Mandatory Reporting Obligations Under the Regulations

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Reporting Obligations Overview

Regulations/Applicability

What to Report
- Unanticipated Problems (UPs)
- Serious or Continuing (S/C) Noncompliance

Protocol Deviations

How to Analyze Information to Determine Whether Reportable

Who Must Report, When & How
Reporting Obligations

- Participants
- LARs
- IRB
- Sponsors
- Funding Agency
- Regulatory Agency
- Institutional Committee(s)
- Institutional Official(s)

Investigator Reporting Obligations
Federal regulations require prompt reporting to the IRB, institutional officials (IOs), and
For federally funded research—the funding department or agency head & OHRP, and/or
For FDA regulated research—FDA of:
- UPs involving risk to subjects or others;
- Serious or continuing noncompliance with 45 CFR 46/FDA regulations or IRB requirements or determinations; and
- Suspension or termination of IRB approval.
OHRP Applicability

➢ Non-exempt human subjects research that is:

- Conducted or supported by HHS;
- Conducted or supported by a non-HHS federal department/agency that has adopted the Common Rule (Common Rule Department/Agency); or
- Covered by a Federalwide Assurance (FWA), regardless of funding source

✓ Checked the box

Terms of FWA
http://www.hhs.gov/ohrp/assurances/forms/filasurt.html
FDA Applicability

- Experiments that involve a test article and one or more human subjects and is either:
  - An IND or IDE regulated clinical trial or
  - Not an IND/IDE regulated clinical trial, but the results of which are to be submitted to, or held for inspection by, FDA to support research or marketing permits.
Unanticipated Problems
Any incident, experience, or outcome meeting the following criteria:

- **Unexpected** (nature, severity, or frequency);
- **Related or possibly related to research procedures**;
- Suggests that the research places subjects or **others** at a **greater risk of harm** than previously known or recognized; &
- Usually requires some action to address the incident, experience or outcome.
UPs (cont’d)

- Places … others at a greater risk of harm than previously known/recognized
  - Family/friends of subjects
  - Research team members
  - Society at large
- Greater risk of harm
  - Actual harm not needed; simply exposing subjects/others to harm is sufficient
  - Not just limited to physical harm
    - Psychological
    - Economic
    - Social
Serious or Continuing Noncompliance
Any accidental or intentional failure to follow:
- Common Rule/FDA regulations or
- IRB requirements or determinations (e.g., following the protocol)

Failure to follow includes:
- Performing acts that violate the above;
- Failing to act when required to do so.

Includes noncompliance by institution’s employee(s) or agent(s) involved in research
- Research team members
- IRB members/staff
- Institutional Officials (IOs)

CIRB SOPs (Section 10.3) definition of Noncompliance
- A failure to meet the requirements of the applicable Federal regulations and/or the requirements of the CIRB.
Serious Noncompliance

➢ Not defined in regulations; refer to CIRB SOPs
➢ CIRB SOPs (Section 10.3) definition:

➢ Serious noncompliance:
   □ Noncompliance that adversely affects the rights and welfare of study participants or results in any untoward medical occurrence that meets the criteria of “serious” or significantly impacts the integrity of study data.
   □ Serious is defined as side effects that may require hospitalization or may be irreversible, long-term, life-threatening, or fatal. The CIRB may also consider as serious those events which, based on appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes above.
Implementing more than minor protocol changes without IRB approval, except when necessary to prevent immediate hazard(s) to subjects;

Conducting non-exempt human subjects research without IRB review and approval;

Failing to obtain the legally effective informed consent of subjects, when required by the IRB, prior to involvement of subjects in non-exempt human subjects research activities.
Continuing Noncompliance

- Not defined in regulations; refer to CIRB SOPs
- CIRB SOPs (Section 10.3) definition:
  - Continuing noncompliance
    - A systematic and habitual disregard of the requirements or decisions of the CIRB or of Federal regulations. Continuing noncompliance is an indication of a pattern that, if unaddressed, could jeopardize the rights and welfare of research participants or the integrity of the study data due to noncompliance with the protocol, Federal regulations, and/or the requirements of the CIRB.
Possible Sources of UPs & S/C Noncompliance

- AEs/SAEs UADEs
- Premature Suspensions or Terminations
- Monitoring Reports
- Participant Complaints
- Protocol Deviations
- Literature/News
- Observations
- UPs & S/C Noncompliance
Every event must be assessed as:

