THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

# *Policy on Reporting Protocol Deviations, Protocol Violations and Unanticipated Problems*

## SCOPE

This policy applies to all Human Subject Research conducted under the University of Texas MD Anderson Cancer Center (MD Anderson) Institutional Review Board (IRB) oversight. Industry sponsored studies may have additional requirements beyond what is stipulated in this policy.

## PURPOSE

It is the policy of the MD Anderson IRB to comply with the regulations governing human subject research to ensure that variations from approved research protocols are appropriately documented, and communicated to the MD Anderson IRB.

## DEFINITIONS

### Protocol Deviation

Noncompliance with the required elements of the protocol that does not have a significant impact on the subject's rights, safety, welfare, and/or the integrity of the data.
Deviations may be caused by the action of, or the omission of, the subject, the PI, the research team, or natural events.

NOTE: Continuing non-compliance with the protocol may be considered a violation.
Deviations are submitted as logs annually at continuing review. Protocol deviations are typically minor in nature and will not significantly affect the integrity of the study nor patients' safety and welfare.
Most industry sponsors allow investigators to track these types of events on a spreadsheet or log that is maintained in the essential documents (regulatory binder)

### Protocol Violation

Accidental or unintentional change to, or non-compliance with the IRB approved protocol without prior sponsor and IRB approval. Violations generally increase risk or decrease benefit, and may significantly alter the clinical effectiveness of the treatment or the evaluation of its toxicity and may adversely affect the participant's rights, safety, or welfare, or the integrity of the data.

Examples include but are not limited to:

Informed Consent

- Consent form not signed and dated by the patient

- Protocol specific procedures conducted prior to obtaining informed consent
- Consent form used was not current IRB-approved version at the time of patient registration
- Patient not re-consented within timelines described in IRB policy

Eligibility
- Enrollment of ineligible patient

Treatment and Procedures
- Incorrect agent/treatment/procedure used
- Additional agent/treatment/procedure used which is excluded by protocol
- Errors in dosing (error greater than +/- 10%)
- Dose modifications not followed per protocol or unjustified
- Unjustified continuation of treatment

Adverse Events
- Serious or Unexpected Adverse Events not reported as required by protocol and IRB policy

Evaluations
- Protocol-specified laboratory, diagnostic tests, or evaluations to assess patient eligibility, safety, or response not completed

## Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated problems are not limited to study participants, and may also include others such as family members and research staff.

Examples of Unanticipated Problems may include:

- Participant complaints
- Breach of confidentiality of research data
- Lost, stolen or destruction of confidential information
- Disqualification or suspension of investigator's
- Changes made to research without prior IRB approval

- Expected events not reported in a timely manner as required by the protocol or IRB policy

NOTE: Adverse Events that are related to the research procedures or treatment and that may adversely affect the safety or welfare of participating subjects or others and that are unanticipated may also be considered unanticipated problems. Please see IRB Policy on Reporting Adverse Events for Drugs and Devices).

## PROCEDURES

### Reporting Requirements for Protocol Deviations, Violations and Unanticipated Problems

#### Requirements for Prompt Reporting to the IRB

#### Protocol Deviations

The Principal Investigator (PI) is responsible for ensuring that clear documentation is available in the study Essential Documents that describes all protocol deviations and corrective action taken.

The deviation log must be submitted to the IRB during continuing review. The IRB will make a notation on the continuing review approval memo acknowledging receipt of the deviation log. The approval memo should be kept with the study Essential Documents along with a copy of the deviation log.

PIs should note that repetitive deviations may warrant a change to the protocol or the Informed Consent Document (ICD).

Procedures not required as part of the protocol (i.e., those procedures designated as optional) are generally not used for evaluation or assessment of patient eligibility, safety, or response. Delayed or missed optional procedures considered to be low risk (e.g., blood or specimen collections for pharmacokinetic or pharmacodynamics assessments) are not required to be reported as protocol deviations, and thus do not need to be included in the deviation log.

#### Protocol Violations and Unanticipated Problems

The PI is responsible for ensuring that all protocol violations and unanticipated problems are reported to the IRB by completing the Protocol Violation Notification Form or the Unanticipated Problems Form.

The PI is responsible for the accurate documentation, investigation and follow-up of all violations/unanticipated problems.

The PI is also responsible for informing the Sponsor or funding agency of any violation/unanticipated problem to participants or others, as appropriate.

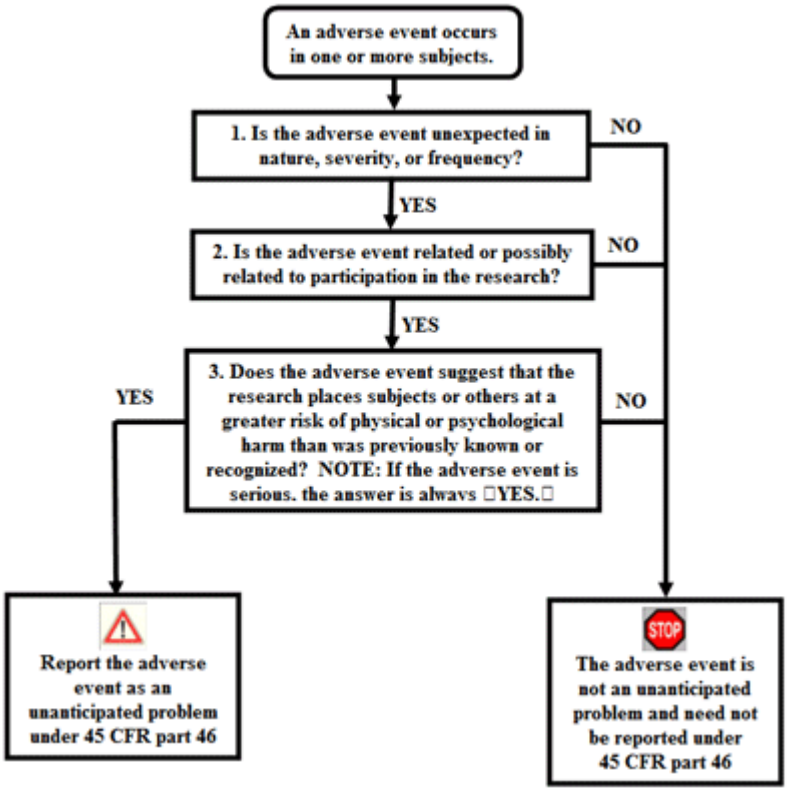
The IRB will issue an official decision letter to the PI acknowledging receipt of the violation/unanticipated problem and outline any actions that should be taken. This decision letter should be kept in the PI's regulatory binder along with the completed violation/unanticipated problem form. The PI must promptly respond to any IRB requests for additional information or action.

