Rush University Medical Center
Policies and Procedures

Procedure Number:	RA-IRB-209
Category:	Research
Title:	Reporting and Review of Unanticipated Problems, Including Adverse Events
Type:	Policy and Procedure
Revised:	7/2014 (replaces December 2012)
Applies To:	Rush Investigators/Study Staff, IRB Administrative Staff, IRB Members

Policy:

In compliance with federal regulations, all unanticipated problems in non-animal research must be promptly reported to the Rush Institutional Review Board (IRB). Events occurring in protocols that are under the jurisdiction of the Rush Institutional Biosafety Committee (IBC) must also be reported to the Rush IBC per their policies and procedures.

Federal guidance and regulations define an unanticipated problem as an event or events that meet all of the following criteria:

An **Unanticipated Problem (UP)** includes any incident, experience, or outcome that meet all of the following criteria:

1. **unanticipated or 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, probably 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); and
3. suggests that the research **places participants or others at a greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

Events that meet the criteria as unanticipated problems (which may include adverse events (AEs), serious adverse events (SAEs), unanticipated adverse device effects, and/or other unanticipated events) must be reported to the Rush IRB within 10 working days of notification to the study team. Funding agencies may require different or additional reporting events to officials of those agencies. It is the Investigator's responsibility to be aware of such requirements and ensure that events are reported to those agencies compliantly. For example, any unanticipated problem that occurs in a Department of Defense (DoD)-supported research must be promptly reported by the Investigator to the DoD human research protection officer in a timely manner, no longer than 30 calendar days after discovery.

Reports must include a clear explanation by the Sponsor or Investigator of why this event/effect constitutes a reportable event under the unanticipated problem criteria listed above.

Rush investigators should ask Sponsors to forward only those reportable events that satisfy all of the UP criteria.

If an external Sponsor still forwards event reports that do not meet the reporting criteria above, the Principal Investigator must document that the event reports were reviewed but not reported. Documentation can be in the form of a letter, spreadsheet, or physical signature on copies of each event report. Depending on the terms of the study contract, the study team may still seek reimbursement from the Sponsor for the review of reports, as this activity constitutes review of events even if the events were not reportable under this policy.

For Sponsor-Investigator studies, where the Investigator is also the Sponsor, unanticipated problems involving risks to subjects or others must be reported to the Rush IRB in the previously specified timeframe, as well as appropriate regulatory agency, as appropriate. These reports to regulatory agencies must be made within 10 working days of notification.

Any event or problem that is determined by the IRB to be reportable to regulatory agencies will be presented to senior Research Administrators by the Director of Human Subjects' Protection (or his/her designee) at a weekly scheduled administrators meeting.

Events from Gene Transfer Studies

For studies involving gene transfer; unanticipated problems and adverse events must be reported immediately to the Rush IRB and the Rush Institutional Biosafety Committee (IBC).

Definitions

Assessment of whether the event is or is not related to the investigational agent is defined as follows:

1. **Definitely related:** The UP/AE is clearly related to the investigational agent(s)
2. **Probably related:** The UP/AE is likely related to the investigational agent(s).
3. **Possibly related:** The UP/AE may be related to the investigational agent(s).
4. **Unlikely related:** The UP/AE is doubtfully related to the investigational agent(s).
5. **Unrelated:** The UP/AE is clearly not related to the investigational agent(s).

An **Unanticipated Adverse Device Effect** includes 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 supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

An **Adverse Event (AE)** is defined as 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 use of an investigational (medicinal/device) process (treatment/product) during the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

A **Serious Adverse Event (SAE)** is an AE that results in any of the following outcomes:

- death
- life-threatening event (an event that places the patient or subject, in the view of the investigator, at immediate risk of death from the event)
- inpatient hospitalization or prolongation of existing hospitalization
- persistent or significant disability/incapacity
- congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An **internal problem or event** is defined as an event or occurrence with a study subject recruited at Rush University Medical Center, Rush Oak Park, or by an investigator working on behalf of Rush University Medical Center or Rush Oak Park at another location. It also includes subjects recruited for studies of which the Rush IRB is the IRB of Record

An **external problem or event** is defined as an event or occurrence that does not meet the criteria as an internal problem or event.

Procedure:

Reports to the Rush IRB must be made through the Rush Research Portal (RRP). Any study staff listed in Section 1.0 of the study application may complete the adverse event reporting form under the "New Reportable Event" tab, however only the Principal Investigator (PI) is permitted to submit the form for review. The event is not considered reported to the IRB until the PI clicks "Submit" in the RRP. If the PI is unable to perform this function, the study team should contact the RCTA for further assistance.

Reports to the Rush IBC should be made per its policies and procedures.

