The MetroHealth System Human Research Protection Program

Reportable Events Guidance Document: Reporting Requirements for Investigators After IRB Approval

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Overview

The purpose of this guidance document is to provide investigators with information on how to report unanticipated problems and non-compliance in accordance with federal and institutional requirements. The document provides definitions and examples of the different types of post approval events and information that should be reported to the IRB. The IRB will then work with investigators to determine if an event needs to be reported to the Office of Human Research Protections (OHRP) and/or the Food and Drug Administration (FDA). Investigators must adhere to specified reporting timeframes for submitting this information to the IRB.

What do we need to report to OHRP?

1. Unanticipated problems involving risks to subjects or others. Meaning, any internal adverse event that is 1) unanticipated, related, or possibly related to the study AND places the subjects or others at greater risk of harm than was previously known.
2. Non-compliance that is either serious or continuing. Non-compliance is defined as any activity associated with the conduct of research that fails to comply with: the research plan approved by the IRB, the federal regulations, or institutional policies governing human subject research.
3. Any time the IRB suspends or terminates IRB approval.

What do we need to report to the FDA?

1. For clinical trials conducted under IND regulations-
    - A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioderma, agranulocytosis or hepatic injury)
    - A singe occurrence, or more often a smaller occurrence, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (i.e. tendon rupture)
    - An adverse event that is described or addressed in the investigator's brochure, protocol or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations or with greater frequency.

2. For clinical trials conducted under IDE regulations-

    - Any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with the device that was not previously identified in nature, severity or degree.

- Any unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

****** When submitting reportable events to the IRB, please be sure to explain the event in sufficient detail to be able to allow the IRB to make a determination. It is helpful to include the following: who, what, where, when, how and why- without including any protected health information.

I. Adverse Events (aka Unanticipated Problems)

An adverse event is defined as any unfavorable medical or psychological occurrence in a human subject associated with the subject's participation in the research. (45 CFR 46.103(b)(5)(i)). Adverse events can be either internal or external. An internal adverse event is one that is experienced by subjects enrolled at MetroHealth or site(s) under the jurisdiction of the MetroHealth IRB (where we are the IRB of record). An external event involves subjects enrolled at study sites under the jurisdiction of other IRBs.

Adverse events should be reported to the IRB whether they occur during the course of the study, after study completion, or after subject withdrawal or completion if it impacts the safety and welfare of either currently or previously enrolled subjects.

Internal Adverse Events

The following are required for an internal adverse event to be considered an adverse event:

1. Unanticipated- in terms of nature, severity, or frequency;
2. Related or possibly related to the research; AND
3. Place the subject or others at a greater risk of harm (including physical, psychological, economic, or social harm) than previously known.

If it does not meet all three criteria, then it is not considered to be an adverse event and does not need to be reported to the IRB.[1] When trying to determine whether the adverse event is unanticipated, look to the study documents to see if it is listed in the protocol, ICF, or package insert. If it is there, then it is likely anticipated. However, watch out for adverse events that are anticipated, but occur with greater frequency warranting changes to the protocol or ICF. Most problems are anticipated because of the 1) known side effects/toxicities, 2) the natural progression of the disease, or 3) the subjects predisposed risk factors.

Serious Adverse Event

A serious adverse event *automatically* places the subject at a greater risk of harm than previously known. These often warrant changes to the protocol or ICF or other corrective actions to protect the safety and welfare of the subject. The following qualify as serious.

- Results in death
- Is life threatening

[1] With the exception of an internal subject death. If the death occurred while enrolled in study, was anticipated and related or possibly related to the study, then it needs to be reported at the time of continuing review.

