

**Unanticipated
Problems Potentially
Involving Risks to
Subjects or Others**

**UVM Research
Protections Office**

Unanticipated Problems (UAPs)

- The IRB is responsible per federal guidelines to review any unanticipated problems involving risks to subjects or others occurring in approved research (FDA: 21 CFR 56.108 (b)(1) & DHHS: 45 CFR 46.103(b)(5)(i))
- The IRB reviews unanticipated problems to determine if the risk/benefit ratio of a protocol has changed

What is an Unanticipated Problem?

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

- ✓ *unexpected*
- ✓ *related or possibly related to research*
- ✓ *suggests study presents greater risk than previously recognized*

Is the incident UNEXPECTED?

1. unexpected

(in terms of nature (*type of event*), severity (*extent of harmfulness*), or frequency (*number of like events higher than anticipated*) 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;

Is the incident RELATED to the study?

2. related or possibly related

to participation in the research

(*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);

In the eyes of the IRB, the PI is in the best position to make this determination.

Does the incident involve HARM or the POTENTIAL for Harm?

3. 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.

What is Reportable to the Committee?

The following slides outline what types of incidents need to be reported to the IRB.

Under What Categories Do Most UAPs occur?

1. LOCAL ADVERSE EVENTS
2. NEW SAFETY INFORMATION
3. PROTOCOL DEVIATIONS
4. OTHER UNANTICIPATED PROBLEMS

Local versus Non-Local Events

The IRB requires RNI reporting on local subjects only.

- **Local**

Subject is enrolled at UVM, UVMMC, or other research site under the jurisdiction of the UVM IRB

- **Non-Local**

- Multi-center studies
- Subjects are enrolled elsewhere
- Subjects are NOT UVM or UVMMC subjects

LOCAL ADVERSE EVENTS

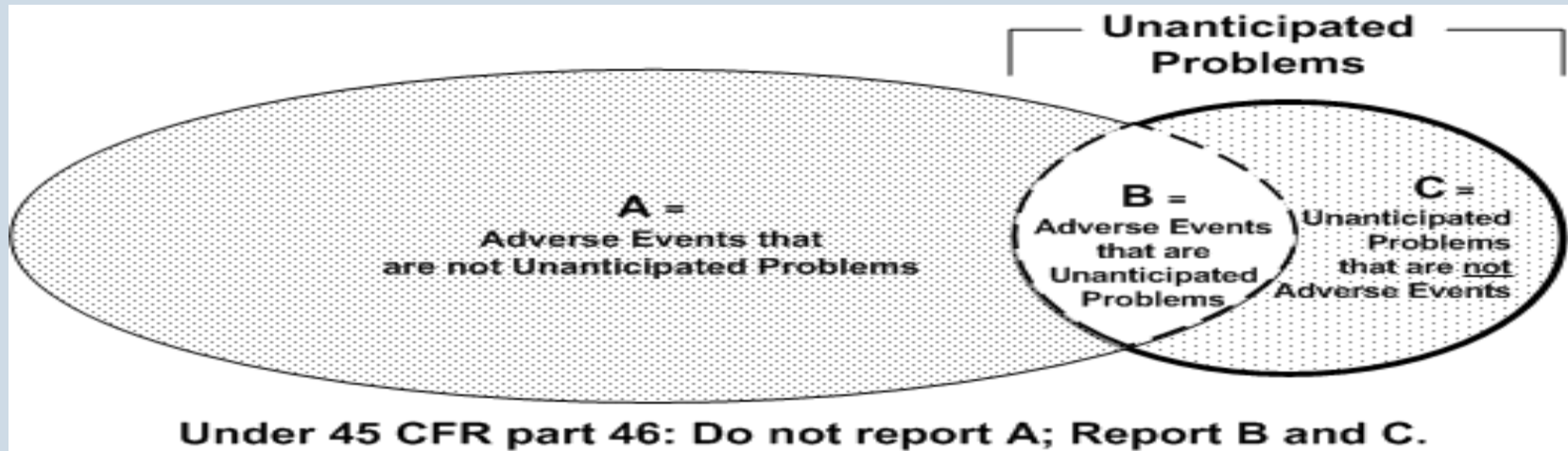
Report both serious AND non-serious adverse events that are both:

- *unexpected (defined earlier)*

AND

- *possibly, probably, or definitely related to study participation*

LOCAL ADVERSE EVENTS



1. The vast majority of adverse events (area A) occurring in the context of research are expected in light of (1) the known toxicities and side effects of the research procedures; (2) the expected natural progression of subjects' underlying diseases; and (3) subjects' predisposing risk factors. Thus, most individual adverse events do not meet this criterion for an unanticipated problem and do not need to be reported.

