New HRPO Requirements for Reportable Events

June 12, 2018

Richard Guido, MD, IRB Chair

Ann Lee, MSN, CRNP, CIP
Regulatory Affairs Specialist
Outline

• Regulatory basis for reporting policies
• Importance of consistency between IRBs
• Evaluation of Pitt IRB policies and IRBs across the country
• Impact of PittPRO
• Discussion
HHS Regulatory Requirements

Institutions engaged in human subjects research conducted or supported by HHS must have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of any unanticipated problem involving risks to subjects or others

(45 CFR 46.103(b)(5))
HHS Regulatory Requirements

For research covered by an assurance approved for federalwide use by OHRP, HHS regulations at 45 CFR 46.103(a) require that institutions promptly report any unanticipated problems to OHRP.
Unanticipated Problems Involving Risk To Subjects or Others
[OHRP Guidance (2007)]

Any incident, experience or outcome that meets all of the following criteria:

- **Unexpected** (in terms of nature, severity, or frequency)
- **Related or possibly related** to participation in the research
- 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

http://www.hhs.gov/ohrp/policy/advevntguid.html
Any unfavorable medical occurrence in human subjects, including abnormal signs (e.g., abnormal physical exam or laboratory findings), symptoms, or disease temporally associated with, but not necessarily considered related to, the subject’s participation in the research.
OHRP’s Venn Diagram

A = Adverse Events that are not Unanticipated Problems

B = Adverse Events that are Unanticipated Problems

C = Unanticipated Problems that are not Adverse Events

Under 45 CFR part 46: Do not report A; Report B and C.
Investigators are required to report promptly “to the IRB… all unanticipated problems involving risks to human subjects or others,” including adverse events that should be considered unanticipated problems (§§ 56.108(b)(1), 312.53(c)(1)(vii), and 312.66).
FDA Guidance (January 2009)

AE should be considered an unanticipated problem involving risk to human subjects and reported to the HRPO, only if:

- unexpected and,
- serious and,
- would have implications for the conduct of the study (significant, and usually safety-related change in the protocol like revising inclusion/exclusion criteria, new monitoring requirements, ICF or IB)

FDA Guidance (January 2009)

• An individual AE occurrence ordinarily does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

• FDA provided specific examples of AE’s that would meet the definition of an unanticipated problem involving risk to subjects.

FDA Guidance (January 2009)

- Most AE’s generally require an evaluation of their relevance and significance to the study
- Aggregate analysis of other occurrences of the same (or similar) event
- DSMB, DSMB, DSMB!!!!!
What about protocol non-compliance (deviations)?
Non-Compliance

Failure on the part of the investigator or any member of the study team to follow the terms of University of Pittsburgh IRB approved protocol or to abide by applicable laws or regulations, or University of Pittsburgh IRB policies. This includes protocol deviations.

Incidents of noncompliance on the part of research participants which do not involve risk need not be reported to the IRB.
Non-Compliance / Protocol Deviations

- Inconsistencies between HHS and FDA regulations
- Inconsistencies within FDA regulations for drugs and devices
HHS and FDA Regulations

Prospective approval is required for changes to the research protocol except for deviations performed to eliminate apparent immediate hazards to the subject in compliance with 45 CFR 46.103 (b) (4) and 21 CFR 56.108(a)(4)
FDA Compliance Program Manual
(Chapter 48)

Protocol deviations: generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change…Like protocol amendments, deviations initiated by the clinical investigator must be reviewed and approved by the IRB and the sponsor prior to implementation, unless the change is necessary to eliminate apparent immediate hazards to the human subjects (21 CFR 312.66), or to protect the life or physical well-being of the subject (21 CFR 812.35 (a)(2)), and generally communicated to FDA.
Non-Compliance / Deviations

No real guidance from FDA or OHRP about what or how deviations should be reported to IRBs after they occur.
Types of Reportable Events

