

OHRs Policy & Procedure for DEVIATION/VIOLATION/EXCEPTION REPORTING TO DFCI IRB

During the conduct of the study, changes to the protocol may be proposed or unintentional changes in the conduct of the study may be discovered. Changes to the IRB-approved protocol, planned or otherwise, are governed by:

- Federal and state regulations
- Dana-Farber/Harvard Cancer Center (DF/HCC) Standard Operating Procedures (SOPs) for Clinical Research

Federal regulations specifically require the IRB of record to review proposed changes in a **research activity**, and to ensure that such changes in approved research are not initiated without prospective IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject [45 CFR Part 46.103(b)(4)(iii) and 21 CFR Part 56.108(a)(4)]. Investigators are also responsible for conducting human subjects 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 sponsor requirements during the conduct of a research study results in a **protocol deviation, violation or exception** and as such must be reported to the DFCI IRB.

The following reference information is provided below:

- Definitions of key terms
- Overview of specific reporting requirements
- Examples of major and minor deviations, violations and exceptions

Note: Planned ongoing protocol changes (amendments) to an IRB-approved protocol must be submitted as a formal protocol amendment and not as a protocol deviation.

DEFINITIONS

The following definitions apply throughout this guidance document:

Research Activity: All aspects of the conduct of the research study outlined in the protocol submission and reviewed and approved by the IRB, e.g., recruitment methods, consent process, treatment plan, data collection, procedures used to protect privacy and confidentiality, etc.

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g., enrollment of a subject who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not prospectively approved by the IRB prior to its initiation or implementation.

- **Major Deviation/Violation:** a deviation or violation that impacts the risks and benefits of the study; may impact subject safety, affect the integrity of study data and/or affect subject's willingness to participate in the study.
- **Minor Deviation/Violation:** a deviation or violation that does not impact subject safety, compromise the integrity of study data and/or affect subject's willingness to participate in the study.

REPORTING REQUIREMENTS

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. Reports of protocol deviations, violations and exceptions should be submitted to the sponsor as outlined in the sponsor's protocol.

All **protocol exceptions** must be requested of the IRB prior to subject enrollment using the **DFCI IRB - MAJOR DEVIATION/VIOLATION/EXCEPTION FORM** found on the OHRS website.

All **major violations** must be reported to the IRB within ten (10) working days of discovery using the **DFCI IRB - MAJOR DEVIATION/VIOLATION/EXCEPTION FORM** found on the OHRS website.

All **major deviations** must be reported to the IRB within five (5) working days of when it is known that a deviation from the protocol is anticipated using the **DFCI IRB - MAJOR DEVIATION/VIOLATION/EXCEPTION FORM** found on the OHRS website. Whenever possible, major deviations should be reported two to three (2-3) days before the event date so that the IRB has sufficient time to review and take action.

All **minor deviations** need not be submitted to the IRB for prospective review. Rather, they should be documented using the **DFCI IRB – DEVIATION/VIOLATION LOG**. The log can be found on the OHRS website.

- For sponsored trials, proper documentation of sponsor acknowledgement and/or approval for each minor deviation is required and should be kept with the log.
- Three or more minor deviations of the same type are considered a major violation and must be submitted to the IRB via the Major Deviation Form.

All **minor violations** are to be documented using the **DFCI IRB – DEVIATION/VIOLATION LOG** and submitted to the DFCI IRB at continuing review. The log can be found on the OHRS website.

Minor Events Reported at Multiple DF/HCC institutions

The overall study team 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.

Example: Protocol 09-999 is approved to be conducted BIDMC, DFCI and MGH. The overall PI is at MGH. At BIDMC, the study team failed to take the vital signs of subject x; at MGH the study team failed to take the vital signs of subject y; and at DFCI, the study team failed to take the vital signs of subject z. The latter missed vital sign is now the third minor violation of the same type for the study – missed vital signs. There is now one major violation that must be reported to the IRB by the overall PI with 10 working days of discovery.

