REPORTABLE EVENTS
GUIDANCE FOR STUDY PERSONNEL

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Federal regulations require institutions to report information that falls into the following categories:

1. Unanticipated problems involving risk to subjects or others (including adverse events and other types of problems)
2. Serious or continuing non-compliance

The guidance below outlines KUMC's requirements for investigators, to help ensure compliance with the federal regulations. These events should be reported in the under the "Reportable New Information" (RNI) option.

Definitions

Unexpected: events that the PI assesses as differing in nature, severity or frequency from risk information previously reviewed and approved by the IRB (i.e., differs from the informed consent or Investigator Brochure).

Related or probably related: events are those that are, in the opinion of the KUMC investigator, more likely than not attributable to study participation. In determining whether the event is likely attributable to study participation, the KUMC investigator uses his or her expertise about the condition under study, experience with the study drug, available data from related studies, and information from the study sponsor in the case of multi-center trials. The KUMC investigator also evaluates the temporal relationship with study interactions or interventions and whether symptoms decrease or disappear when a test article is withdrawn. Events are not considered to be related if they are judged to be caused by the clinical state or clearly attributable to unrelated circumstances.

Internal events: those that occur to subjects under the responsibility of the KUMC principal investigator, regardless of the location of the problem.

- Internal events include those that happen at **any site** for which the KUMC IRB is the Reviewing IRB for the project.
- Internal events also include those that happen to subjects enrolled by a KUMC investigator even when an external IRB is the Reviewing IRB.

Unanticipated adverse device effects: 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.

Noncompliance:

1. Failure on the part of investigators or other research personnel to adhere to the terms of IRB approval.
2. Failure on the part of investigators or other research personnel to abide by applicable laws or regulations or KUMC policies, including failure to submit research for IRB review and approval before implementing the research.
3. Failure of the IRB to comply with requirements of 45 CFR 46.

Serious Noncompliance: a failure to comply with laws or regulations, KUMC policies, or the requirements or determinations of the IRB when that failure seriously increases risk of harm to participants, adversely affects the rights and welfare of the participants or undermines data integrity.

Continuing Noncompliance: a pattern of minor noncompliance that, if unaddressed, may compromise the integrity of the research or may result in harm to participants.

REPORTING ADVERSE EVENTS

Reports of adverse events (whether internal or external) should be promptly reported to the KUMC IRB* if they meet one or more of the following criteria:

Projects involving a study drug/biologic

1) All internal adverse drug events, serious or non-serious, that are unexpected **and** that are judged by the KUMC principal investigator to be related or probably related to participation in the research;
2) Other unexpected adverse drug events, regardless of severity, that may result in changes to the research protocol or informed consent process/document;
3) External adverse drug events from a multi-center trial where the sponsor has determined that the event constitutes an unanticipated problem and is implementing corrective actions such as protocol or informed consent changes, eligibility revisions, or enhancing safety monitoring.

Projects involving a study device

4) Unanticipated adverse device effects
5) Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Death of a study subject is considered a harm and requires prompt reporting if it meets the following criteria:

1) ***Drug/biologic Study:*** Death of a KUMC subject that is unexpected *and* related or probably related to the study drug/biologic must be reported.
2) ***Device Study:*** Death of a KUMC subject that may be related to the study device must be reported.
3) ***Projects that do not involve a test article:*** Death of a KUMC subject in a project that does not involve a drug, biologic or device if the death may be related to study participation.
4) ***Death of a non-KUMC subject*** is reportable if **all** the below apply:
   a) It is not expected given the nature of the research procedures and the subject population;
   b) It is related to the research;
   c) It occurs at an internal or external study site that is under the purview of the KUMC IRB,
   d) It suggests that the research places subjects or others at greater risk of harm.

Reporting Time Frames for reporting to the IRB

1) **Adverse Events**
   a) Internal problems must be reported within **5** working days.
   b) External problems must be reported within **20** working days.
2) **Deaths**
   a) Report by e-mail to IRBhelp@kumc.edu within **24 hours** of notification to the PI or research team
   b) Follow by submitting an RNI written report within **5** working days.

