CARILION CLINIC INSTITUTIONAL REVIEW BOARD
Standard Operating Guidelines

Title: 6.4: Conduct of Research: NON-COMPLIANCE, SUSPENSION, TERMINATION, UNANTICIPATED PROBLEM	
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Primary Sponsor: Department of the Human Research Protections Office	**Approved By:** Director of the Human Research Protections Office

Objective:

To outline procedures for handling non-compliance with regard to research activities.

General Description:

Carilion IRB is required to review and approve human subjects research that meets the criteria in the federal regulations and institutional requirements. The approval is limited to the specific protocol procedures, materials, forms, and processes described in the IRB application. Principal Investigators (PI) and research team members must comply with all ethical standards, institutional policies, governmental regulations and IRB conditions placed on the conduct of the trial.

Non-compliance that occurs in the conduct of IRB approved research requires corrective action. The Carilion IRB and institutional officials may consider a range of options to address documented cases of non-compliance. The Carilion IRB will determine the actions required and will take into consideration the nature, severity, and frequency of the non-compliance and the risk that non-compliance poses to human subjects.

The Carilion IRB adheres to federal regulations (Pre-2018 Common Rule: 45 CFR 46.103(a), 45 CFR 46.103(b)(5), 45 CFR 46.113 & 21 CFR 56.113 and 2018 Common Rule: 45 CFR 46.108(a)(4), 21 CFR 56.108(b)), which require prompt reporting of any of the following to the appropriate institutional leaders/officials and the sponsoring Federal department or agency (i.e., Office for Human Research Protection [OHRP] and/or FDA (if FDA regulated)), as applicable:

- serious and/or continuing non-compliance with the requirements or determinations of the IRB;
- suspension or termination of previously approved research;
- unanticipated problems involving risks to subjects or others.

Procedure:

The investigator should track protocol deviations, protocol violations, or any potential non-compliance or potential unanticipated problems. A Promptly Reportable Information Form should be completed with a corrective action plan and submitted in PRISM by the PI and/or the research team within 7 business days of identification, as applicable.

The Carilion Human Research Protections Office (HRPO) will act on the identification of potential non-compliance and/or an unanticipated problem.

The IRB Chair or designee will assess the report for proper management. Information may need to be gathered to supplement the report. The initial report to the appropriate institutional leaders/officials and the sponsoring Federal department or agency (i.e., Office for Human Research Protection [OHRP] and/or FDA (if FDA regulated)), will include a description of the incident, the preliminary steps taken, and a statement indicating whether an audit will be performed, as applicable. If an audit is conducted, a full report will follow. The report will include the following:

- Name of protocol if non-compliance is study specific
- Name of principal investigator
- Name of any sponsor or funding agency
- A description of the unanticipated problem, the serious or continuing non-compliance, or the reason for suspension or termination of IRB approval
- A description of any corrective action or modifications to the research required by the IRB or the institution, to date

Possible outcomes of the information gathering may include:

Referral to the convened IRB if the problem may involve 1) apparent serious and/or continuing non-compliance or 2) an apparent unanticipated problem;

- Finding of non-compliance that is neither serious nor continuing with or without corrective actions required;
- Referral to other appropriate processes (e.g., misconduct investigation);
- Assess whether suspension/termination is necessary.

Suspension/Termination of Research

When a non-compliance notification is received, the IRB Chair and/or designee, will first determine if immediate suspension of subject enrollment is required for the project in question as well as for any other project with the same investigator. This decision will be based on the seriousness of the situation. The first consideration will be subject safety. The non-compliance activity may merit suspension when there is greater than minimal risk to a subject or the rights and/or welfare of a subject have been seriously jeopardized.

The institution authorizes the Institutional Official (IO), or an IRB Chair, to suspend or terminate a human subjects research study (or associated studies) when an event occurs and, in their judgment, taking such action cannot wait until a convened IRB meeting in order to protect the rights and welfare of participants. Additional institutional leaders/officials and legal services will be utilized if necessary. An action taken by the IO or an IRB Chair to suspend or terminate research will be reported to the IRB at the next convened meeting.