Note: Any permanent change to the protocol constitutes an amendment that must be submitted to the IRB for approval prior to initiation.

EXAMPLES

Major Deviations and Violations

This list of examples is intended as a guide and is not all-inclusive:

- Failure to obtain informed consent, i.e., there is no documentation of informed consent
- Informed consent obtained after initiation of study procedures
- Inappropriate documentation of informed consent, including:
 - missing subject signature
 - missing investigator signature
 - copy not given to the person signing the form
 - someone other than the subject dated the consent form
 - Informed consent for therapeutic studies obtained by someone other than individuals authorized to obtain consent, e.g. someone other than a licensed physician investigator
 - Use of invalid consent form, i.e. consent form without IRB approval stamp, or outdated/expired consent form
- Enrollment of a subject who did not meet all inclusion/exclusion criteria
- Performance of a study procedure not approved by the IRB
- Failure to report serious adverse event to the IRB and/or sponsor
- Failure to perform a required study visit or procedure that, in the opinion of the PI, may affect subject safety or data integrity
- Study visit or procedure is conducted outside of required timeframe that, in the opinion of the PI, may affect subject safety or data integrity
- All drug/study medication dispensing or dosing errors
- Breaches of confidentiality
- Inappropriate destruction of study records
- Failure to follow safety monitoring plan

- Over-enrollment to a protocol
- Repeated or continued negligence in performance of study procedures
- Repeated or continued inability of a subject to comply with the research activity
- Dosing or treatment plan change with the potential for altered therapeutic efficacy and/or adequate evaluation of toxicity
- The number of missed oral medication doses indicates a problem with compliance with study procedures on the part of the subject, a problem with the ability of the study staff to monitor subject compliance, and/or the number of missed oral doses impacts the risk/benefit ratio.
- Enrollment of subjects after IRB-approval of study has expired
- Failure to submit continuing review application to the IRB before study expiration
- 3 or more minor deviations for the same subject
- 3 or more minor deviations of the same type

Examples of when to report a Major Deviation or Violation with **missed oral medications** or a **missed day of treatment** with a continuous therapy:

Type of Therapy:	Cycle or Tx Time Period:	Number of Missed doses or days of treatment
Daily Oral Medication	22-28 Days	More than 3 doses missed in that time period
	15-21 Days	More than 2 doses missed in that time period
	6-14 Days	More than 1 dose missed in that time period
	1-5 Days	Any doses are missed in that time period
Continuous Therapy	28-44 Days	More than 3 days of treatment missed
	15-27 Days	More than 2 days of treatment missed
	6-14 Days	More than 1 day of treatment missed
	5 Days or Less	Any Days of treatment are missed

Minor Deviations and Violations

This list of examples is intended as a guide and is not all-inclusive:

- Implementation of unapproved recruitment procedures
- Missing original signed and dated consent form (only a photocopy available)
- Missing pages of executed consent form
- Failure to follow the approved study procedure that, in the opinion of the PI, does not affect subject safety or data integrity:
 - Study procedure conducted out of sequence
 - Omitting a IRB approved research activity on a protocol (e.g. mailing out or collecting QOL surveys, evaluating and documenting performance status)
 - Failure to perform a required lab test
 - Missing lab results
 - Study visit conducted outside of required timeframe
- Failure of subject to return study medication

Examples of when to report a Minor Deviation or Violation with **missed oral medications** or a **missed day of treatment** with a continuous therapy:

Type of Therapy:	Cycle or Tx Time Period:	Number of Missed doses or days of treatment:
Daily Oral Medication	22-28 Days	3 or fewer doses missed in that time period
	15-21 Days	2 or fewer doses missed in that time period
	6-14 Days	1 dose is missed in that time period
Continuous Therapy	28-44 Days	3 or fewer days of treatment missed
	15-27 Days	2 or fewer days of treatment missed
	6-14 Days	1 day of treatment is missed