**Guidance: Unanticipated Problems**

**Policy:**  The Principal Investigator is responsible for the management, accurate documentation, and timely reporting of unanticipated problems involving risks to subjects or others.

**Key Terms**

**Adverse Event:** Any undesirable and unintended, although not necessarily unexpected, effect of the research occurring in human subjects as a result of (a) the interventions and interactions used in the research; or (b) the collection of identifiable private information under the research.

**Adverse Event** (clinical trials): An AE is any untoward medical occurrence in a research subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

**Important Medical Events:** Medical and scientific judgment should be exercised to report other medical events that may not fall under the serious adverse event criteria, if these important events jeopardize the patient or may require intervention to prevent a serious adverse event.

**Internal Adverse Event -** An event involving UT Houston research subject or a research subject at an institution for which the UT Houston CPHS serves as the IRB of Record (including Memorial Hermann Hospital and Harris County Hospital District).

**External Adverse Event -** An event involving research subjects enrolled by other institutions in multicenter research projects that fall under the purview of an external IRB (i.e. not UT Houston CPHS). These may be submitted as Medwatch reports (FDA Form 3500A), CIOMS reports, IND Safety Reports and SUSAR reports.

**Unanticipated Problem:** Problems that (1) are not expected given the nature of the research procedures and the subject population being studied; and (2) suggest that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known or recognized.

**Unexpected adverse drug experience:** Any adverse experience the specificity or severity of which is not consistent with the current Investigator Brochure, or if an Investigator Brochure is not required, that is not consistent with the specificity or severity in the risk information described in the general investigational plan or elsewhere in the current application, as amended.

**Problems to Report to CPHS -**

1. Internal Adverse Events that meet the following criteria:

* Event is unexpected in terms of nature, severity or frequency as described in IRB approved protocol and consent documents.
* Related or possibly related to participation in the research.
* Suggests that this places subjects or others at greater risk of harm (physical, psychological, economic or social) than was previously known or recognized.

1. External Adverse Events that meet the following criteria:

* Event is unexpected in terms of nature, severity or frequency as described in IRB approved protocol and consent documents.
* Related or possibly related to participation in the research.
* Suggests that this places subjects or others at greater risk of harm than was previously known or recognized by providing an analysis of the significance of the current event with respect to previous events.
* Includes a corrective action plan.

1. Death of a research subject at this site.
2. Information that indicates a change to the risks or potential benefits of the research. For example:

* An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB.
* A paper is published from another study that shows that the risks or potential benefits of the research may be different than initially presented to the IRB.

1. A breach of confidentiality.
2. Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
3. Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant.
4. Incarceration of a participant in a protocol not approved to enroll prisoners.
5. Event that requires prompt reporting to the sponsor.
6. Sponsor imposed suspension for risk.
7. Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the study team.
8. Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm.
9. Sponsor imposed suspension for risk.
10. Unanticipated adverse device effect.
11. Any other problem determined by the study team to be an unanticipated problem involving risks to subjects or others.

**Identifying Problems –** The study protocol should describe what would be regarded as adverse events and as serious adverse events including clinically significant laboratory values. The protocol should also include details of the protocol specific reporting procedures, including the individual responsible for each step, how decisions will be made regarding determining relatedness and grading severity, how reports will be distributed and what follow up are required. The Principal Investigator should ensure that study team members are trained to identify adverse events. Some methods of identifying problems include:

* Asking participants at every visit whether they have had any health problems since the last visit.
* Reviewing medical records to identify prescriptions, hospitalizations etc.
* Reviewing study documents such as pharmacy records to ensure the correct dosage of the study drug was given.

**Managing Problems -** The PI should ensure that adequate medical care is provided to the subject for treatment of adverse events. If the trial is blinded, the PI should evaluate whether breaking the blind would be necessary for the immediate medical care of the subject. The PI should consider if discontinuing the investigational product, reduce dosage or interrupting use of the investigational product might help the subject. The PI should follow the subject and assess the adverse event until stabilized/resolved. The PI should document the adverse event and the management in the source documents. Documentation should include:

* + - Details of the event,
    - Causality and severity of event,
    - Date of onset and end date of event,
    - Treatment provided to subject including medication prescribed,
    - Outcome of the event.

**Assessing Problems -** The Principal Investigator must review the event and make a judgement about the expectedness, seriousness and causality of the event.

* **Expectedness -** The investigator must make a judgement on whether the event is expected or unexpected. An unexpected adverse reaction is one, the nature and severity of which is not consistent with information in the relevant source document (s). For a medicinal product not yet approved for marketing in Singapore, the Investigator Brochure will serve as the source document. Reports that add significant information on specificity or severity of a known, already documented serious adverse event constitute unexpected events. For example, an event more specific or more severe than described in the Investigator’s Brochure would be considered unexpected.
* **Causality –** The PI should evaluate all cases to assess causality. The expression ‘reasonable causal relationship’ is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship. For purposes of reporting, adverse event reports associated with marketed drugs usually imply causality. The following conditions might help to assess causality:
  + - * the event has a reasonable temporal relationship to the intervention
      * the event could not have been produced by the underlying disease states
      * the event could not have been due to other non-study interventions
      * the event follows a known pattern of response to the intervention
      * the event disappears with cessation of intervention

**Corrective Action Plan –** In addition to managing the problem, the PI should evaluate the steps necessary to prevent a similar problem in the future. This may include:

* Changes to the study protocol,
* Changes to eligibility criteria,
* Changes to data and safety monitoring plan,
* Changes to consent form,
* Training study staff,
* Any other plan that may reduce the risk of the problem occurring in the future.

**Reporting:** The PI must submit safety reports to:

* CPHS – when it meets the criteria for reporting as described below.
* Sponsor - for industry sponsored trials using the template of reporting as agreed with the sponsor at the start of the trial
* FDA - clinical trials for which the PI is the sponsor-investigator.

**Timelines for Reporting to CPHS –** Investigators must report the reportable events described above to CPHS via iRIS within 7 days, unless the report involves the death of a participant, in which case the report needs to be provided to CPHS within 24 hours.

1. All problems involving local deaths, should be reported immediately – **within 24 hours** after first knowledge by the investigator.
2. All other problems must be reported as soon as possible but not later than **7 calendar days** after first knowledge by the investigator.

**Applicable Regulations and Guidelines**

* OHRP Unanticipated Problem Guidance - <http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm>
* FDA AE Reporting to IRBs Guidance - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079753.pdf>
* FDA Safety Reporting Guidance for INDs – <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf>
* OHRP Regulations – 45 CFR 46
* FDA IND Regulations - 21 CFR 312
* FDA IDE Regulations - 21 CFR 812

**Applicable Institutional Policies and Guidelines**

* Feasibility Assessment – GCP Guidance

**Attachments**

* Unanticipated Problems Log

**If you find errors in this document, contact** [**clinicaltrials@uth.tmc.edu**](mailto:clinicaltrials@uth.tmc.edu)

|  |  |
| --- | --- |
| **Document Number:** | 402-018 |
| **Author:** | Clinical Trials Resource Center |
| **Effective:** | June 1, 2011 |
| **Revision History:** | None |
|  |  |
|  |  |