2. A small proportion of adverse events are unanticipated problems (area B) and need to be reported to the IRB.

3. Unanticipated problems include other incidents, experiences, and outcomes that are not adverse events (area C) and need to be reported to the IRB.

1. LOCAL ADVERSE EVENTS

For those local adverse events meeting the criteria as an unanticipated problem involving risk to subjects submit through the UVMClick system under “reportable new information (RNI)”

- [How to Create and Submit an RNI](#)

Determination of Higher Risk Reporting

The IRB may, in coordination with other institutional oversight committees, categorize a protocol as “higher risk” and require the Investigator to report all local adverse events promptly to the IRB, regardless of whether the event is related or expected.

This determination will be made at time of initial review or anytime after initial review if the IRB feels it is warranted.

This determination and the reporting requirements will be clearly communicated back to the Investigator.

Determination of Higher Risk Reporting

Examples of clinical trials for which the IRB may institute more stringent reporting are:

- local, investigator-initiated early phase study
(Phase I, Phase I/II)
- local, investigator-initiated trial in extremely vulnerable populations, e.g., very sick patients
- subjects unable to consent for themselves
- previous history of noncompliance
- protocols involving prisoners

2. INTERIM FINDINGS or NEW SAFETY INFORMATION

New Safety Information that requires a change to the protocol or consent form must be reported to the IRB by submitting a modification through the UVMClick system.

- Revised Investigator Drug/Device Brochures (IDB);
- Toxicity Reports or Action Letters;
- Data and Safety Monitoring Reports/Progress Reports;
- Literature Reviews; or
- other safety information that may impact human subject welfare.

How to submit a modification

2. INTERIM FINDINGS

New Safety Information that does not require a change to the protocol or consent form must be reported to the IRB utilizing the UVMClick system under “reportable new information”

INVESTIGATIONAL NEW DRUG (IND) SAFETY REPORTS

IND safety reports do not require submission to the IRB

IND Safety Reports do not necessarily meet the reportable criteria and are recognized by OHRP and the FDA to not yield information that is useful to IRBs.

The reports often lack context and detail, are often incomplete and unanalyzed, and as such, inhibit an IRB's ability to assure the protection of human subjects.

However, if an individual IND report results in a revision to the protocol or consent

Submit a "Modification" through the UVMClick system along with a copy of the specific IND safety report and a revised protocol and consent

Generally study sponsors will let PI's know when this revision to the protocol is needed

3. PROTOCOL DEVIATIONS

A protocol deviation is a divergence or departure from the expected conduct of an IRB-approved study that is not consistent with the current, approved research protocol, consent process or document or study addenda.

The significance of a protocol deviation, in terms of subject safety, depends on the nature of the deviation and the study.

Those protocol deviations that involve harm or have the potential to impact the health or welfare of the subject(s) or others must be reported to the IRB by submitting a RNI submission through UVMClick.

Examples of reportable deviations are below:

- *Medication or Laboratory Errors that involve potential harm;
- Improper or Unapproved Consent Process or Consent Form;
- Unintentional change to the protocol without prior IRB approval;
- Intentional change to the protocol without prior IRB approval to eliminate immediate hazard to research subject.

PROTOCOL DEVIATIONS

**The principal investigator, as the expert in the field, must determine if there is potential for harm with any medication errors.*

3. PROTOCOL DEVIATIONS

Protocol deviations (e.g., missed appointment, labs one day late) that do not involve harm or have the potential to impact the health or welfare of the subject(s) or others do not need to be individually reported.

Deviations not affecting risk to subjects or others should be summarized and reported at time of continuing review.

