Columbia University IRB
Guidance for Processing of
Unanticipated Problem Reports of External Adverse Events
October 29, 2013

This document provides guidance for determining when an adverse event at a non-Columbia institution, in a multicenter study in which Columbia is a participating site, should be submitted to the Columbia IRB. Procedures that the IRB will follow upon receipt of such reports are also described.

Applicability: Reports of adverse events that have occurred at non-Columbia institutions participating in multicenter studies as study sites when Columbia is not the lead institution.

Review process:

1. If the **monitoring entity has provided a determination that the adverse event meets the criteria to be considered an unanticipated problem involving risks to subjects or others, and therefore indicates that a change to the protocol and/or consent requirements is warranted**:
   - The report of the UP should be submitted via the Rascal Unanticipated Problems module;
   - IRB staff will:
     - conduct a pre-review and ask, if this information is not included in the report or the modification has not been submitted in Rascal, when the modification will be submitted;
     - Leave the UP report in the IRB queue until the modification is submitted, unless subjects need to be notified immediately in which case the UP report will be logged in;
       - If it appears that subjects need to be notified of new risks, IRB staff will consult with the IRB Chair to determine whether IRB action should be taken.
     - Log in the UP report to be reviewed by an IRB member when the modification is submitted.

2. If the **monitoring entity has provided a determination that the adverse event meets the criteria to be considered an unanticipated problem involving risks to subjects or others, and has indicated that NO change to the protocol and/or consent requirements is warranted**:
   - The UP should not be reported to the IRB.
   - IRB staff will return the UP report if it is submitted, with notification that the event does not meet our reporting requirement for external AEs in multicenter studies, even if the event meets the criteria to be considered a UP (unanticipated, related, increases risk).

3. If the **monitoring entity has provided a determination that the adverse event meets the criteria to be considered an unanticipated problem involving risks to subjects or others, but has not indicated that a change to the protocol and/or consent requirements is warranted**:
   - The UP should not be reported to the IRB until the determination of whether a change is indicated has been made by the monitoring entity.
   - IRB staff will return the UP report if it is submitted at this stage, with guidance that the UP does not meet the CU IRB reporting requirements for external events in multicenter trials, because no change to the protocol and/or consent requirements has been determined to be necessary, and that the UP should be resubmitted if the monitoring entity makes a determination that a change is required.

4. If the **monitoring entity <u>has not provided a determination</u> that the adverse event meets the criteria to be considered an unanticipated problem involving risks to subjects or others**:
   - The UP should not be reported to the IRB until the determinations of whether the AE is a UP and whether a change is indicated has been made by the monitoring entity.
   - IRB staff will return the UP report if it is submitted at this stage, with guidance that the AE does not meet the CU IRB reporting requirements for external events in multicenter trials, because it has not been determined to be a UP, and that the AE should be resubmitted if the monitoring entity makes a determination that the AE is a UP, and that a change is required.

5. If the **monitoring entity has provided a determination that the adverse event <u>does not meet the criteria to be considered an unanticipated problem</u> involving risks to subjects or others, and has indicated that <u>NO change to the protocol and/or consent requirements</u> is warranted**:
   - The UP should not be reported to the IRB.
   - IRB staff will return the report if it is submitted, with guidance that the adverse event does not meet our reporting requirement because it is not considered a UP (unanticipated, related, increases risk).

	Monitoring entity determination of whether AE is UP	Monitoring entity determination of whether change required	Submit in Rascal?	IRB staff processing if submitted	IRB Chair or member review
1	Yes	Yes	Yes	Check if mod also submitted; if no, ask when it is expected. Retain UP in the IRB queue if mod is not ready and subjects do not need to be notified of new or increased risks. Review UP and mod together if possible; review UP first if subjects need to be notified about increased or new risks	Yes
2	Yes	No	No	Return; advise that AE does not meet UP reporting requirements for external MC events	N/A
3	Yes	None	Not until determination is made	Return; advise to submit only if determination that change is required, and with mod information	N/A
4	None	None	Not until both determinations are made	Return; advise to submit only if determination of UP and that change is required, and with mod information	N/A
5	No	No	No	Return; advise to submit only if determination of UP and that change is required, and with mod information	N/A

IRB staff will consult with the respective IRB Chair if information submitted in a UP report appears to indicate that actions different from the general guidelines above should be taken.

Appendix A provides regulatory guidance regarding reporting external events.

Appendix B provides sample correspondence that the IRB will use when returning reports to researchers.

Appendix A: Regulatory Guidance

FDA guidance regarding external events (excerpts from guidance document):

In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, ***only*** if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure). An individual AE occurrence ***ordinarily*** does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

IND:
In a multicenter study, it is clear that individual investigators must rely on the sponsor to provide them information about AEs occurring at other study sites. It is also clear that the sponsor receives AE information from all study sites and typically has more experience and expertise with the study drug than an investigator. Accordingly, the sponsor is in a better position to process and analyze the significance of AE information from multiple sites and—when the determination relies on information from multiple study sites or other information not readily accessible to the individual investigators (e.g., a sponsor's preclinical data that supports the determination)—to make a determination about whether an AE is an unanticipated problem. Furthermore, the regulations require the sponsor of an IND to promptly review all information relevant to the safety of the drug and to consider the significance of the report within the context of other reports (§ 312.32)7

The regulations state that for studies conducted under 21 CFR part 312, investigators must report all "unanticipated problems" to the IRB (§§ 312.66, 312.53(c)(1)(vii), and 56.108(b)(1)). However, as discussed above, we recognize that for multicenter studies, the sponsor is in a better position to process and analyze adverse event information for the entire study and to assess whether an adverse event occurrence is both *unanticipated* and a *problem* for the study.

