Defining and Streamlining IRB Review of Reportable Events: A Practical Approach

HCCA
Research Compliance Conference
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Introductions

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Children's Healthcare of Atlanta

- Three hospitals
- Seven urgent care facilities
- 28 neighborhood clinics
- Over 10,000 employees
- One of the largest pediatric clinical care providers in the U.S.
- Treated over 375,000 unique patients in 2016
- $56.8 million in total research funding awards in 2016, $30 million in NIH funding

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Children's IRB and Compliance

- 600 Active Protocols
- 5 Staff
- 1 Convened IRB Meeting/Month

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Learning Objectives

- Review regulatory requirements for IRB review of important events in research
- Share best practices to streamline investigator reporting to IRBs and IRB review
- Discuss workflow to promote efficiency of IRB review and consistency of IRB determinations

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Regulatory Event Types

- Adverse Events (AE)
- Unanticipated Problems Involving Risks to Subjects or Others (UP)
- Noncompliance (NC)
- Serious Noncompliance (SNC)
- Continuing Noncompliance (CNC)

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Adverse Events

- Any untoward or unfavorable medical occurrence including any abnormal sign, symptom or disease, temporally associated with participation in the research.
- Encompass both physical and psychological harms
- Most commonly occur in the context of biomedical research

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Internal AEs vs. External AEs

- Internal: AEs experienced by subjects enrolled by the investigator at your institution.
- External: AEs experienced by subjects enrolled at other institutions.

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Serious Adverse Events

- Results in death
- Life-threatening
- Result in or prolong hospitalization
- Result in a persistent or significant disability/incapacity
- Cause a congenital anomaly or birth defect; OR
- May jeopardize subject's health and require medical or surgical intervention to prevent one of the above examples.

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Unanticipated Problems

OHRP considers UPs to include incidents that meet all three of the following criteria:

- o Unexpected;
- o Related; AND
- o Suggests that the research places subjects or others at a greater risk of harm than was previously known.

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Unexpected

Any event that occurs and is not consistent with either:

- Known or foreseeable risks described in study documents; OR
- The expected natural progression of underlying condition and subject's risk factor profile.

Most events are *expected* in the context of research.

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Related

Events are typically caused by one or more of the following:

- **Research procedures**;
- Underlying condition; OR
- Other circumstances unrelated to research or condition.

If the event is at least partially caused by research procedures, it can be considered possibly related.

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Greater Risk of Harm

- A **serious adverse event**:
- Any event that places subjects or others at **greater risk of harm** than was previously known.
  - Physical
  - Psychological
  - Economic
  - Social

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Unanticipated Problems

- Often require changes to the protocol, consent or Investigator's Brochure
- Often increase the risk level of the study
- May require increased monitoring of subjects
- Sometimes lead to suspension in IRB approval or closure by DSMBs

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UP Reporting

- Require full board review by the IRB
- Must be reported to OHRP and FDA

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AE or UP

OHRP

- Was the AE unexpected?
- Was the AE related or possibly related?
- Does the AE place subjects or others at a greater risk of harm?

FDA

- Was the AE unexpected?
- Does the AE have implications for the conduct of the study?
- Was the AE serious?

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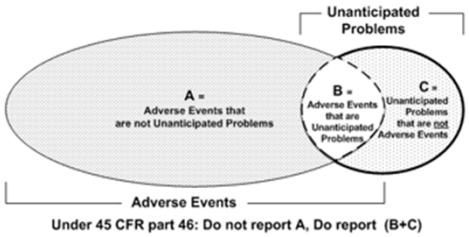
AE or UP



Under 45 CFR part 46: Do not report A, Do report (B+C)

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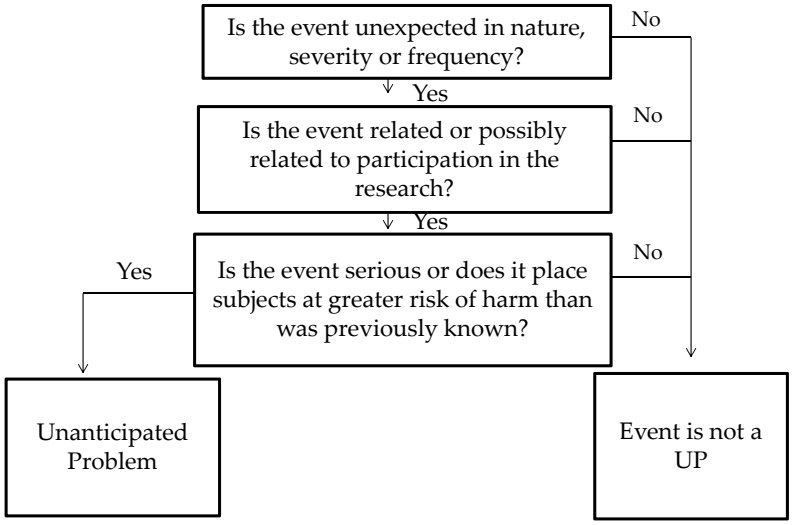
AE, UP or Both?