Internal event reports must include supporting documentation (such as: medical record notations, death certificate, and/or physician notes) with the identity of the subject obscured or removed. External events must include event reports (i.e MedWatch reports) that clearly indicate that the event meets the criteria to be an unanticipated problem.

All reports of unanticipated problems (internal and external) must include a statement by the Principal Investigator as to what changes to the risk profile of the study are warranted or rationale as to why changes are not recommended. If the event results in changes to the study documentation (consents, protocol, etc.), an amendment must be submitted simultaneously with the submission of the report. The amendment should clearly state that the changes were as a result of a specific report.

Investigators should report any event if it is unclear whether or

not it meets the requirement for reporting. Additionally, Investigators may request that events that do not meet the criteria for reporting (including unanticipated problems involving no more than minimal risk to subjects) be reviewed by the Rush IRB. Justification for review of the events must be included in the reporting form. Further clarification may be obtained by contacting IRB Administration.

Investigators must also report unanticipated problems involving risk to Rush subjects or others to the study sponsor for further reporting to the Food and Drug Administration (FDA) or other federal entities, as appropriate.

Data Safety Monitoring Reports and Other Safety Information

Reports from any Data Safety Monitoring Board, Data Safety Monitoring Committee, Data Safety Monitoring Group, or other committee involved in reviewing and considering the safety implications of adverse events or effects on the study must be submitted via amendment in the RRP as soon as they are received.

Any information that indicates a change to the risk or potential benefits of the research must also be reported to the Rush IRB via amendment. Such information includes, but it not limited to:

- published results from another study that shows the risks or potential benefits of your research may be different than initially presented to the IRB,
- a change in drug or device labeling,
- withdrawal from marketing of a drug, device, or biologic used in a research protocol,
- sponsor imposed suspension of study activities due to risks,
- any event that requires prompt reporting to the sponsor.

Investigators should report the following to the Rush IRB via amendment, but also contact IRB Administrative staff to receive further instruction:

- a subject has been incarcerated and the study is not approved to enroll prisoners, or
- subject complaints when the compliant indicates unexpected risks or cannot be resolved by the research team,
- changes made to the research without prior IRB review and approval in order to eliminate apparent immediate harm.

Unanticipated problems and adverse events that occur in

gene transfer studies must be reported immediately to both the Rush IRB and the Rush Institutional Biosafety Committee (IBC).

Any breach of confidentiality must be reported to Corporate Compliance and the Rush IRB immediately.

Review of Reports by Rush IRB

All submitted events are evaluated by the IRB Administrative staff to ensure that pertinent information, including supporting documentation, is included. IRB Administrative staff or a member of a subcommittee compromised of IRB members and IRB Administrative staff with scientific backgrounds ("subcommittee") will also ensure that the event meets the definition of an unanticipated problem.

Any event that does not meet the criteria for an unanticipated problem will be returned to the study team with an explanation as to why the criteria were not met. The Investigator may return the report with an explanation as to why they feel the event should be reported to the Rush IRB. This request for reconsideration will be forwarded to a member of the subcommittee compromised of IRB members and IRB Administrative staff with scientific backgrounds. This individual will review the report and determine whether full IRB review is needed.

Any event that meets the criteria for an unanticipated problem will be forwarded for full IRB committee for review. The committee has the option to acknowledge the report, ask for more information, or table the report for review at a future meeting. Additionally, the IRB will determine whether the event constitutes non-compliance under Rush policy CC-RC-0005. As part of their review, the IRB may require the study team to do one or more of the following:

- Revise the currently approved consent form in order to relay information that may affect subjects' willingness to continue to take part in the research;
- Revise the study protocol;
- Notify past and/or current subjects, including a requirement for subjects to re-consent to participation;

The IRB may vote to modify the continuing review schedule or require study activities to be monitored under RA-IRB-108. The IRB may also suspend or terminate a study under Policy RA-IRB-213 as a result of an unanticipated problem or series of problems.

Along with the event reports, reviewers have access to the entire study documentation, including approved consents,

protocols, amendments and other reported unanticipated problems.

All IRB decisions will be communicated to the study team via the RRP by IRB Administrative Staff.

Reference	45 CFR 46.103(b)(5) 21 CFR 56.108(b) 21 CFR 312.66 21 CFR 812.150 (a)(1) Department of Health and Human Services (DHHS) Office of Human Research Protections (OHRP) Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to subjects or Others and Adverse Events (dated January 15, 2007), Food and Drug Administration Guidance for Clinical Investigators, Sponsors, and IRBs, Adverse Event Reporting to IRBs – Improving Human Subject Protection (dated January 2009)
Related Documents	Flowchart for Reporting of Adverse Event and Unanticipated Problems in Human Subjects Research

Last reviewed: 5/13/2014

How do I determine whether this event needs to be reported?

This flowchart outlines how to determine which unanticipated problems, including adverse events require reporting under Rush policies and procedures.