After suspension of an IRB approval, the IRB has the authority to terminate the research if the event(s) prompting the suspension of research approval cannot be corrected in a way that serves the best interests of the research participants. The IRB may also terminate a research study if the non-compliance with the IRB requirements is serious and/or continuing and the proposed corrective action plan is not sufficient to alleviate or rectify the non-compliance.

The IRB or authorized person(s) ordering the suspension/termination must:

- Consider actions to protect the rights and welfare of currently enrolled participants;

- Consider whether procedures for withdrawal of enrolled participants take into account their rights and welfare (e.g., making arrangements for medical care outside of a research study, transfer to another researcher, and continuation in the research under independent monitoring);
- Consider informing current participants of the suspension/termination;
- Require that any adverse events or outcomes are reported to the IRB.

A notice of suspension/termination, effective immediately, will be sent to the investigator, co- or sub-investigator(s), appropriate Carilion institutional official(s), sponsor or funding agency and members of the reviewing IRB. The notification includes the requirement to halt further subject enrollment.

The notification will indicate that an allegation is being evaluated, what the allegation involves, and the estimated timeframe for completion. The allegation investigation will be conducted within 30 days so that prompt reporting may occur. A written report of the committee's decision will be provided to the investigator, Institutional Official, IRB Chair, HRPO Director, and other Carilion institutional leaders/officials.

Every effort should be made to contact the Carilion PI promptly via phone or email. Official written notice of any IRB study suspension/termination must be provided to the Carilion PI. The PI will be informed of the following:

- Effective date of suspension or termination;
- Reason for suspension or termination;
- Corrective actions necessary, request for corrective actions, or instructions for closure of the study, as appropriate;
- To whom the notice is copied; and
- Specific instructions pertaining to currently enrolled research participants, as applicable.

The PI of the study may voluntarily decide to suspend or terminate a study due to various reasons including but not limited to the occurrence of an unanticipated problem, evidence of non-compliance or serious and/or continuing non-compliance. If this occurs, the PI must notify the IRB in writing within 5 business days after this suspension or termination, and describe what steps have or will be taken to protect the currently enrolled participants, and what corrective actions, if applicable, will be taken to address the cause for the research suspension or termination. This report will be reviewed at a convened IRB meeting. After reviewing the report, the IRB will decide whether or not to suspend or terminate the IRB approval as well.

Suspension imposed by the IRB on some or all of the research protocol may be lifted when the IRB/HRPO finds that participants are adequately protected from risk in order to continue in the study safely. Suspension may also be lifted when the IRB/HRPO finds that the corrective action plan has been adequately addressed such that participants are fully protected and events preceding the suspension are unlikely to recur.

When suspension is not necessary, such as when the non-compliance activity in question involves no greater than minimal risk to subjects, the issue will be resolved between any combination of the following individuals: the IRB Chair, HRPO Director, PI, and the appropriate Carilion institutional leaders/official(s), including but not limited to the Institutional Official, Department Chair, or faculty supervisor.

One of the goals of any non-compliance review and follow-up is education. The IRB staff will use discretion in determining the manner of education that works best in each situation. All communication will be documented.

Serious and/or Continuing Non-compliance & Unanticipated Problems
Identification of issues that constitute non-serious or non-continuing non-compliance may be evaluated and managed by the IRB Chair, HRPO staff, or the IRB. Problems that indicate significant risk or severity will be evaluated to determine if they constitute an unanticipated problem and whether immediate actions are necessary to ensure the ongoing protection of research subjects. All reports of non-compliance should be evaluated to determine if the criteria for an unanticipated problem involving risk to subjects or others are applicable.

