigator and institutional issues
When appropriate, the IRB will consider issues regarding the investigator and the institution(s) where the research is being conducted during its continuing review, including: 1) Changes in the investigator's situation or qualifications (e.g., suspension of hospital privileges, change in medical license status, or increase in number of research studies conducted by the investigator); 2) Evaluation, investigation, and resolution of any complaints related to the investigator's conduct of the research; 3) Changes in the acceptability of the research in terms of institutional commitments (e.g., personnel and financial resources, adequacy of facilities) and applicable regulations, State and local law, or standards of professional conduct or practice.
- Research progress
 - 1) The IRB will assess whether the information provided by the investigator at the time of continuing review is consistent with the research protocol previously approved by the IRB. If this information suggests that the investigator is not conducting the research in accordance with either the IRB-approved protocol or the requirements or determinations of the IRB, the IRB will either defer re-approving the research or re-approve the research for a limited period of time (e.g., one month) and seek an explanation from the investigator regarding the apparent discrepancies.
 - 2) The IRB will evaluate the number of subjects enrolled in the research at the time of continuing review to ascertain whether enrollment is consistent with the planned number of subjects described in the IRB-approved protocol. A marked difference between the actual and expected rates of enrollment may indicate a problem with the research project that requires further evaluation, including whether the research project is likely to provide sufficient data to answer the scientific question(s) being posed.

- 3) The IRB's will review the number of subjects who discontinued their participation and a summary of the reasons for the withdrawals, if known. IRB review of this information may shed light on problems related to the conduct of the research. For example, a high rate of subject withdrawal secondary to serious adverse events may indicate that the risks of the research are greater than expected and may lead the IRB to conclude that the research should not be approved for continuation because the risks to subjects are not being minimized or are not reasonable in relation to the anticipated benefits to the subjects and the importance of the knowledge that may reasonably be expected to result.

Frequency of Continuing Review

Additionally, the IRB will determine that the frequency and extent of continuing review for each study is adequate to ensure the continued protection of the rights and welfare of research subjects. The duration for which IRB approval is granted is based on the level of risk to subjects and, if applicable, the analysis of this risk compared to the risk of alternative care, or standard care if such a standard exists. Factors considered in setting the frequency of review include the degree of risk involved and the vulnerability of the study subject population.

The IRB performs this risk assessment as part of the review of each protocol, either by the reviewer using the expedited procedure for protocols qualifying for such a review, or at a convened meeting. When the risk is great, particularly in relation to the risk associated with receiving standard care, the IRB will consider requiring that continuing review be conducted in less than one year, either determined by the time interval from approval or the number of subjects entered on the study. Some examples of protocols that may be considered for review more frequently than annually include:

- Studies involving planned emergency research (21 CFR 50.24);
- Studies involving a significant risk device;
- Studies in which a healthy volunteer may undergo anesthesia or a medical procedure involving sedation, but with no direct health benefits;
- Studies in which individuals with impaired decision making capacity will be enrolled;
- Studies for which there is little external oversight or data safety monitoring; or
- Studies involving gene transfer or xeno-transplantation.

The period of IRB approval, whether annually or more frequently than annually, will be documented in the written minutes of the convened meeting. The approval notification sent to the investigator will also specify the time/date determined by the IRB for when the protocol's IRB approval will expire.

If it required full IRB approval initially, then the continuing review will also require full IRB approval. However, continuing review may be expedited under some conditions. If expedited, the continuing review must occur within one year of the date the IRB Chair (or designee) gave the final approval to the protocol.

Verification From Sources Other than Investigators

Whether the continuing review is by full-board or expedited, the IRB may request verification from sources other than the researcher that no material changes have occurred since the initial or previous continuing review. Such independent verification may be considered in the following situations:

- Studies being conducted by persons who have previously failed to comply with all regulations or IRB requirements, including investigator non-responsiveness to requests for information;

- Studies for which the investigator's conduct was questionable as detected at the time of continuing review or audit;
- Carilion investigator-initiated studies for which substantial segments are conducted off site, either by the Carilion investigator or by a collaborator;
- Complaints from research participants that appear not to be adequately addressed by the investigator;
- Studies for which the investigator also serves as sponsor;
- Studies with an unexpected frequency (high or low) or severity of reported serious adverse events;
- Studies with a high participant dropout rate;
- Studies where the IRB discovers previously undisclosed information regarding the investigator and/or a co-investigator after the IRB has approved the investigator and without an acceptable explanation by the investigator;
- Complicated studies involving an unusual level or types of risk to subjects;
- Studies requiring compliance with Carilion hospital policies, including medication use, device use, and safe medication practices;
- Studies requiring auditing of medication use, storage and procedures;
- Studies requiring compliance with complex Carilion hospital nursing policies when patient care nurses are involved in the conduct of the research;
- Studies for which unanswered questions exist about the conduct of the research.