Accordingly, to satisfy the investigator's obligation to notify the IRB of unanticipated problems, an investigator participating in a multicenter study may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor. In addition, if the investigator knows that the sponsor has reported the unanticipated problem directly to the IRB, because the investigator, sponsor, and IRB made an explicit agreement for the sponsor to report directly to the IRB,8 and because the investigator was copied on the report from the sponsor to the IRB, FDA intends to exercise its enforcement discretion and would not expect an investigator to provide the IRB with a duplicate copy of the report received from the sponsor.

IDE:
The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as "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)). UADEs must be reported by the clinical investigator to the sponsor and the reviewing 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)).

Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to 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)).

The IDE regulations, therefore, require sponsors to submit reports to IRBs in a manner consistent with the recommendations made above for the reporting of unanticipated problems under the IND regulations.

FDA guidance: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf

OHRP guidance regarding external events (excerpts from guidance document):

The phrase "unanticipated problems involving risks to subjects or others" is found but not defined in the HHS regulations at 45 CFR part 46. OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

1. 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;

2. 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); and

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.

OHRP recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research. OHRP notes that an incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

B. Reporting of *external* adverse events by *investigators to IRBs*

Investigators and IRBs at many institutions routinely receive a large volume of reports of external adverse events experienced by subjects enrolled in multicenter clinical trials. These external adverse event reports frequently represent the majority of adverse event reports submitted by investigators to

IRBs. OHRP notes that reports of individual external adverse events often lack sufficient information to allow investigators or IRBs at each institution engaged in a multicenter clinical trial to make meaningful judgments about whether the adverse events are unexpected, are related or possibly related to participation in the research, or suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

OHRP advises that it is neither useful nor necessary under the HHS regulations at 45 CFR part 46 for reports of individual adverse events occurring in subjects enrolled in multicenter studies to be distributed routinely to investigators or IRBs at all institutions conducting the research. Individual adverse events should only be reported to investigators and IRBs at all institutions when a determination has been made that the events meet the criteria for an unanticipated problem. In general, the investigators and IRBs at all these institutions are not appropriately situated to assess the significance of individual external adverse events. Ideally, adverse events occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/DMC) in accordance with a monitoring plan described in the IRB-approved protocol.

Only when a particular adverse event or series of adverse events is determined to meet the criteria for an unanticipated problem should a report of the adverse event(s) be submitted to the IRB at each institution under the HHS regulations at 45 CFR part 46. Typically, such reports to the IRBs are submitted by investigators. OHRP recommends that any distributed reports include: (1) a clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem; and (2) a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem.

When an investigator receives a report of an external adverse event, the investigator should review the report and assess whether it identifies the adverse event as being:

1. unexpected;
2. related or possibly related to participation in the research; and
3. serious or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

Only external adverse events that are identified in the report as meeting all three criteria must be reported promptly by the investigator to the IRB as unanticipated problems under HHS regulations at 45 CFR 46.103(b)(5). OHRP expects that individual external adverse events rarely will meet these criteria for an unanticipated problem.

OHRP guidance: http://www.hhs.gov/ohrp/policy/advevntguid.html

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Appendix B

SAMPLE RETURN CORRESPONDENCE (IRB to Researcher, upon return of submission in Rascal)

*Return correspondence, if the **monitoring entity has indicated that a) no changes to the protocol, IB/Instructions, and/or consent form/process are warranted, and b) subjects do not need to be notified**:*

As per current IRB procedures, ***EXTERNAL*** SAES only need to be reported to the IRB if they:

A. Were unexpected
B. Were related or at least possibly related to participation in the research
C. Suggest that the research places subjects or other at greater risks of harm AND as such warrants changes in the research, Investigator Brochure, consent process or requires subjects to be notified.

Please note that this decision is consistent with the OHRP and FDA guidance on reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events.

Per the information provided in the submission for this UP, this external SAE does not have an implication on the conduct of the research. Therefore this UP is being returned to you for withdrawal. If additional information becomes available that warrants changes in the research please re-submit.
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*Return correspondence, if the **monitoring entity has not yet determined whether a) changes to the protocol, IB/Instructions, and/or consent form/process are warranted, or b) if subjects need to be notified**:*

As per current IRB procedures, ***EXTERNAL*** SAES only need to be reported to the IRB if they were:

A. Were unexpected
B. Were related or at least possibly related to participation in the research
C. Suggest that the research places subjects or other at greater risks of harm AND as such warrants changes in the research, Investigator Brochure, consent process or requires subjects to be notified.

Please note that this decision is consistent with the OHRP and FDA guidance on reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events.

Per the information provided in the submission for this UP, a determination has not yet been made by the monitoring entity regarding whether this external SAE has an implication on the conduct of the research. Therefore this UP is being returned to you until such a decision is made. If additional information becomes available that warrants changes in the research please re-submit.