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

Policy on Reporting Adverse Events for Drugs and Devices

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, involving investigational new drugs or devices, commercially available drugs, biologic products, approved devices.

PURPOSE

It is the policy of the MD Anderson IRB to comply with the regulations governing human subject research.

DEFINITIONS

Adverse Event (AE)
Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

For the purpose of this policy, adverse event is synonymous with adverse experience.

Serious Adverse Event (SAE)
Any AE associated with the subject's participation in research that:

- results in death;
- is life-threatening, (places the subject at immediate risk of death from the event as it occurred);
- results in in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant incapacity or substantial disruption of a person's ability to conduct normal life functions;
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Protocol-related documents
Refers to the IRB-approved research protocol, informed consent document, investigator brochure, protocol, package insert, or label.

Unanticipated AE (UAE)
Any AE, the specificity or severity of which is not consistent with the current investigator brochure (IB); or is not consistent with the risk information described in the protocol-related documents.

For the purpose of this policy, unanticipated is synonymous with unexpected.

Expected AE (EAE)
Any AE, the specificity or severity of which is consistent with the current IB; or is consistent with the risk information described in the protocol-related documents.

For the purpose of this policy, expected is synonymous with anticipated.

AE Attribution
The determination of whether an AE is related to the research (medical treatment or intervention):

- Definite – It is clearly related
- Probable – It is likely related
- Possible – It may be related
- Unlikely – It is doubtfully related
- Unrelated – It is clearly NOT related

AE Severity
Refers to the intensity (grading) of a specific AE. For the purpose of this policy, toxicity is synonymous with AE.

Internal AE (IAE)
An AE experienced by subjects enrolled by investigators in research protocols conducted under the oversight of a MD Anderson IRB, this includes research conducted at an affiliated site (i.e., Houston Area Locations).

External AE (EAE)
An AE experienced in subjects who are not enrolled in a MD Anderson protocol or is on a protocol at a site that is under the oversight of another IRB.

Safety Report
Safety report is a written summary of on-going safety evaluation of clinical trials prepared by the sponsor with the purpose of informing different participating sites and to fulfill with safety reporting requirements.

Dear Investigators Letter (DIL)
DIL are correspondence, usually from the sponsor, intended to alert investigators about important new or updated information regarding a drug or a product.

External IRB
MDA may rely on an external IRB, meaning the IRB of another institution or organization, or an independent (commercial) IRB, for review and approval of human subject research in certain circumstances (refer to Chapter 13.1 of the Human Research Protection Program Manual [HRPP Manual]).

Unanticipated Adverse Device Event (UADE)
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a

supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)).

PROCEDURES

Reporting Requirements for Internal AEs (Drugs and Devices)

Requirements for Prompt Reporting to the IRB

The MD Anderson IRB requires that the investigators submit a prompt report for IAEs assessed as unanticipated, serious and related to the research and that requires modifications to the protocol-related documents. The investigators are responsible for providing a meaningful summary, analysis or explanation of the event reported in order to enable the IRB to make further determinations regarding the protection of the participants.

An individual AE occurrence most of the time will not require modifications to the protocol-related documents because, as an isolated event, its implications for the study cannot be understood.

Other IAEs requiring prompt reporting:

1. One or more occurrences of possibly or probably treatment/device related serious events that would not otherwise be expected in the study population.
2. Multiple occurrences of an AE that, based on aggregated analysis, is determined to be an unanticipated problem and could involve risk to human subjects.
3. An expected IAE that occurs at a specificity or severity that is inconsistent with prior observations.
4. An expected IAE for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence.
5. Any other AE or safety finding that would cause the sponsor to modify the protocol-related documents, or would prompt other action by the IRB to ensure the protection of human subjects.
6. Deaths if unanticipated and related to study intervention. Investigators are responsible for assessing the cause of death.

Timeline for prompt reporting to the IRB

All IAEs meeting criteria for prompt reporting must be reported to the IRB within 10 working days from the time the investigator becomes aware of the event.

IAEs that meet the criteria for prompt reporting will be sent to the IRB Chair or designee for review. If the IRB Chair or designee determines that the report does not meet criteria for prompt reporting, the IAE is returned to the investigator with a notification to report the event during continuing review. If the Chair or designee determines that the report meets the criteria for prompt reporting and requires modifications to the protocol-related documents, the IAE is forwarded to the Executive IRB for convened board review.

IAEs not requiring prompt reporting must be reported to the IRB as part of the continuing review process.

During the continuing review process, the investigators are responsible for providing the IRB with a substantive and meaningful report of adverse events observed. This could be submitted in an aggregated summary, tabulated format and/or, if applicable, safety reports provided by the sponsor.

Reporting Requirements for UADEs

UADEs must be reported by the clinical investigator to the sponsor and to the MD Anderson IRB, as described below:

- For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)).
- If MD Anderson is the Sponsor, it must immediately conduct an evaluation of an UADE and must report the results of the evaluation to the FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§812.46(b), 812.150(b)(1)).

Reporting Requirements for External AEs and Safety Reports

Investigators are notified of EAEs from the Sponsor generally by Medwatch report or DIL.

The MD Anderson IRB requires that the investigators submit EAEs **only** if modifications to the protocol-related documents are required. The Sponsor in this situation is responsible for determining if safety related changes are required.

Safety Reports not requiring modifications to the protocol-related documents will be reported to the IRB as part of the continuing review process.

The MD Anderson IRB will not review EAE's that do not meet the reporting requirements described above and will not acknowledge the reports.