- Results in inpatient hospitalization or prolonged hospitalization
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Based on appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the above outcomes

External Adverse Events

External individual adverse events are to be reviewed in a timely manner and kept on file by the Principal Investigator. They do not have to be reported to the IRB because these reports lack sufficient information to allow the IRB to make a meaningful judgment about whether the unanticipated problems are research related placing the subject at greater risk of harm than previously known. This determination is better made by the sponsor, coordinating center, or DSMB and will come in the form of a report explaining why it was determined to be an unanticipated problem with any protocol/ICF changes recommended. However, if after reviewing the external adverse events the PI has concluded that an immediate change to the protocol or informed consent document is necessary to address the risk(s) raised by the event, the PI should file an external adverse reportable event within ten days detailing the recommended changes.

II. Non-Compliance

Non-compliance is defined as any action or activity associated with the conduct or oversight of research involving human participants that fails to comply with either:

1. The research plan as approved by the IRB;
2. Federal regulations; or
3. Institutional policies governing human subject research

Noncompliance may range from minor to serious, be unintentional or willful, and may occur once or several times. Noncompliance may result from the action of the investigator, research personnel, or a participant, and may or may not impact the rights and welfare of research participants or others or the integrity of the study.

A protocol deviation is any variance from an IRB approved protocol and is considered to be a form of non-compliance. There are two types of protocol deviations: major and minor. Minor protocol deviations are incidents involving non-compliance with the protocol that typically do not have a significant impact on the subject's rights, safety, welfare, or the integrity of the research process/data. Major protocol deviations are more serious incidents which do impact the subject's rights, safety, welfare or the integrity of the research process/data.

Serious Non-Compliance

Serious non-compliance that needs to be reported to OHRP is defined as any behavior, action, or omission to the conduct of human subjects research that:

- Adversely affect the rights and welfare of participants;
- Result in a detrimental change to a participant's clinical or emotional condition or status;

- Compromise the integrity or validity of the research;
- Result from willful or knowing misconduct on the part of the investigator(s) or study staff; or
- Harm or pose an increased risk of substantive harm to a research participant.

Examples of serious non-compliance that need to be reported to OHRP may include, but are not limited to, the following:

- Conducting non-exempt research without first obtaining IRB approval
- Performing a study procedure not approved by the IRB; or failing to perform a required study visit or procedure that, in either case may impact subject safety or data integrity
- Enrolling a participant in a risk study that failed to meet the inclusion/exclusion criteria
- Failing to obtain informed consent
- Failing to retain signed copies of informed consent documents
- Informed consent obtained by someone not approved to obtain consent for the protocol
- Any medication error involving dosing, administration or preparation of the study medication(s)
- Failing to submit a continuing review application to the IRB before the expiration date
- Continuing research activities after IRB approval has expired
- Failing to follow the safety monitoring plan
- Enrolling subjects after IRB approval of a study has expired
- Failing to report serious adverse events or unanticipated problems in accordance with IRB reporting requirements

Non-Serious Non-Compliance

Non-serious non-compliance is any behavior, action, or omission in the conduct or oversight of research involving human participants that deviates from the approved research plan, federal regulations, or institutional policies but does or did not:

- Harm or pose an increased risk of substantive harm to a research participant;
- Result in a detrimental change to a participant's clinical or emotional condition or status;
- Have a substantive impact on the value of the data collected; or
- Result from willful or knowing misconduct on the part of the investigator(s) or study staff.

Examples of non-serious non-compliance may include, but are not limited to, the following:

- Missing pages from an executed informed consent document
- Failure of subject to show up for a study visit
- Failure of subject to return study medication
- Failure to follow the approved protocol that in the opinion of the PI does not impact the safety and welfare of the subjects such as: 1) study procedure conducted out of sequence or 2) failure to perform a required lab test or procedure.

