

Section 23: Deviations / Violations / Exceptions

23.1 Overview

During the conduct of the study, changes to the research may be proposed or unintentional changes in the conduct of the research may be discovered. Changes to the IRB-approved study, planned or otherwise, are governed by federal and state regulations and Dana-Farber/Harvard Cancer Center (DF/HCC) Standard Operating Procedures (SOPs) for Clinical Research.

Investigators are also responsible for conducting human subject's research in accordance with:

- Dana-Farber Cancer Institute (DFCI) Institutional Review Board (IRB) reviews and determinations
- DFCI IRB Policies and Procedures for the Protection of Human Subjects in Research
- Quality Assurance Office for Clinical Trials (QACT) requirements
- All applicable Regulatory Sponsor requirements

Non-compliance with IRB reviews and determinations, DFCI IRB policies and procedures, QACT requirements, DF/HCC SOPs or regulatory sponsor requirements during the conduct of a research study may result in a deviation, violation or exception and as such must be reported to the DFCI IRB.

Planned ongoing study changes (amendments) to IRB-approved research must be submitted as a formal amendment and not as a deviation, violation or exception. Please refer to Section 22: "Amendments to Previously Approved Research" of this guide for further information on amendments.

23.2 Deviations and Violations

A deviation is any prospective request of the IRB to deviate from the defined procedures set forth in the IRB-approved study; from DF/HCC policies and procedures; or from the regulatory sponsor's requirements. A violation is a report to the IRB of a deviation which has already occurred and was not prospectively reviewed by the IRB prior to its initiation or implementation.

The IRB further defines the severity of deviations and violations into "Major" and "Minor" categories. A major deviation/violation is a deviation or violation that impacts the risks and benefits of the study; impacts participant safety, affects the integrity of study data or affects a participant's willingness to participate in the study. A Minor Deviation/Violation is deviation or violation that does not impact participant safety, compromise the integrity of study data or affect participant's willingness to participate in the study. It is the responsibility of the Principal Investigator (PI) to determine whether a deviation or violation is major or minor and to ensure proper reporting to the IRB. Examples of major versus minor deviations/violations may be found within the OHRS Information sheet titled "Deviation/Violation/Exception Reporting to the DFCI IRB".

Reporting Major Deviations/Violations

All Major Deviations/Violations are to be reported using the Major Deviation/Violation/Exception Form found on the OHRS website and submitted to the IRB electronically via OHRS submit. All major deviations must be reported to the within five working days of when it is known that a deviation is anticipated. Major deviations should be reported as soon as possible before the event date so that the IRB has sufficient time to review and take action. All deviations should also include documented approval of the regulatory sponsor. All major violations must be reported within ten working days of discovery. Reports of deviations and violations should be submitted to the sponsor as outlined in the sponsor's protocol.

Review of Major Deviations/Violations

Once the Major Deviation/Violation has been received by OHRS, it will be triaged and routed for either an expedited IRB review or review by the convened IRB. During the review, the IRB will determine whether the information in the report is sufficient and if the corrective action plan is appropriate or not. As a result of the review, IRB will make one of the following determinations:

1. No further action is required, the investigators assessment of the situation and the corrective action plan are appropriate;
2. Further action is required. Actions to be taken by the study team will be outlined by OHRS for the study team to respond to in a point-by-point manner;
3. Disapproved; the request to deviate from the protocol can not go forward.*

*This determination may only be made by the convened IRB. If the major deviation/violation is reviewed under expedited review procedures and the reviewer determines the report/request can not go forward, the report must be routed to the convened IRB for a final determination which may include disapproval.

The outcome of the review will be sent to the study team via email. If further action is required the study team will be asked to respond to the conditions in a point-by-point manner. The study team response will then be re-routed for further IRB review. If no further action is required, or the request is disapproved, the study team will receive an email from OHRS documenting the final outcome and institutional representatives such as pharmacy, nursing and QACT will be copied on the correspondence as applicable.

Reporting Minor Deviations/Violations

Minor deviations do not need to be submitted to the IRB for prospective review. Rather, they should be documented using the Deviation/Violation Log. For sponsored trials, proper documentation of regulatory sponsor acknowledgement and/or approval for each minor deviation is required and should be kept with the log. If three or more minor deviations/violations of the same type (or for the same participant) are found in the Log to impact the safety of participants, compromise the integrity of the study data and/or affect participant's willingness to participate in the study the events must be reported to the IRB via the Major Deviation/Violation/Exception Form.

The DF/HCC Lead Site is responsible for maintaining the minor deviation/violation log for all DF/HCC sites participating in the study and submitting it to the IRB with the continuing review form. A protocol that is approved and taking place at more than one site is still considered one protocol.

The Log can be found on the OHRS website and must be submitted no less than once per year at continuing review. The Overall PI is required to attest in the continuing review form that the minor deviations/violations have all been reviewed. If there are no minor deviations to be reported within the continuing review period, this must be indicated on the continuing review form. The IRB will review the Log at the time of continuing review and a determination regarding the Log will be made along with the continuing review.

23.3 Exceptions

An exception is a request to deviate from IRB-approved eligibility criteria and applies to cases in which a participant will be enrolled into a trial even though they do not meet all of the eligibility criteria. As a general rule, exception requests must be followed up by an amendment to the study in line with the proposed exception.

Reporting Exceptions

All Exceptions are to be reported using the Major Deviation/Violation/Exception Form found on the OHRS website and submitted to the IRB electronically via OHRS submit. Whenever possible, exceptions should be reported two to three business days before the event date so that the IRB has sufficient time to review and take action. All exception requests require documented regulatory sponsor approval and if the submission is high-priority, OHRS staff should be advised personally of the submission either by phone or email.

Exception requests should clearly document:

1. An explanation of why the study is the best option for the individual;
2. A description of the criteria that makes the individual ineligible to enroll in the study;
3. Documented regulatory sponsor approval for the exception request;
4. And a statement as to whether or not an amendment will be submitted as a result of the exception request and if not justification for why an amendment will not be submitted.

Review of Exceptions

Once the Exception has been received by OHRS, it will be triaged and routed for either an expedited IRB review or review by the convened IRB. During the review, the IRB will determine whether the information in the report is sufficient and if the corrective action plan is appropriate or not. As a result of the review, IRB will make one of the following determinations:

1. No further action is required, the investigators assessment of the situation and the corrective action plan are appropriate;
2. Further action is required. Actions to be taken by the study team will be outlined by OHRS for the study team to respond to in a point-by-point manner;
3. Disapproved; the request to deviate from the eligibility criteria can not go forward.*

*This determination may only be made by the convened IRB. If the major deviation/violation is reviewed under expedited review procedures and the reviewer determines the report/request can not go forward, the report must be routed to the convened IRB for a final determination which may include disapproval.

If further action is required the study team will be asked to respond to the conditions in a point-by-point manner. The study team response will then be re-routed for further IRB review. If no further action is required, or the request is disapproved, the study team will receive an email from OHRS documenting the final outcome. The outcome of the review will be sent via email and institutional representatives such as pharmacy, nursing and QACT will be copied on the correspondence as applicable.