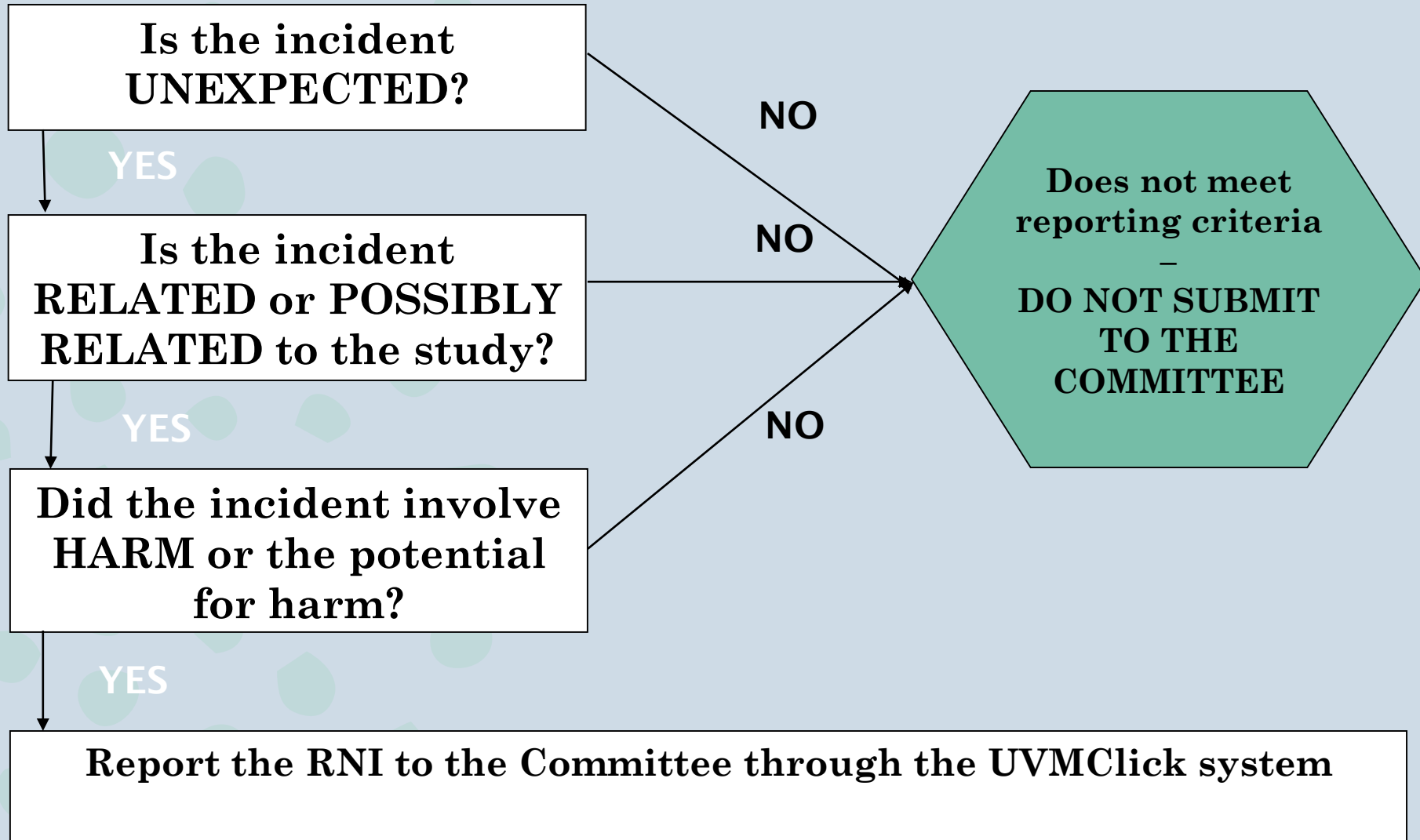
4. OTHER UNANTICIPATED PROBLEMS

Below are examples of other types of protocol-related problems that must be reported to the IRB:

- Complaint by a subject;
- Breach of confidentiality/HIPAA violation;
- Enforcement action e.g., unfavorable audit report, suspension or disqualification of investigator, FDA Form 483 or Warning Letter;
- Study personnel misconduct;
- Study personnel not on protocol;
- Incarceration of a research subject during participation;
- Other untoward events that present risk to the subject, investigator, research staff or others.
- These unanticipated problems are to be reported to the IRB utilizing the UVMClick system under “reportable new information”

Determining What Incidents to Report

Remember incidents can include, local adverse events, interim findings, deviations, or others that involve risk to subjects or others.



Determining What Incidents to Report

Exception: All consent form deviations are required to be reported to the RPO.

IRB Committee members will determine if the deviation increased risk to subjects

Exception: All adverse events are reportable if the protocol is deemed “high risk” by the Committee

Determining When to Report UAPs

All unanticipated problems are to be reported as soon as possible.

If all information is not available within 7 days, submit an initial report at 7 days and then follow-up with the IRB as information becomes available.

Examples of Unanticipated Problems that Do Not Involve Adverse Events and Need to be Reported Under the HHS Regulations at 45 CFR Part 46

An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work.

This is an unanticipated problem that must be reported because the incident was

- (a) unexpected (i.e., the investigators did not anticipate the theft);
- (b) related to participation in the research; and
- (c) placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.

Examples of Unanticipated Problems that Do Not Involve Adverse Events and Need to be Reported Under the HHS Regulations at 45 CFR Part 46

As a result of a processing error by a pharmacy technician, a subject enrolled in a multicenter clinical trial receives a dose of an experimental agent that is 10-times higher than the dose dictated by the IRB-approved protocol. While the dosing error increased the risk of toxic manifestations of the experimental agent, the subject experienced no detectable harm or adverse effect after an appropriate period of careful observation.