Continuing Non-Compliance

Continuing non-compliance is a pattern of non-compliance that:

1. Indicates a lack of understanding or disregard for the regulations or institutional requirements that protect the rights and welfare of participants and others;
2. Compromises the scientific integrity of a study such that important conclusions can no longer be reached;
3. Suggests a likelihood that noncompliance will continue without intervention; or
4. Involves frequent instances of minor noncompliance

Examples of continuing non-compliance include, but are not limited to, the following:

- Late submissions of continuing reviews or other items that need to be reported to the IRB;
- Repeated failure to respond to requests from the IRB to resolve non-compliance;
- Repeated protocol deviations

Corrective Action Plan

When submitting unexpected problems, serious or continuing non-compliance, the investigator must submit a proposed corrective action plan with the non-compliance. In crafting an effective plan, the investigator needs to really think about *why* the event occurred. Is it a system problem? Problem with procedure or something in the protocol? A training issue? Once the "why" is determined, the plan must address ways to prevent it from happening again. Additional education/training is virtually always appropriate. The IRB will make the final determination regarding the sufficiency of the corrective action plan.

Actions by the IRB

- The IRB has the authority to take whatever action it deems appropriate, up to and including suspending or terminating approval of research.
- Such actions may include, but are not limited to:
  - ☐ Remediation or educational measures required of PI and research team.
  - ☐ Monitoring of research activities by appropriate person(s).
  - ☐ Notification of past or current research participants.
  - ☐ Re-consenting of participants.
- Additional actions may include, but are not limited to:
  - ☐ More frequent continuing review (renewal of approval) schedule.
  - ☐ Periodic audits by the HRPP Compliance Manager.
  - ☐ Restrictions to the PI's research practice (e.g., limiting the privilege to minimal risk or supervised projects).
  - ☐ PI may put the study on a voluntary partial or full hold.
  - ☐ Suspension or termination of approval for one or more of the PI's studies.

TABLE

	Within 3 Days of When the Study Team Became Aware	**Within 10 Days of When the Study Team Became Aware**	**At the Time of Continuing Review**
Internal Adverse Events (also known as Unanticipated Problems)	Internal Subject Death that- • Occurred while enrolled in a study • Is ***unanticipated*** AND • Related or possibly study related	Internal Adverse Event that is- ***1. Unanticipated*** o Didn't know it was going to happen at all **or** o Didn't know it was going to happen as frequently **or** o Didn't know it was going to happen as severely 2. ***Related or possibly study related*** to the procedures involved in research o If the problem is **solely** caused by the underlying disease, disorder, or condition, then it is not considered to be research related AND 3. Places subjects or others at ***greater risk of harm than was previously known***. o *Serious adverse events* automatically place the subject at a greater risk of harm than previously known (*See* examples below).	Internal Subject Death that- • Occurred while enrolled in a study • Is anticipated AND • Related or possibly study related * We do not have to report these to OHRP, but as a program, we want to keep track of these.
Non-Compliance (Protocol Deviations)	Any variance made to eliminate apparent immediate hazard to subject	• Major Protocol Deviations- including but not limited to: o Failing to obtain informed consent o Informed consent obtained by someone not approved to obtain consent for the protocol	• Any protocol deviation that does not constitute a major deviation

	Within 3 Days of When the Study Team Became Aware	Within 10 Days of When the Study Team Became Aware	At the Time of Continuing Review
		o Enrolling a participant in a risk study that failed to meet the inclusion/exclusion criteria o Failing to follow the safety monitoring plan	
Non-Compliance (with MHS policies governing human subjects research)		• Serious Non-compliance with policies • Continuing Non-compliance with MHS policies (*See* page three above)	• Non-serious non-compliance
Incidents that are: Unexpected, related, or possibly related to the research and places the subject at a greater risk of harm than previously known		Including but not limited to: • Any breaches of confidentiality • Research subject complaints • Loss of adequate resources to support the research	
Updated Study Information	Any hold, suspension, or termination of research by sponsor, Investigator, funding agency, or regulatory agency (i.e., FDA)	☐ DSMB reports ☐ Audit or monitoring reports ☐ FDA Safety Alerts ☐ Investigator Brochures ☐ Changes in FDA labeling or withdrawal from marketing of a drug, biologic or device used in a research protocol	