- An isolated event; and
- In the aggregate, if applicable;
- To determine whether the isolated event or aggregate analysis of same or similar events, i.e., trend, meets:
  - UP Criteria;
  - Serious Noncompliance Criteria; or
  - Continuing Noncompliance Criteria

*Think Isolated Event Analysis*  
*As Well As Trend Analysis!*
Protocol Deviations (PDs)

- Expected/future PDs are not reviewed by the CIRB
- PDs reported to the CIRB fall into one of the two categories:
  - Potential Unanticipated Problems (UP) or
  - Potential Serious or Continuing Noncompliance (SCNC)
How to Analyze PDs to Determine Whether PD Constitutes a Reportable Event
While reviewing the algorithm to determine if a PD is an UP keep in mind:

* The CIRB defines “unexpected” as incidents, experiences, or outcomes that occur while the CIRB-approved protocol is followed as written.
* Unexpected events are those that are NOT included in the CIRB-approved protocol, informed consent document, or Investigator's Brochure.
* If all answers are “Yes” or if the PI and research team are uncertain, the incident should be reported to the CIRB as a potential UP.
CIRB’s Algorithm to Determine Whether an Event is a UP

1. **Was the protocol followed as written?**
   - No → **Review for potential noncompliance**
   - Yes ↓

2. **Is the incident, experience or outcome unexpected (in nature, severity or frequency) per the CIRB’s definition?**
   - No ↓
   - Yes ↓**Stop here**

3. **Is it related or possibly related to the research?**
   - No ↓
   - Yes ↓

4. **Is there any indication that the experience, incident or outcome places participants or others at greater risk of harm than previously recognized?**
   - No ↓
   - Yes ↓

**This is a potential unanticipated problem and should be reported to the CIRB**
While reviewing the algorithm to determine if an event is SCNC keep in mind:

- The CIRB defines “serious” as:
  - Noncompliance that adversely affects the rights and welfare of study participants or results in any untoward medical occurrence that meets the criteria of “serious” or significantly impacts the integrity of study data
  - Side effects that may require hospitalization or may be irreversible, long-term, life-threatening, or fatal

- There are two algorithms associated with this determination on the following slides
CIRB’s Algorithm to Determine Whether an Event is Noncompliance (step 1)


2. NO → NO → NO → THIS IS NONCOMPLIANCE

SEE ALGORITHM FOR SERIOUS NONCOMPLIANCE
CIRB’s Algorithm to Determine Whether an Event is Serious Noncompliance (step 2)

- WAS THE STUDY PARTICIPANT SERIOUSLY HARMED USING THE FDA DEFINITION OF “SERIOUS”? [YES/NO]
  - NO → WAS THE INTEGRITY OF THE DATA IMPACTED NEGATIVELY? [YES/NO]
    - NO → THIS IS NOT SERIOUS NONCOMPLIANCE
    - YES → THIS IS POTENTIAL SERIOUS NONCOMPLIANCE AND SHOULD BE REPORTED TO THE CIRB
Who Must Report, When & How
If the incident is determined by the PI to be a potential UP and/or potential SCNC, it should be reported to the CIRB by the PI or designee.

If it is uncertain whether or not to report an incident, proceed with reporting to the CIRB.

If the CIRB determines the event is not serious noncompliance, similar incidents in the future do not need to be reported to the CIRB. They are still noncompliant, but not reportable noncompliant.
When to Report?

- Promptly
  - Not defined by regulations, rather by institutional policy
CIRB Policy
- Locally Occurring Unanticipated Problems:
  - PI notifies the CIRB within 7 days of its receipt of the information related to serious adverse events that meets the criteria of an UP.
  - PI notifies the CIRB within 14 days of its receipt of information related to other potential UP. (i.e. those not related to SAEs)
- SCNC must be reported promptly
Determine if the incident is a potential UP or SCNC utilizing the CIRB’ algorithms located on the CIRB’s website

- Algorithm to Assess a Potential Unanticipated Problem
- Algorithm to Assess Potential Noncompliance

If it is determined by the PI that event is potentially a UP and/or SCNC, utilize the CIRB’s worksheet located in IRBManager.

- Unanticipated Problem And/Or Noncompliance Reporting Worksheet

CIRB’s Quickguide is available on the CIRB’s website and outlines the submission process step-by-step

- Completing the Unanticipated Problem and/or the Noncompliance Reporting Worksheet