If additional information is needed to make a non-compliance determination, the HRPO may initiate information gathering activities, which may include reviewing study documentation or corresponding with the PI and research personnel. The investigator may be required to produce, at a minimum, all signed consent forms and/or data related to the study project. The IRB Chair/ IRB reviewer(s) may participate with the HRPO as needed.

If the incident appears to be isolated and of a non-serious/non-continuing nature or not an unanticipated problem, the incident will remain internal. A letter from the HRPO office to the investigator describing the IRB findings will be written. Information from the investigator describing corrective actions will be required. If all corrective actions are satisfactory, no further action will be required. If the IRB Chair/reviewer(s) determine that the problem is not determined to be an unanticipated problem involving risks to participants or others, reporting to OHRP and other appropriate entities is not required unless the problem constitutes serious or continuing non-compliance or if the research is suspended or terminated.

If the information received indicates non-compliance that is potentially **serious and/or continuing, and/or an unanticipated problem based on the definitions provided in this guideline**, the final assessment and determination will be made by board action within a convened IRB meeting, where the board members vote to take this action. The IRB will determine whether the corrective action is adequate and whether any additional action is needed. If non-compliance is determined to be serious and/or continuing, OHRP will be notified, regardless of the funding source, within 30 business days. If an incident report to OHRP does not reflect the final outcome of the incident, the IRB will send OHRP a follow-up report when all corrective actions related to an incident have been addressed to the satisfaction of the IRB. If the study is FDA regulated, the FDA will also be notified. The IRB will also notify the PI, the sponsor, the IO, other appropriate institutional leaders/officials at Carilion, and the Carilion Research & Development Department.

The IRB and HRPO will consider the following items when reviewing serious and/or continuing non-compliance matters:

- Providing the principal investigator the opportunity to discuss the issues of non-compliance at the next board meeting
- Requiring modification of the research protocol and/or consent
- Requiring additional education for those involved
- Requiring more frequent and/or more detailed reporting to the IRB (e.g., continuing review), which may include verification from sources other than the investigator that information provided is correct

- Suspending enrollment of subjects to the involved study or other studies of the investigator
- Terminating the involved project or other projects of the investigator
- Withholding approval of future projects proposed by the investigator
- Notification of current participants when such information may relate to participants'' willingness to continue to take part in the research;
- Requiring that current participants re-consent to participation when such information may relate to subjects' willingness to continue participating in the research;
- Providing additional information provided to past participants
- Monitoring of the research and/or consent process
- Suspension of IRB approval for a portion or all of the research
- Disqualify the investigator(s) from conducting research involving human subjects at Carilion
- Referral to other organizational entities (e.g., legal counsel, ancillary committees, IO)
- Require disclosure to publisher
- Other corrective actions not listed here
- No action (if appropriate)

NOTE: The IRB should not require the destruction of the research data set as this may contradict other institutional policies regarding data retention and ownership. However, such a requirement would be within the purview of other institutional leaders/officials and offices.

The investigator will be provided with the final determination of the actions to be taken. If, at any point in this process, the non-compliance issue is determined to be an issue of scientific misconduct, then it will be referred to the appropriate oversight body.

Any individual dissatisfied with the outcome of a non-compliance investigation may make a verbal or written appeal to the IO. The official will then review all information pertaining to the investigation to determine whether proper policies and procedures were followed. If it is determined that there are grounds to reconsider the IRB's decision, the matter will be referred back to the IRB that originally reviewed the incident for reconsideration.

IRB Reporting Requirements

The following elements must be included in the report to the oversight authorities, which should be kept concise and include details which directly supports the actions taken:

1. Name of the institution conducting the research;
2. Title of the research project and/or grant proposal;
3. Name of the Principal Investigator on the protocol;
4. The number assigned to the study by the IRB;
5. The number of any applicable federal award(s);
6. For FDA reports of suspension or termination: the name of the drug, biologic, or device and the IND number or the IDE number/non-significant risk (NSR) status of the device;
7. A description of the event or events resulting in the unanticipated problem, serious/continuing non-compliance, and/or suspension or termination;
8. The findings of the organization;
9. Actions taken by the organization, including any IRB actions taken related to the matter, and reasons for those actions; and
10. Clear identification that the issue is resolved or specific plans for continued investigation or action.