Reportable Events

- Adverse Events that are Unanticipated Problems Involving Risk to Subjects or Others
- “Other” Unanticipated Problems Involving Risk to Subject or Others
- Deviation or Non-Compliance
Reports of Non-Compliance: 684
Unique protocols: 309
  • Full board: 195
  • Expedited: 114

Reports from 229 PIs
Two or more events submitted by 104 PIs

Active protocols at UPIRB: 4,333

PIs with protocols at UPIRB: 1,627
Consistency Needed Between IRBs

• Same regulatory basis for policies and procedures

• Single IRB review
  – Need to follow reporting policies of the IRB of record for your study
Consistency Needed Between IRBs

- Move to more standardized IRB electronic submission systems
  - PittPRO requires a specific format for the reports.

- Reportable New Information
National Review of IRB Policies

• Generally consistent regarding unanticipated problems involving risk to subject or others

• Wide variation in reporting of deviations
How does Pitt IRB’s compare?

• UAPs
  – *Fairly similar overall*
  – Separate reporting pathways for AEs and UAPs not always required
  – Deviations that are UAPs need to be reported as UAPs
How does Pitt IRB’s compare?

• Non-Compliance (Deviations)
  – **Pitt is more conservative overall**
  – Other IRBs require 2 levels of reporting
    • Reportable event – deviations that affect the rights and welfare of human subjects or compromise the quality of the data
    • Maintain a log of “minor” deviations which occurred during the review period.
      – May be submitted at time of annual review
University of Pittsburgh IRB requires the reporting of:

• Adverse events and other unanticipated events which meet the definition of an “unanticipated problem involving risks to human subjects or others”

or

• Non-compliance
Protocol Deviation or Non-Compliance: Current Pitt Requirements

Investigators must submit all incidents of non-compliance/protocol deviations within 10 working days of the investigator becoming aware of the event.
Reporting Policy: Proposed

University of Pittsburgh IRB requires the reporting of:
Events which meet the definition of an “unanticipated problem involving risks to human subjects or others”

Non-compliance which:
- significantly adversely affects the rights or welfare of participants,
- or
- significantly compromises the quality of the research data
- or
- may represent serious and/or continuing non-compliance
Protocol Deviation or Non-Compliance

Current Reporting Requirement

• Investigators must submit all incidents of non-compliance/protocol deviations within 10 working days of the investigator becoming aware of the event.

Proposed Reporting Requirement

Non-compliance that:

• significantly adversely affects the rights or welfare of participants, or
• significantly compromises the quality of the research data, or
• may represent serious and/or continuing non-compliance.
What’s Changed?

• Investigator and Research team will make initial determination as to if an event needs to be reported
Management of Non-Compliance that is not reported

- Documentation in study chart
- Documentation in a log for the study
- Managed as part of the Data Safety Monitoring Plan
Non-Compliance Log

• **Mandatory** for greater than minimal risk studies
• **Mandatory** for studies that meet the federal definition of a “clinical trial”
• **Mandatory** if required by funding agency
• Recommended for all other studies
• Not required to be submitted at annual review
• Must be available upon request
## Example of Log