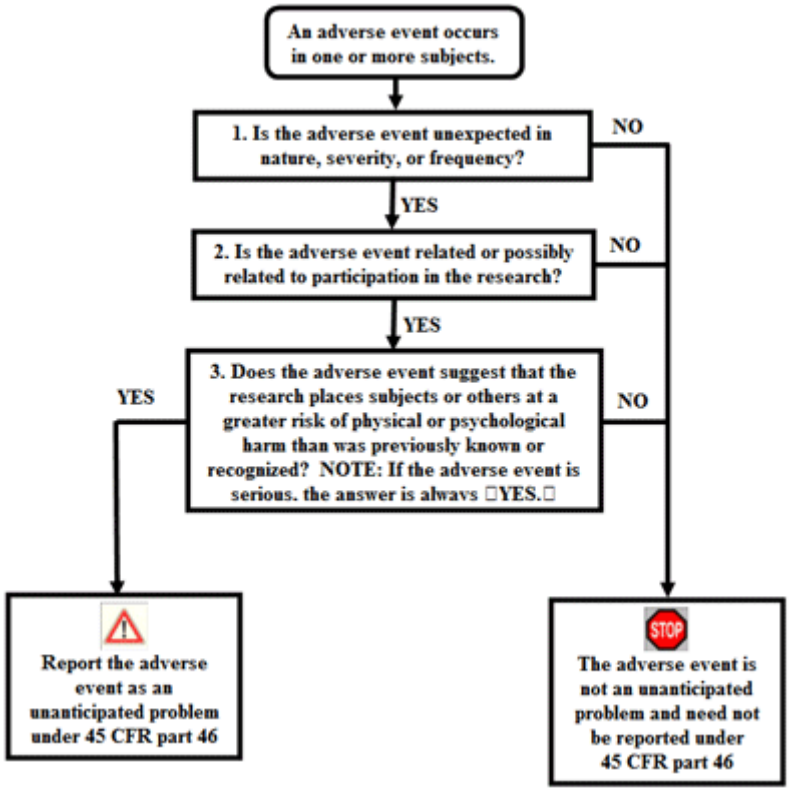
Reporting Requirements for Protocols under an External IRB Oversight

For studies that are under the oversight of an external IRB (e.g., NCI CIRB, Western IRB, etc), the investigator must follow the reporting requirements for the external IRB for submitting local adverse events, UAEs, UADEs, unanticipated problems and other safety issues related to the study. Investigators should reference the external IRBs investigator manual or confer with the external IRB for additional information.

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.

Expected Adverse Events or Adverse Events which are determined by the investigator to be

unrelated to the Research Intervention will not be reviewed by the IRB. 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.



FORMS

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

Internal SAE Report Form for Prompt Reporting:
The Internal SAE Form should be utilized to report events that occur to subjects enrolled on a MD Anderson protocol.

Internal SAE Addendum Form for Prompt Reporting:
May be completed if the protocol sponsor requires a protocol specific form to be completed for subjects enrolled on a MD Anderson protocol (i.e., Medwatch report, DIL). This addendum should be completed and attached to the sponsor form for submission.

Departmental External SAE Report Form for Prompt Reporting:
External SAEs of single or multiple protocols using the same drug, within a department can be submitted using the Departmental External AE Form for Prompt Reporting.

Safety Report
Safety summary reports received from the sponsors must be submitted using the safety report submission memo.

Form Completion

1. All the forms must be completed in full.
2. Please provide the correct protocol status (for example, Active or CNPE etc).
3. If the SAE is noted as “ongoing” at the time of initial reporting, a follow-up report will be required when the outcome of the SAE is known or when the event is considered to be permanent.
4. For follow-up reports, the date that the research team is notified should be the same as that of the initial report and the date submitted should be the actual date the follow-up report is submitted.
5. A concise synopsis describing the event must be provided. For follow-up reports, an updated synopsis must be provided.
6. If a report is being submitted outside of the stated time frames in this policy, a justification must be provided. (Note: failure to report an SAE in time may be considered a violation and repeated occurrences may constitute “continuing non-compliance”)
7. For reasons of confidentiality, subject names must NOT be included in any report or must be blacked out on patient reports. Subject identifiers such as participant ID or CORe accession numbers should be used instead.
8. All report forms must include the attribution and grade of the event.
9. The report form must be signed by the PI. The form can be signed by the attending physician, but only when the PI is not available.

All forms can be found in Chapter 3.10 of the HRPP Manual.

REFERENCES

21 CFR 56.108(b)
21 CFR 310.305
21 CFR 312.32
21 CFR 314.80
21 CFR 812
45 CFR 46.103
45 CFR 46.109
45 CFR 46.111
45 CFR 46.113
ICH GCP 4.11

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

Guidance for Clinical Investigators, Sponsors and IRBs Adverse Event Reporting to IRBs- Improving Human Subject Protection, January 2009 FDA Guidance.

Date	Action	Initials	Description
11, 1, 2006	Review	RT RF LE	Institutional Review Board 3 (IRB3) Review
3, 26, 2008	Review	RF	IRB3 Review
4, 23, 2008	Review	RF	IRB3 Review
3, 29, 2009	Review	RF	IRB3 Review
11, 10, 2010	Review	RF	IRB3 Review
05, 23, 2012	Review	RF	IRB3 Review
06, 27, 2012	Review	RF	IRB3 Review
6.27.2019	Revised	MT	Updated the policy to provide further clarifications on internal vs external submission with regards to what requires prompt reporting. Added additional definitions, added the UP algorithm for adverse events.