Reporting Process

1) Complete the Reportable Adverse Events Form and push "Submit" to generate a PDF of the form.
2) Upload the PDF in the eIRB system as an RNI, along with supporting documentation:
   a) For internal events, include documents that explain the details and impact of the event, such as redacted EMR records.
   b) For adverse events occurring in a multi-site trial, include the sponsor's determination that the event is potentially an unanticipated problem AND the sponsor's plan of action to address the problem.

***Studies overseen by an external IRB**

KUMC investigators under an external IRB must meet the requirements of KUMC and also of the reviewing IRB. Please refer to Step 8 on our webpage about relying on external IRBs.

REPORTING OTHER TYPES OF UNANTICIPATED PROBLEMS

Prompt reporting (within 5 working days of the study team's awareness) is required in the eIRB system, via an RNI submission, for the following types of problems:

1) Information that indicates a new or increased risk, or a potential safety issue. For example:
   - Interim analysis, safety monitoring report, or investigator finding that indicates new risks.**
   - Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic.
   - Subject complaint that indicates increased risk of harm to self or others.
   - Any changes significantly affecting the conduct of the research.
2) Audit, inspection, or inquiry by a federal agency that resulted in corrective actions.
3) Monitoring reports for which the sponsor determines the findings could affect the safety of participants or influence the conduct of the study.
4) Potential breach of confidentiality (e.g., unauthorized access or release of data, lost records/laptop
5) Change to the protocol taken without prior IRB review in order to eliminate an apparent immediate hazard to a subject
6) Incarceration of a subject in a study not approved by the IRB to involve prisoners.
7) Complaint of a subject that cannot be resolved by the research team.
8) Premature suspension or termination of the research by the sponsor, investigator, or institution.
9) Any other unanticipated problem that involves harm, potential risk to subjects or potential impact on the conduct of the study (e.g., disruption of drug availability, equipment malfunction, loss of funding, data integrity concern)

Please Note: When an investigator brochure, package insert, or device labeling is revised as a result of a new or increased risk, these items must be submitted to the IRB for review as a **Modification and not as RNI**, so that they can be accessed as IRB-approved documents in the Documents tab of the study.

Review of Prompt Reports of Adverse Events and other Unanticipated Problems

The IRB staff will review the submission to confirm that the report has been completed in its entirety and that the event appears to meet KUMC reporting criteria. If the event does not meet reporting criteria, it may be returned without review or acknowledged administratively. If the form has omissions or contradictory information, the staff will send a request for clarification through the eIRB system.

Per regulations, the IRB will review and take further action to ensure the safety and welfare of study subjects and report to federal authorities as necessary. Additional information on the review of Adverse Events and other Unanticipated Problems can be found in section 5.3 in the IRB SOP 05.0 Reviews of Ongoing Research, 2018 requirements

REPORTS OF NON-COMPLIANCE

Prompt reporting is:

1) **ALWAYS required** for:
   a) Failure to obtain informed consent, or to re-consent, when required by the IRB.
   b) Modifying the protocol without IRB approval, except to avoid immediate hazard to subjects.
   c) Conducting the research prior to IRB approval, during an IRB suspension or after IRB approval expires.

2) **Required if, in the opinion of the principal investigator,** the noncompliance event **causes harm, increases risk of harm, adversely affects the rights and welfare of participants or undermines the scientific integrity of the data**. Reportable events may not cause actual harm but potentially put increase risk of harm. Examples include:
   - Enrolling an ineligible subject without prior acknowledgement from the IRB and sponsor
   - Dosing errors made by the study team or other health care professionals
   - Failure to monitor subject's study drug compliance, if required by the protocol or sponsor
   - Failure to involve an interpreter/witness when consenting a non-English speaking subject
   - Omitting protocol-required activities
   - Error resulting in unanticipated costs
   - Undisclosed financial conflict of interest
   - Unapproved investigators working on the study
   - Monitoring reports for which the sponsor determines the protocol deviations could affect the safety of participants or influence the conduct of the study.