Violations/unanticipated problems should be reported to the IRB within 10 working days of the PI becoming aware of the event.

The IRB recognizes that, in some cases, the requirements for prompt reporting may be met by submitting a preliminary report to the IRB with a follow-up report submitted at a later date as more information becomes available.

Unanticipated problems must also be reported to the MD Anderson Office of Human Subjects Protection (OHSP) to determine if reporting to federal authorities is required. Investigators should utilize the Potential Unanticipated Problem Form for reporting unanticipated problems to OHSP.

The flow chart below provides an algorithm for determining whether an adverse event meets the definition of an unanticipated problem involving risk to subjects or others.



## POSSIBLE ACTIONS THE IRB MAY TAKE

An IRB Chair or designee will initially review each submission.

The IRB Chair or designee may approve, approve contingent, defer until additional information is available, or make a determination that the submitted event requires review at a convened IRB meeting, should the event be considered more than minimal risk to the research participant(s).

The IRB may require actions that include, but are not limited to the following:

- Accept the PI's corrective action plan, and require no further action
- Require the PI to make changes to the Informed Consent document
- Require the PI to make changes to the protocol, and other study documents
- Require re-consenting or informing current or previously enrolled research subjects (to occur whenever the information may relate to the subjects' willingness to continue participation in the research)
- Require steps to reduce any immediate risks to subjects or others
- Require modification of the continuing review schedule
- Suspend or terminate the research study
- Request additional information
- Confer with other institutional departments (e.g., Legal, Institutional Compliance, Office of Protocol Support and Management, or the Institutional Official)
- Request a targeted audit of the PI's research studies
- Consult with the PI's Division or Department Head
- Assignment of the oversight of the protocol to an independent monitoring board (e.g., Data Safety Monitoring Board or outside entity, if appropriate)
- Require education and training of the PI and research team
- Take other actions appropriate for the local context

Within 30 days of submission of the event to the IRB, the IRB will report any serious, life-threatening issues related to the research to the Institutional Official and/or the supporting agency including the Food and Drug Administration (FDA) and OHRP, as required by this policy (see IRB Policy on IRB Committee Determinations for Reviewing Research, Non-Compliance, Suspending or Terminating Research and IRB reporting procedures to Institutional and External Officials).

Failure to comply with this policy may result in temporary or permanent suspension of the research and/or the PI's
research privileges.

In accordance with 45 CFR 46.113, any suspensions or terminations of approval will be reported promptly to the PI, to the appropriate institutional officials, and possibly the Federal department or agency head responsible for oversight or funding of the research.

## FORMS

IRB approved forms must be signed by the PI prior to submission.

Protocol Deviation Log:
The Deviation Log should be utilized to log deviations that occur to subjects enrolled on a MD Anderson protocol to be submitted at the annual Continuing Review.

Protocol Violation Tracking Form:
The Violation Form should be utilized to submit any MD Anderson protocol violations within 10 working days of the Principal Investigator learning of the violation.

Unanticipated Problem Form:
The Unanticipated Problem Form should be utilized to submit events that meet all three of the criteria for Unanticipated Problems as described above. These events are to be submitted within 10 working days of the Principal Investigator learning of the event.

### Form Completion

1. All the forms must be completed in full.
2. A concise synopsis describing the event must be provided.
3. If a report is being submitted outside of the stated time frames in this policy, a justification must be provided.
4. For reasons of confidentiality, subject names must NOT be included in any report. Subject identifiers such as participant ID or CORe accession numbers should be used instead.
5. The report form must be signed by the PI.

**All forms and brief instructions on how to submit the above referenced forms can be found in Chapter 3.10 of the HRPP Manual.**

## REFERENCES


21 CFR 56.108
21 CFR 56.109
21 CFR 56.111
ICH GCP 4.5
45 CFR 46.103
45 CFR 46.109
45 CFR 46.111
45 CFR 46.113

OHRP and HSS Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007.

| Revision Date | Description |
|---|---|
| 07/20/2005 | Institutional Review Board 3 (IRB3) Review and Approval |
| 11/02/2005 | IRB3 Review and Approval |
| 05/26/2008 | IRB3 Review and Approval |
| 4/24/2013 | Convened IRB3 Board reviewed and approved the following changes to the policy: Amended Protocol Deviation Requirements to exclude those events related to optional procedures; clarified that documentation for deviations must be reflected in the Study Essential Documents; other minor grammatical corrections throughout document. |
| 07/24/2019 | Convened IRB3 Board reviewed and approved the following changes to the policy: The timeline for Violations and Unanticipated Problem submissions was updated. UP algorithm was included. Links to the Protocol Deviation Log, Unanticipated Problem Form, and Protocol Violation Tracking Form have been included. |