Guidance - Prompt Event Reporting to the IRB

Prompt Event Reporting Flowchart

Purpose

The purpose of this document is to describe the requirements for prompt event reporting to the IRB.

Federal regulations [45 CFR 46.103(b) (5) and 21 CFR 56.108(b) (1)] require the IRB to ensure that Investigators promptly report "any unanticipated problems involving risk to subjects or others" (UP) or any serious or continuing non-compliance to the IRB.

Glossary of Key Terms

Adverse Event: An adverse event is any untoward or unfavorable medical occurrence in a human subject; including any abnormal sign, symptom or disease that is temporarily related to the research, whether or not it is related to the subject's participation in the research.

In order for an adverse event to meet the definition of an unanticipated problem involving risks to subjects or other, the event must meet the Unanticipated Problem (UP) criteria outlined below.

Continuing Non-compliance: A pattern of repeated actions, instances of omission by an investigator or study team member.

> **Note:** "Continuing non-compliance" is a problem that persists (i.e. there has not been compliance with the corrective action plan) after the IRB has identified non- compliance, completed an analysis and directed the investigator to undertake corrective action.

External UP: A UP that involves subjects, data, or specimens for which the Geisinger IRB is not the IRB of Record.

IRB of Record: A reviewing IRB that assumes IRB responsibilities for another organization that is designated to do so through an approved Federalwide Assurance (FWA) on file with the Federal Office of Human Research Protection (OHRP) and where a formal, written IRB Authorization Agreement, in which the reviewing IRB agrees to serve as the IRB of Record, has been executed.

Internal UP: A UP that involves subjects, data, or specimens for which the Geisinger IRB is the IRB of Record.

Non-compliance: Failure to comply with federal regulations, state laws, Geisinger policies or procedures, and/or the policies, requirements or determinations of the Institutional Review Board, or provisions of the IRB-approved research study.

Office of Research Compliance (ORC): The ORC is committed to the development of a Research Compliance Program that provides information support and administrative systems necessary to ensure compliance with regulations and policies governing research in the most efficient and effective manner possible. ORC has full authority to review all research-related documents, financial records, contracts, and any other information necessary to ensure compliance with regulatory requirements pertaining to research. The ORC works with the IRB to assist with investigations of alleged non-compliance and assists with

reporting to the Institutional Official and/or external authorities as appropriate.

Prompt Event Reporting: A Prompt Event Report Form is used by an investigator to report any problem, event, other act, or omission in human subject research to the IRB.

Protocol Violation/Deviation: Any change, divergence or departure from the study design or research procedures that has not been approved by the IRB. Major protocol violations/deviations are considered non-compliance.

- **Major Protocol Violation/Deviation:** Any change that affects the rights and welfare of subjects and others, increases risks to subjects and others, decreases potential benefits, or compromises the integrity or validity of the research.

- **Minor Protocol Violation/Deviation:** Any change that did not increase the risk or decrease the benefit or significantly affect the subject's rights, safety or welfare and/or the integrity of research data (e.g. a routine lab missed at a visit and re-drawn, shortening the duration between a planned study visit, using an outdated HIPAA form or consent form when there are no differences between the two forms other than the approval date).

Serious Non-compliance: An incident of non-compliance that may compromise the rights and welfare of a subject or compromise the integrity of the research or study data.

Unanticipated Problem (UP): A UP or event involving risks to subjects or others is any problem or event which, in the opinion of the Geisinger Investigator, meets all three of the following criteria:

1. **Related**: A problem or event is "related" if it is possibly related to participation in the research (i.e. investigational product or research procedures).
2. **Unanticipated**: A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence and is:
    - Not already described as a potential risk in the approved informed consent
    - Not already described as a potential risk in the approved protocol
    - Not listed in the Investigator's Brochure
    - Not part of an underlying disease
    - Occurred at an increased frequency or at an increased severity than expected
3. **Serious**: Serious problems or events that result in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or places subjects or others at a greater risk of harm than was previously known or recognized. Note that actual harm need not have occurred for there to be a change in the risk/benefit ratio.

How to Report

The Investigator must report a UP to the IRB, using the iRIS electronic IRB system **within five working days** of becoming aware of the problem or event.

All reportable events submitted to the IRB and meeting the UP criteria will be assigned to an IRB Analyst or Specialist for preliminary review. If the IRB Analyst or Specialist considers the event is a UP, a convened IRB reviews the report and determines whether it is a UP or not. The investigator is notified in writing and the review, determination, and investigator communication is documented in the IRB electronic system.

