DEVIATION / VIOLATION / EXCEPTION and OTHER EVENT REPORTING TO DFCI IRB

OVERVIEW and DEFINITIONS

During the conduct of a 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 46.108(a)(3)(iii) and 21 CFR Part 56.108(a)(4)].

Investigators are also responsible for conducting human subject 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 constitutes a **protocol deviation, violation or exception** and as such must be reported to the DFCI IRB.

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.

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

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

Major Deviation/Violation/Exception: 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 a 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 a subject's willingness to participate in the study.

POLICY STATEMENTS

1. It is the responsibility of the DF/HCC Principal Investigator (PI) to determine whether an event is a major or minor event and to ensure proper reporting to the IRB.

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

3. The IRB will not approve blanket requests to deviate from a protocol; an amendment must be submitted for deviations and exceptions that will apply to more than one participant.

4. Documentation of sponsor acknowledgement and/or approval is required for all applicable trials. This includes approval from the DF/HCC PI where that individual is the sponsor of the trial. Requests will not be reviewed by a member of the IRB until sponsor documentation is provided.

5. The IRB does not require reporting of scheduling delays due to state or federal holidays, inclement weather, or circumstances beyond the control of the research team and/or the subject as protocol deviations.

6. Conflicts with a subject's work schedule or planned vacation are considered protocol deviations and must be reported. The DF/HCC PI must determine if subject scheduling delays results in either a major or minor protocol violation.

7. Investigators are responsible for knowing the reporting requirement to their institutional risk management department. Please make sure that any reported other events, if appropriate, have also been reported to the applicable risk management group.

8. The following applies to Prospective Eligibility Exception and Deviation Requests:
   A. No Eligibility Exceptions or Deviation Requests will be permitted for CTEP-managed and Cooperative Group trials.
   B. No Eligibility Exceptions will be permitted on Randomized Trials.
   C. No Eligibility Exceptions will be permitted for any trial under an IND where there is a reasonable chance that that trial will be used in the IND submission for FDA approval.
   D. No Eligibility Exceptions or Deviations Requests will be permitted without sponsor approval.
   E. For any approved Eligibility Exceptions there is an expectation that an amendment to the protocol will be submitted within 30 days. No additional Eligibility Exceptions of the same type will be permitted by the IRB without the submission of an amendment. If the amendment is not submitted as required, the IRB may take steps to close the study to new accrual until the required amendment is submitted.
   F. All Eligibility Exception requests must include a confirmation from the DF/HCC Principal Investigator that the request does not impact subject safety, data analysis and a plan for safety monitoring is in place.

9. The following applies to Minor Events:
   A. The Overall PI is required to attest in the continuing review form and log that the minor deviations/violations have all been reviewed. If three or more minor deviations/violations of the same type (or for the same subject) are found in the Minor Log to impact the safety of participants, compromise the integrity of the study data and/or affect a subject's willingness to participate in the study, the events must be submitted to the IRB as a Major Event.
   B. For sponsored trials, proper documentation of sponsor acknowledgement and/or approval for each Minor Event is required and should be kept with the minor log in the lead study site binder.

REPORTING REQUIREMENTS

	Reporting Time Fram (Business Days)	Reporting Form	OHRS Document Subtype
Exception Request	3 days before event date	Major Deviation/Violation/Exception – Other Event Reporting Form	Exception Request
Major Deviation	3 days before event date	Major Deviation/Violation/Exception – Other Event Reporting Form	Deviation Request
Major Violation	Within10 Days of event discovery	Major Deviation/Violation/Exception – Other Event Reporting Form	Violation Report
Other Event	Within10 Days of event discovery	Major Deviation/Violation/Exception – Other Event Reporting Form	Other Event Report
Minor Deviation	Added to log within 30 days of event	Minor Log – Submitted with Continuing Review at least Annually	Minor Deviation / Violation Log
Minor Violation	Added to log within 30 days of event	Minor Log – Submitted with Continuing Review at least Annually	Minor Deviation / Violation Log

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 at least annually with the continuing review form.** A protocol that is approved and taking place at more than one site is still considered one protocol.

Reporting and Policy Questions

Please email the Office for Human Research Studies (OHRS) for assistance at:
OHRSEvent_Reporting@dfci.harvard.edu
Emails will be responded to within one business day. Urgent inquiries should be followed up with a call to the OHRS main number at **(617) 632-3029**.

Examples of Major Deviations / Violations / Exceptions

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

Consent:

- 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

Eligibility:

- Enrollment of a subject who did not meet all inclusion / exclusion criteria

Treatment:

- Performance of a study procedure not approved by the IRB
- 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 which, in the opinion of the PI, may affect subject safety or data integrity
- All drug/study medication dispensing or dosing errors regardless of the percentage of the error.
- Breaches of confidentiality
- 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 inadequate evaluation of toxicity
- Inappropriate destruction of study records
- 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.
- Research conducted on a study after IRB-approval of study has expired
- Subject's continued non-compliance with oral study treatment if it is thought to significantly clinically affect the efficacy of treatment or integrity of the data.

Adverse Event Reporting and Study Conduct Problems:

- Failure to report serious adverse event to the IRB and/or sponsor
- Failure to follow safety monitoring plan
- Recurrent missing documentation in study records
- Frequent data inaccuracies and errors in submitted data

Other:

- Three or more minor deviations for the same subject, or of the same type, but **ONLY** if it impacts the safety of participants, compromises the integrity of the study data and/or affects subject's willingness to participate in the study.
- Request to disclose subject specific research results to a subject or subjects family

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 Treatment 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

Note: If the non-compliance is thought to significantly clinically affect the efficacy of treatment or integrity of the data it should be reported as a major violation.

Examples of 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 an 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

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 Treatment 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

Note: If the non-compliance is thought to significantly clinically affect the efficacy of treatment or integrity of the data it should be reported as a major violation.