Independent verification of information may be requested by the IRB at a convened meeting, or by the IRB Chair/Vice-Chair/designee in the course of performing a review using the expedited procedure. Such verification may include:

- An audit or Research Education Session by Carilion staff
- Observation of the consent process
- Review of communications between the FDA and the sponsor/IND holder
- NIH communications and reviews
- DSMB/DMC reports
- Back translation of consent form or other material to be used by research subjects
- Letters of review or approval from other collaborating IRBs or a Central IRB
- A site monitor report
- A sponsor/CRO audit
- Correspondence with the sponsor/CRO
- Other materials as deemed appropriate

When the IRB finds the need for independently verified information, it will notify the investigator in writing of any outstanding issues or requests. This will usually occur in the context of a modifications request to the investigator. The IRB will not give final approval to the study until it has received and reviewed the independently verified information and found it to be satisfactory.

Expiration of Approval

Research activities must not be conducted beyond the expiration date of IRB approval. A lapse in IRB approval of research occurs whenever an investigator fails to provide continuing review information to the IRB or the IRB has not conducted continuing review and re-approved the research – with or without conditions – as of the expiration date of IRB approval. In such circumstances, all research activities involving human subjects must stop after IRB approval expires, *unless* it is determined to be in the best interests of already enrolled subjects to continue participating in the research. Enrollment of new subjects cannot occur after the expiration of IRB approval. Continuing participation of already enrolled subjects in a research

project during the period when IRB approval has lapsed may be appropriate, for example, when the research interventions hold out the prospect of direct benefit to the subjects or when withholding those interventions poses increased risk to the subjects.

The determination regarding whether it is in the best interests of already enrolled subjects to continue to participate in the research after IRB approval has expired may be made initially by the investigator, but the investigator as soon as possible should submit a request for confirmation that the IRB agrees with this determination. The determination by the IRB may be made by the IRB chairperson, by another IRB member or group of IRB members designated by the IRB chairperson, or at a convened meeting of the IRB. Furthermore, this determination may be made for all enrolled subjects as a group or for each individual subject. If the investigator or IRB determines that it is not in the best interests of already enrolled subjects to continue to participate, investigators must stop all human subjects research activities, including intervening or interacting with subjects and obtaining or analyzing identifiable private information about human subjects.

If the principal investigator wishes to continue research on a protocol whose approval has expired then the continuing review process should be completed as soon as possible. The IRB typically allows a grace period of 90 days. After the 90 day period, the study will be administratively closed and a new submission to the IRB will be required. The IRB Chair or designee may, at their discretion, close the study if sufficient progress is not being made on the continuing review of the expired study. If the research has been completed, the principal investigator should submit a Conclusion Form and supply the IRB with a summary of research findings if applicable. If the study team wishes to reopen a study that has already been closed, they must notify the IRB within 90 days of the conclusion and include a justification for reopening the study. After the 90 days, a new submission may be required to the IRB to continue the study.

Annual Check-in Process

The IRB may determine that an Annual Check-in review process is appropriate for studies which are approved according to Expedited Criteria and do not require a full Continuing Review. These studies are minimal risk and not FDA-regulated.

The items listed below need to be submitted to the IRB office:

- Annual Check-in Review Application in PRIS3M system
- Email 1 copy of the most recently signed consent form to irb@carilionclinic.org with the PRIS3M study number in the subject line.

The IRB typically allows a grace period of 90 days for the annual check-in due date. After the 90-day period, the study will be administratively closed and a new submission to the IRB will be required. If the research has been completed, the principal investigator should submit a Conclusion Form and supply the IRB with a summary of research findings if applicable.

If the study team wishes to reopen a study that has already been concluded, they must notify the IRB within 90 days of the conclusion and include a justification for reopening the study. After 90 days, a new submission may be required to the IRB to continue the study.