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Noncompliance

Noncompliance (NC)

- Failure to comply with research plan, regulations or institutional policies and procedures
- Action or inaction of study team that fails to comply with federal or state regulations or institutional policies
- Failure to follow the requirements or determinations of the IRB

Serious Noncompliance (SNC)

- Increases risks to subjects;
- Decreases potential benefits;
- Has a substantive effect on value of data collected; OR
- Results from willful misconduct of the study team

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Continuing Noncompliance (CNC)

- Pattern of noncompliance;
- Compromises the integrity of the study data;
- Persists after the investigator knew or should have known about it

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Protocol Deviation

- A deviation from the IRB-approved protocol in any way
- May constitute NC

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Corrective and Preventive Action Plans

- Prior to developing a CAPA, a Root Cause Analysis should be done
- CAPAs are vital to correct an immediate problem and find ways to avoid recurrences

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NC, SNC, CNC, PD, UP?

- SNC: increases risk, decreases benefit, effect on data or willful misconduct
- CNC: pattern, compromises the integrity of study data or persists after PI should have known
- PD: deviation from the IRB approved study in any way
- UP: unexpected, related, is serious/places subjects at greater risk of harm

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Streamlining Event Reporting

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Investigator Reporting

- Move from a culture of event over or under reporting to reporting meaningful events that increase risks to subjects or compromise the integrity of the study data
- Create tools and forms to assist investigators in assessing events for IRB reporting
- Investigator training
- IRB pushes events back to investigators that do not need to be reported

Event Reporting Form
Event Reporting Guidance

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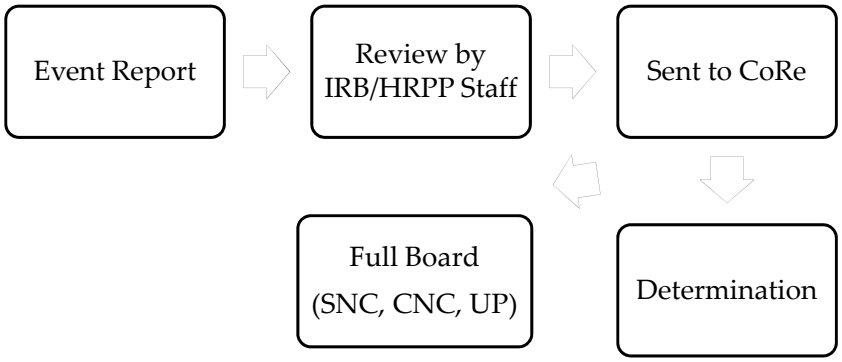
Operationalizing IRB Review of Event Reports



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Compliance Review (CoRe) Team

- Qualified group of IRB members/staff that triage reports and make preliminary determinations

- 2 IRB staff
- IRB Chair/Vice Chair
- Director of Research
- Research Compliance Manager

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NON-COMPLIANCE WORKSHEET

Date:	IRB #:	Investigator:

Study Name:

Study Summary:

Previous NC for this study or study team:

Issue:

Corrective Action Plan:

Final Determination

Yes	No	Non-Compliance
Yes	No	Serious Non-Compliance
Yes	No	Continuing Non-Compliance
Yes	No	Unanticipated Problem

Considerations (check those that apply)

	Modify the protocol		Terminate IRB approval
	Modify the information disclosed at consent		Suspend IRB approval
	Provide additional information to current subjects (if information may relate to subject's willingness to continue.		Transfer subjects to another investigator
	Provide information to past subjects.		Make arrangements for clinical care outside the research.
	Re-consent current subjects.		Allow continuation of some research activities under the supervision of an independent monitor.
	Increase the frequency of continuing review.		Require follow-up of subjects for safety reasons.
	Require disclosure to editors that data was collected without IRB approval.		Require adverse events or outcomes to be reported to the IRB and sponsor.
	Observe the consent process.		Obtain additional information.
	Require additional training of the investigator/staff.		Re-consent/Consent is required prior to use of data.
	Notify investigators at other sites.		Other:

Comments:

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Models for Full Board Review

Designated Meeting

- Familiar with Reportable Events
- Faster Processing for Letters
- More experience with CAPA guidance
- May produce more consistent determinations

Review at Regular Meetings

- Familiar with studies
- May reduce time to meeting
- Broader expertise

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Questions

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Resources

- Unanticipated Problems Involving Risks & Adverse Events Guidance (OHRP)
- Unanticipated Problems Tip Sheet (AAHRPP)
- Investigator Responsibilities/Compliance Guidance (FDA)
- Adverse Event Reporting to IRBs—Improving Human Subject Protection (FDA)
- Event Reporting and Non-Compliance Forms (CHOA)

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