Nevertheless, this constitutes an unanticipated problem for the institution where the dosing error occurred that must be reported because the incident was

- (a) unexpected;
- (b) related to participation in the research; and
- (c) placed subject at a greater risk of physical harm than was previously known or recognized.

Examples of Adverse Events that Represent Unanticipated Problems and Need to be Reported Under the HHS Regulations at 45 CFR Part 46

A subject with seizures enrolls in a randomized, phase 3 clinical trial comparing a new investigational anti-seizure agent to a standard, FDA-approved anti-seizure medication. The subject is randomized to the group receiving the investigational agent. One month after enrollment, the subject is hospitalized with severe fatigue and on further evaluation is noted to have severe anemia (hematocrit decreased from 45% pre-randomization to 20%). Further hematologic evaluation suggests an immune-mediated hemolytic anemia.

The known risk profile of the investigational agent does not include anemia, and the IRB-approved protocol and informed consent document for the study do not identify anemia as a risk of the research. The investigators determine that the hemolytic anemia is possibly due to the investigational agent.

This is an example of an unanticipated problem that must be reported because the hematologic toxicity was

- (a) unexpected in nature;
- (b) possibly related to participation in the research; and
- (c) serious.

Examples of Adverse Events that Represent Unanticipated Problems and Need to be Reported Under the HHS Regulations at 45 CFR Part 46

A behavioral researcher conducts a study in college students that involves completion of a detailed survey asking questions about early childhood experiences. The research was judged to involve no more than minimal risk and was approved by the IRB chairperson under an expedited review procedure. During the completion of the survey, one student subject has a transient psychological reaction manifested by intense sadness and depressed mood that resolved without intervention after a few hours.

The protocol and informed consent document for the research did not describe any risk of such negative psychological reactions. Upon further evaluation, the investigator determines that the subject's negative psychological reaction resulted from certain survey questions that triggered repressed memories of physical abuse as a child. The investigator had not expected that such reactions would be triggered by the survey questions.

This is an example of an unanticipated problem that must be reported in the context of social and behavioral research because, although not serious, the adverse event was (a) unexpected; (b) related to participation in the research; and (c) suggested that the research places subjects at a greater risk of psychological harm than was previously known or recognized.

Examples of Adverse Events that Do Not Represent Unanticipated Problems and Do Not Need to be Reported under the HHS Regulations at 45 CFR Part 46

A subject participating in a phase 3, randomized, double-blind, controlled clinical trial comparing the relative safety and efficacy of a new chemotherapy agent combined with the current standard chemotherapy regimen, versus placebo combined with the current standard chemotherapy regimen, for the management of multiple myeloma develops neutropenia and sepsis. The subject subsequently develops multi-organ failure and dies. Prolonged bone marrow suppression resulting in neutropenia and risk of life-threatening infections is a known complication of the chemotherapy regimens being tested in this clinical trial and these risks are described in the IRB-approved protocol and informed consent document.

The investigators conclude that the subject's infection and death are directly related to the research interventions. A review of data on all subjects enrolled so far reveals that the incidence of severe neutropenia, infection, and death are within the expected frequency.

This example is not an unanticipated problem because the occurrence of severe infections and death – in terms of nature, severity, and frequency – was expected.

Examples of Adverse Events that Do Not Represent Unanticipated Problems and Do Not Need to be Reported under the HHS Regulations at 45 CFR Part 46

A subject is enrolled in a phase 3, randomized clinical trial evaluating the relative safety and efficacy of vascular stent placement versus carotid endarterectomy for the treatment of patients with severe carotid artery stenosis and recent transient ischemic attacks. The patient is assigned to the stent placement study group and undergoes stent placement in the right carotid artery. Immediately following the procedure, the patient suffers a severe ischemic stroke resulting in complete left-sided paralysis. The IRB-approved protocol and informed consent document for the study indicated that there was a 5-10% chance of stroke for both study groups.

To date, 25 subjects have been enrolled in the clinical trial, and 2 have suffered a stroke shortly after undergoing the study intervention, including the current subject. The DSMB responsible for monitoring the study concludes that the subject's stroke resulted from the research intervention.

This example is not an unanticipated problem because the occurrence of stroke was expected and the frequency at which strokes were occurring in subjects enrolled so far was at the expected level.

In Summary

An unanticipated problem is any incident, experience, or outcome that meets all three criteria below:

1. Unexpected; AND
2. Related or Possibly Related; AND
3. Greater risk of harm than was previously known or recognized.