The distribution of the written report begins with federal agencies that have oversight due to funding, conduct, or an assurance of compliance. A report is sent to OHRP, the FDA (if FDA-regulated research), and other "Common Rule Signatory" departments and agencies that require reporting separate from OHRP.
Copies of the report are directed to:

1. The Principal Investigator,
2. The Carilion IRB Chair,
3. The Institutional Official,
4. The Department of Research & Development, as appropriate (for reporting to any sponsoring organization),
5. The Department Chair of the Principal Investigator, and
6. Other collaborating sites involved in the research, as appropriate.
7. The lead Principal Investigator of a multisite study, when applicable
8. Other IRB officials, as specified by the IRB

The timing for official distribution of the report to oversight agencies should be as soon as practicable, with the primary attention first given to taking any actions (if necessary) to ensure the ongoing protection of human research participants. It may be necessary to contact an agency prior to filing a report in order to alert the agency to a very serious problem.

For multi-site research, the Carilion HRPO manages events that occur at a Carilion research site, involving Carilion employees or patients, and/or events for which the Carilion IRB is serving as the IRB of record. All determinations of serious or continuing non-compliance made by an external IRB regarding a Carilion research setting involving Carilion patients or employees should also be submitted to the Carilion HRPO. The Carilion HRPO has responsibility for reporting to relevant regulatory agencies. The Carilion HRPO retains the authority to make institutional determinations of serious and/or continuing non-compliance, unanticipated problems independent of the determinations made by an external IRB. Suspected serious and/or continuing non-compliance may be referred to a convened IRB for review for institutional review of the event. For studies reviewed by an external IRB, the HRPO will require a report be submitted to the IRB of record for review.

Definitions:

Non-compliance can be defined as any intentional or unintentional activity associated with the conduct or oversight of research involving human participants that fails to comply with the research plan as approved by a designated IRB, or federal regulations or institutional policies governing such research.

The following examples of non-compliance are intended to be a guide to researchers. This list is not all-inclusive: (Note that these examples could constitute serious and/or continuing non-compliance based on the circumstances of the event)

- Failure to obtain an institutional exempt determination prior to beginning exempt research
- Continuing research activities beyond study expiration date or during protocol suspension
- Failure to conduct the research as described in and required by the IRB approved protocol

- Failure to obtain informed consent
- Use of outdated consent forms.
- Implementing changes to a non-exempt protocol without prior IRB approval, unless the change is necessary as a corrective action to eliminate an apparent immediate hazard to participants.

Non-compliance – Serious

- significantly increases risks to participants;
- adversely affects the rights, welfare, or safety of participants;
- significantly decreases potential benefits for participants;
- results in a detrimental change to a participant's clinical or emotional condition or status;
- compromises the scientific integrity or validity of the research study

*The IRB does not have to find that harm has occurred, or was likely to occur, to make a determination of serious non-compliance.

Non-compliance - Continuing

- represents a pattern of ongoing activities that indicate a lack of understanding or disregard for human research requirements that may affect the rights and welfare of research participants or the scientific validity of the research;
- is a second or greater offense of the same type either on a single protocol, or across multiple protocols (regardless of the reviewing IRB) under an individual investigator;
- a pattern of repeated non-compliance which continues after initial discovery and includes inadequate efforts to take corrective actions within a reasonable timeframe or adhere to a previously established corrective action plan;
- this may involve frequent repeated instances of minor non-compliance regarding numerous different aspects of the research after similar non-compliance was previously identified or reported to the IRB

Examples of serious and/or continuing non-compliance may include, but are not limited to:

- Failure to obtain IRB approval prior to initiating human research activities;
- Failure to obtain informed consent/assent/parental permission as required by the IRB approved protocol and/or missing signed consent documentation;
- Failure to report unanticipated problems involving risk to participants or others;

If the investigator or group responsible for the non-compliance is unwilling to work with the HRPO or IRB to develop or to implement a suitable corrective action plan within a reasonable period of time, the IRB of record should evaluate whether there is another instance of apparent continuing non-compliance according to the procedures outlined above.