<table>
<thead>
<tr>
<th>Date of Deviation</th>
<th>Study ID</th>
<th>Description of Deviation (add pages if necessary)</th>
<th>Reason for Deviation</th>
<th>Corrective Action Plan</th>
<th>Sponsor Notification Date (required for IND/IDE studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examples</td>
<td>Current Policy</td>
<td>Proposed Policy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>----------------------------------------------------</td>
<td>--------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performing non-exempt human subject research without obtaining</td>
<td>Report within 10 working days</td>
<td>Report within 10 working days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prospective University IRB approval</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conducting research during a lapse in IRB approval;</td>
<td>Report within 10 working days</td>
<td>Report within 10 working days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implementing protocol modifications without obtaining prospective IRB</td>
<td>Report within 10 working days</td>
<td>Report within 10 working days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>approval</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examples</td>
<td>Current Policy</td>
<td>Proposed Policy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>---------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obtaining consent using an outdated consent form, when the new consent</td>
<td>Report within 10 working days</td>
<td>Report within 10 working days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>form contained new information that may have caused the subject to change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>their mind about participating;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Document reason that it is not required</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>to be reported and place in log.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examples</td>
<td>Current Policy</td>
<td>Proposed Policy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not adhering to inclusion/exclusion criteria</td>
<td>Report within 10 working days</td>
<td>Report within 10 working days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrolling more subjects that approved in the protocol in a greater than minimal risk study</td>
<td>Report within 10 working days</td>
<td>Report within 10 working days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrolling more subjects than approved in a minimal risk study</td>
<td>Report within 10 working days</td>
<td>Document reason that it is not required to be reported and place in log.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performing non-safety related research procedures outside the protocol specified window</td>
<td>Report within 10 working days</td>
<td>Document reason that it is not required to be reported and place in log.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Currently in limited beta testing
• Reportable events = Reportable New Information (RNI)
• Reporting process looks very different
• September 2018 will be start of new reporting requirements
• RNI not associated with a single study
Reportable New Information

1. **RNI short title:** (uniquely identify this new information report)
   
   participant death

2. **Date you became aware of the information:**
   
   6/7/18

3. **Identify the categories that represent the new information:** (check all that apply)

   **Risk:** Information that indicates a new or increased risk, or a safety issue. For example:

   a. New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk.

   b. An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or to describe a new risk.

   c. Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol.

   d. Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm.

   e. Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm.

   f. Any changes significantly affecting the conduct of the research.
Harm: Any harm experienced by a subject or other individual that, in the opinion of the investigator, is unexpected and at least probably related to the research procedures.

a. A harm is "unexpected" when its specificity or severity is inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population.

b. A harm is "probably related" to the research procedures if, in the opinion of the investigator, the research procedures more likely than not caused the harm.

- Non-compliance: Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.
- Audit: Audit, inspection, or inquiry by a federal agency.
- Report: Written reports of study monitors.
- Researcher error: Failure to follow the protocol due to the action or inaction of the investigator or research staff.
- Confidentiality: Breach of confidentiality.
- Unreviewed change: Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.
- Incarceration: Incarceration of a subject in a study not approved by the IRB to involve prisoners.
- Complaint: Complaint of a subject that cannot be resolved by the research team.
- Suspension: Premature suspension or termination of the research by the sponsor, investigator, or institution.

Unanticipated adverse device effect: 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.

Important! Information that does not fit into one of the categories above does not need to be reported to the IRB as new information.
4. * Briefly describe the problem or new information (data of occurrence or discovery, timeline, cause, action taken, changes made):
   We obtained additional information from the participant's wife. He apparently developed chest pains and passed out at home and DOA to Westmoreland ED. I am reporting this event as possibly related since no autopsy was performed and I cannot rule a relationship to the study drug.

5. What actions need to be taken, or what changes are proposed to protect research subjects or others?
   I contacted the study sponsor and the DSMB and awaiting a decision as to whether the consent form will need revision or any changes to the drug administration.

6. In the submitter's opinion:
   a. * Does this information indicate a new or increased risk, or a safety issue?
      ○ Yes  ○ No
   b. * Does the study need revision?
      ○ Yes  ○ No
   c. * Does the consent document need revision?
      ○ Yes  ○ No

   If revisions are required, describe them above and submit a study modification for review.

7. Related studies and modifications:
<table>
<thead>
<tr>
<th>ID</th>
<th>Short Title</th>
<th>Investigator</th>
<th>State</th>
<th>IRB Office</th>
</tr>
</thead>
<tbody>
<tr>
<td>STUDY18030033</td>
<td>Black Simple Study</td>
<td>Rebecca Simms (pi)</td>
<td>Approved</td>
<td>Pitt IRB</td>
</tr>
</tbody>
</table>

8. Attach files containing supporting information:
   Name
   There are no items to display
QUESTIONS?