An UP, as determined by the convened IRB, is reported to the Geisinger Institutional Official and other relevant Federal agencies, when required, within 30 working days from the date of IRB determination. The investigator is notified in writing of this action.

Examples of problems and/or events which may meet UP Criteria:

- ☐ Any accidental or unintentional change to the IRB-approved research protocol that increased risk to subjects or others
- ☐ An event that would have implications for the conduct or design of the research project (e.g., requiring a significant, and usually safety-related, change in the research project such as revising inclusion/exclusion criteria or a new monitoring requirement, revised informed consent, or revised investigator's brochure).
- ☐ Any complaint from a subject that indicates an unanticipated risk or that cannot be resolved by the research staff
- ☐ Problems, events, or new information (e.g. from publications, DSMB reports, interim findings, product labeling changes) that in the opinion of the investigator may adversely affect the rights, safety, or welfare of subjects or others, or which substantially compromise the research data.
- ☐ Breach of confidentiality (e.g. unapproved PHI disclosure, a stolen, unencrypted laptop containing subject data and identifiers, etc.)
- ☐ An unexpected hospitalization - new or prolonged
- ☐ An unexpected life-threatening adverse experience
- ☐ An unexpected death which cannot be attributed to underlying disease
- ☐ A newly-developed disability/incapacity - persistent or significant
- ☐ An unexpected birth defect/anomaly
- ☐ A processing error resulting in a subject receiving a dose of study medication 10 times higher than the dose dictated by the IRB-approved protocol, even if the incorrect dosing produces no detectable adverse effect.

Protocol Violation/Deviation

The timing of investigator reporting of protocol violation/deviations to the IRB, using the iRIS electronic IRB system is dependent on the severity of the protocol violation/deviation.

Major protocol violations/deviations that affect the rights and welfare of subjects and others, increase risks to subjects and others, decrease potential benefits, compromise the integrity or validity of the research; or represent willful or knowing misconduct must be reported by the investigator within five working days of becoming aware of the violation/deviation.

Minor protocol violations/deviations should be summarized and submitted to the IRB at the time of continuing review. A template Event Report Summary Sheet is available for within iRIS Help and the HRPP website. The completed Event Report Summary Sheet can be attached to the continuing review report form.

Examples of problems or events <u>which may meet</u> the definition of Major Protocol Violations/Deviations (non-compliance):

- ☐ Enrolling subjects who did not meet inclusion/exclusion criteria on a greater-than- minimal risk study
- ☐ Performing study procedures not approved by the IRB
- ☐ Performing study procedures before obtaining informed consent
- ☐ Failure to obtain and/or document informed consent
- ☐ Use of an unapproved consent document
- ☐ Changing the protocol without prior IRB approval except when necessary to eliminate

immediate harm to a subject
- ☐ Breach of confidentiality (i.e. any occurrence of unapproved PHI disclosure)
- ☐ Receipt of incorrect treatment or dose by a subject
- ☐ Loss or destruction of samples or data
- ☐ Over-enrollment of subjects on a greater than minimal risk study
- ☐ Unauthorized (i.e. not IRB approved) persons participating in the conduct of a research study

Investigator Responsibilities

When a reportable event occurs, it is the responsibility of the investigator to:

- ☐ Eliminate apparent immediate harm to the subject or others. This can be done prior to submitting the reportable event to the IRB.
- ☐ Determine whether the reportable event meets the UP criteria and/or protocol violation/deviation definition. Consult, as needed, with the IRB on-call Chairperson on issues relating to the UP determination.
- ☐ Report any internal UP and/or major protocol violations/deviations to the IRB within five working days of becoming aware of the problem/event. Use the IRB electronic Reportable Event form to submit the report to the IRB.
- ☐ Monitor subjects to detect additional risks and harm.
- ☐ Report, when appropriate, the unanticipated problem or event to other entities such as sponsors, funding agencies, or Data Safety Monitoring Boards.
- ☐ Modify research procedures as necessary to address newly-identified risks.
- ☐ Submit the modifications to the IRB and obtain IRB approval.
- ☐ Put the research project on Administrative Hold if necessary.

Internal UPs - When an internal UP occurs and Geisinger IRB is the IRB of Record:

- ☐ The investigator completes the Reportable Event form within the IRB electronic system **within five working days** of becoming aware of the problem or event even if it is not yet resolved.
- ☐ The investigator submits a modification application to the IRB if the problem or event requires revision of the protocol and/or consent document.
- ☐ If the convened IRB confirms the UP, the investigator reports the IRB's determination to the research project sponsor, if applicable.