<u>Protocol Deviation</u>

A protocol deviation is a departure from the approved study protocol which may or may not be non-compliance and:

- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan; does not substantively impact the accuracy, reliability or completeness of the data.

The following examples are intended to be a guide to researchers. This list is not all-inclusive.

- Completing a study visit outside of the required timeframe because of the participant's schedule and there are no safety implications, and no impact on the accuracy, reliability or completeness of the data.
- Minimal over-enrollment

Protocol Violation

A protocol violation is a departure from the approved study protocol which is non-compliance and:

- Has harmed or increased risk of harm to one or more research participants
- Has compromised the scientific integrity of the research plan, or reduced the accuracy, reliability or completeness of the data.

The following examples are intended to be a guide to researchers. This list is not all-inclusive.

- Failing to obtain legally effective consent prior to initiating research procedures. (This includes failure to obtain signed consent when required.)
- Medication errors, such as administering the wrong study drug to a participant or the wrong dose of the study drug.
- Failing to conduct a study procedure or administer a study assessment that was meant to assess the safety of the individual's continuation in the study.
- Failure to report protocol changes that were necessary to eliminate apparent immediate hazards to a participant or others within 7 business days.
- Informed consent obtained by someone other than individuals authorized by the IRB to obtain informed consent.
- Enrollment of a participant who did not meet all inclusion/exclusion criteria.
- Performing a study procedure that has not been approved by the IRB.
- Failure to report an Unanticipated Problem to the IRB and/or sponsor of the study.
- Study visit conducted outside the required timeframe that, in the opinion of the investigator, may impact the safety of the participant or reduce the accuracy, reliability or completeness of the data.
- Materially inadequate record keeping.

Suspension

Suspension of research is defined as a temporary or permanent halt to some or all research procedures until the IRB determines whether the research may recommence (with or without modifications to the research) or whether the research must be terminated.

Termination

Termination of research means a permanent stop to the research and all research-related activities.

Unanticipated Problem

Any event, experience, issue, instance, problem or outcome that meets all 3 of the following criteria:

- Is unexpected in terms of the nature, severity or frequency given the research procedures that are described in the protocol –related documents AND in the characteristics of the population under study.
- Is related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research places the participant or others at greater risk of harm (physical, psychological, economic or social) than was previously known or recognized OR results in actual harm of the participant or others. An unanticipated problem generally requires a change in policy or procedure, warrants consideration of substantive changes to the protocol/consent or other immediate corrective actions in order to reduce the risk or eliminate immediate hazard.

The following examples are intended to be a guide to researchers. This list is not all-inclusive.

- Serious Adverse Event;
- Breach of privacy or confidentiality;
- Receipt of wrong dose or contaminated study medication;
- Lab or medication errors (that may involve risk to participants);
- Disqualification or suspension of a study investigator;
- Change in the status of a participant that might affect their eligibility to remain in a study.
- New information that suggests an unexpected change to the risk-benefit assessment or results in sponsor-imposed suspension of study or enrollment due to newly recognized risk:
  - Change in FDA labeling because of adverse consequences
  - Withdrawal of investigational agent due to adverse events
  - Publication in literature, study monitoring reports, DSMB reports, or interim study results

References:
SOG 2.9 Review of Research: REPORTING UNANTICIPATED PROBLEMS, INCLUDING ADVERSE EVENTS
SOP HRP 112: Promptly Reportable Information, New Information