Minor or administrative protocol deviations that typically do not meeting reporting criteria to the IRB:

- Study visits occurring outside the protocol required time frame due to participant's schedule
- Study activities performed close to but not precisely at the time points specified in the protocol

Incidents of non-compliance, both reportable and non-reportable, should be documented and maintained in the study file. To document non-compliance that does not require prompt reporting, study teams can utilize various sources including:

- Investigator signed Non-Compliance Reporting Form PDF
- Internally-developed non-compliance summary log
- Other means supplied by the sponsor or developed by individual study teams, provided the documentation shows the principal investigator's assessment of the event.

Reporting Process

1) Complete the Non-Compliance Reporting Form and push "Submit" to generate a PDF of the form.
2) Obtain the PI's signature on the Non-Compliance PDF.
3) Upload the PDF in the eIRB system as an RNI, along with any supporting documentation.
4) The review will proceed as outlined in SOP 17.1.

PROTOCOL EXCEPTION REQUESTS

KUMC investigators may request prospective approval of a one-time exception to the IRB-approved study protocol as an RNI. These planned, non-emergent exceptions may include but are not limited to:

- Exceptions to eligibility criteria,
- Exceptions to the form or manner of obtaining informed consent,
- Use of out-of-window test results,
- Exceptions to the administration or use of an investigational product.

While an exception request is neither an unanticipated problem nor non-compliance, the RNI function within eIRB allows the exception request to be processed promptly even when other protocol modifications are pending review.

Request Process

1. Complete the Exception Request Form and push the "Submit" to generate a PDF of the form.
2. At the time of submission, please also send an email to IRBhelp@kumc.edu to help ensure prompt review.
3. Study teams should allow at least one business day for IRB review.

The Exception Request Form and the RNI submission process should not be used if a permanent change is needed. Permanent changes should be submitted to the IRB as a study modification.

REPORTABLE EVENTS AND EXTERNAL IRBS

For all types of reportable events, KUMC investigators conducting a study under an external IRB must meet the requirements of KUMC HRPP and also of the reviewing IRB.

Our local acknowledgement letter, issued when the study is first approved by the external IRB, discusses the requirement to notify the KUMC HRPP of any *internal* serious adverse events or potentially serious issues of non-compliance that occur during the study.

Adverse Events
Because the study is under an external IRB, priority should be given to filing the adverse event report with that IRB and then notifying the KUMC HRPP as soon as feasible.

- The HRPP will evaluate whether immediate local actions are needed to ensure safety for our subjects. If not, then the HRPP will await the review by the external IRB.
- During this time, the HRPP will confirm that applicable institutional responsibilities and contractual obligations have been met.
- Unless the event requires urgent local action or a change to local study processes, the KUMC HRPP will await guidance from the external IRB as to whether the event constitutes an unanticipated problem and whether the event must be reported to federal agencies.
- The KUMC HRPP will work collaboratively with the external IRB to address the problem. If a report to federal agencies is required, the KUMC HRPP will provide information and input as outlined in the reliance agreement.

Please note: These steps apply to reports about internal events only (i.e., a subject enrolled by the KUMC study team). If the event is external and the study is under an external IRB, there are no reporting requirements to the KUMC HRPP even if changes are warranted. The external IRB is responsible for ensuring that investigators are made aware and that subjects are protected and appropriately informed of the new information.

Non-Compliance
Reports of non-compliance have implications for the KUMC HRPP as well as the external IRB. For this reason, the non-compliance should be reported to both groups.

- Submit the KUMC non-compliance form discussed above and also use the reporting mechanism designated by the external IRB. The external IRB will follow federal regulations about determining whether the report constitutes serious or continuing non-compliance.
- Locally, the KUMC HRPP will evaluate whether the corrective or preventive actions appear appropriate and whether there is a need for additional training or other support for the study team.
- If the external IRB determines the report is serious or continuing non-compliance, the KUMC HRPP will work collaboratively with the external IRB to address the problem. If a report to federal agencies is required, the KUMC HRPP will provide information and input as outlined in the reliance agreement.

Exception Requests
One-time requests for a protocol exception should be directed to the external IRB, using their request mechanism. Because an approved protocol exception is not considered an unanticipated problem or non-compliance, there is no requirement to notify the KUMC HRPP.