Internal Non-UPs - When an internal Non-UP occurs and Geisinger IRB is the IRB of Record:

- ☐ The investigator reports problems or events that do NOT meet the criteria of an UP to the Geisinger IRB in summary format at the time of the next continuing review.
- ☐ The investigator monitors the severity and frequency of subsequent non- UPs. ***The IRB website includes an Event Report Summary template for non- UPs which is available to researchers.***

External UPs - When an external UP occurs and Geisinger **is NOT** the IRB of Record:

- ☐ The investigator reports external UPs to the Geisinger IRB in summary form annually.
- ☐ If monitoring entities (e.g., an external IRB at the site where the problem or event occurred, the sponsor, or the Data Safety Monitoring Board) require modifications of the protocol or consent documents at all research sites as a result of the problem, the Geisinger investigator submits a modification application using the iRIS electronic IRB system.

External Non-UPs - Non-UPs occurring at other institutions where Geisinger **is NOT** the IRB of Record do not need to be reported to the Geisinger IRB.

Major Protocol Violations/Deviations

When a major protocol violation/deviation occurs at institutions where Geisinger IRB serves as the IRB of Record:

- ☐ The investigator completes the Reportable Event Form within the iRIS electronic IRB system **within five (5) working days** of becoming aware of the protocol violation/event.
- ☐ The investigator submits a modification application to the IRB if the problem or event requires revision of the protocol and/or consent document.
- ☐ If the convened IRB determines the major protocol violation/deviation to be serious and/or continuing non-compliance, the IRB reports to IO and appropriate external group (DHHS, FDA, etc.) and the investigator reports the IRB's determination to the research project sponsor, if applicable.

Minor Protocol Violations/Deviations

When minor protocol violations/deviations occur at institutions where Geisinger IRB serves as the IRB of Record:

- ☐ The investigator reports the protocol violations/deviations in summary format at the time of the next continuing review.

IRB Responsibilities

All reportable UP's are submitted through the iRIS electronic IRB system and assigned to an IRB Analyst or Specialist for preliminary review. If the IRB Analyst or Specialist does not agree or questions the investigator's UP assessment, the investigator is contacted to discuss the event and possible reasons for re-classification as a non-UP. If the IRB Analyst or Specialist agrees with the investigator assessment that the event is an UP, the event is assigned to an IRB Member Reviewer(s) and forwarded for review by a Convened IRB. It is the responsibility of the IRB to:

- ☐ Review the Report submitted by the investigator.
- ☐ Communicate directly with the investigator, as needed to obtain more information regarding the unanticipated problem, event or other act or omission.
- ☐ Evaluate whether the actions taken by the investigator to eliminate apparent harms are adequate and appropriate and if not, direct further action.
- ☐ Determine whether the problem or event meets the UP criteria and constitutes a UP.

Major Protocol Violations/Deviation

All reportable events involving multiple areas of the institution including a protocol violation/deviation are sent to ORC for evaluation and scheduled for review by the Research Investigative Committee (RIC) for review. Violations/deviations that meet the definition of a major violation/deviation may be forwarded to a Convened IRB for further.

When the IRB determination is a UP or Serious and/or Continuing non-compliance

The IRB:

- ☐ Notifies the investigator of the UP and/or serious and/or continuing non-compliance determination and documents the decision and communication to the investigator within the iRIS electronic IRB system
- ☐ Reports the UP and/or serious and/or continuing non-compliance to the Institutional Official, and to Federal agencies (e.g. FDA or OHRP) when required, and to any Federal agency that provides funding support for the research project.
- ☐ Determines whether a study modification is required to address newly-identified risks.
- ☐ May also require additional actions such as, but not limited to:
  - o Suspension of the research

- o Termination of the research
- o Notification of current subjects (required when such information might relate to subjects' willingness to continue to take part in the research)
- o Additional information provided to subjects who have completed study procedures
- o Modification of the research study
- o Modification of the information disclosed during the consent process
- o Require re-consenting of current subjects
- o Monitoring of the research
- o Monitoring of the consent process
- o Referral to other Geisinger entities (e.g., legal counsel, risk management, Institutional Official)
- o Request additional information from the Data Safety Monitoring Board, or other monitoring entity
- o Shorten the continuing review cycle

When the IRB determination is a non-UP, and/or non-serious and non-continuing non-compliance, or no non-compliance

The IRB:

- ☐ Notifies the investigator of the determination.
- ☐ Review the summary and attached documents included with the continuing review report.

References

45 CFR Part 46 Protection of Human Subjects
21 CFR Part 56 Institutional Review Boards
FDA Guidance for Clinical Investigators, Sponsors, and IRBs - Adverse Event