Adverse Events and Problems in Clinical Research: Chasing Certainty….Living with Doubt

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Today’s 3 Goals

1. Review the life-cycle of an adverse event
2. Contrast the safety event reporting requirements for investigators and sponsors
3. Identify which adverse events are reportable to the DUHS IRB (and those which are not!)
Safety Event Reporting at DUHS*
By the numbers…

Total amount of safety events: 2571

Adverse events: 777  (96% expedited)
Correspondence: 294  (97% expedited)
Other problems/events prompt reporting: 110  (89% expedited)
Protocol violation/deviations: 1390  (97% expedited)

*Annual
Goal #1

The life-cycle of an adverse event.
Life Cycle of an Adverse Event

- Clinical observation of an Adverse Event (AE)
- Suspected Adverse Drug Reaction (SADR)
- Scientific Level of Causation
- Adverse Drug Reaction (ADR)

Characterized by:
- Severity
- Populations
- Incidence
- Other Features
Life Cycle of an Adverse Event

- Safety Master Database
- Investigator’s Brochure
- Consent Form
Doubt is not a pleasant condition, but certainty is absurd.

- Voltaire
Life Cycle of an Adverse Event

Safety Master Database → Investigator’s Brochure → Consent Form

Judgment → Judgment
Life Cycle of an Adverse Event

1. Universe of Events
2. Inform Investigators
3. Inform Subjects

- Safety Master Database
- Investigator’s Brochure
- Consent Form

Judgment

Judgment
Reporting responsibilities vary by role.
Reporting responsibilities vary by role
Anticipated
Pre-marketing
Non-preventable
Unexpected
Preventable
Reportable
Harm
Causal
Serious
Expected
Not-Expected
Preventable
Non-reportable
Non-causal
No-harm
Not-serious
Terminology and Context are Important
Types of Safety Events in Clinical Trials

• Adverse Events & Adverse Reactions
  – Including “suspected”
  – Including “serious or life threatening”
  – Including “unexpected”

• Protocol violations
• Protocol deviations
• Unanticipated problems involving risk
• Other (research non-compliance)
Types of Safety Events in Clinical Trials

21 CFR 312.32 defines:

• Adverse Event
  – Serious or life-threatening adverse event
  – Unexpected adverse event

• Adverse Reaction
  – Suspected adverse reaction
  – Serious or life-threatening suspected adverse reaction
  – Unexpected suspected adverse reaction
  – Serious unexpected suspected adverse reaction*

*listed but not specifically defined
Adverse event
Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Adverse reaction
Any adverse event caused by a drug

21 CFR 312.32(a)
Suspected adverse reaction (SADR)

Any AE for which there is a **reasonable possibility** that the **drug** caused the adverse event.

‘Reasonable possibility’ means evidence suggests a causal relationship between the drug and the adverse event.

An SADR implies a **lesser degree** of certainty about causality than an adverse reaction (ADR).

Harmonized with (ICH) E2A guidance
21 CFR 312.32(a)
Serious Adverse Events

- SAE’s are adverse events that result in any of the following outcomes:
  - death
  - life threatening reaction
  - inpatient hospitalization or prolonged hospitalization
  - persistent/significant disability/incapacity
  - congenital anomaly
  - significant medical event based on medical judgment
Serious Adverse Events
(A deeper dive....)

• Serious AE’s also include:
  – adverse events that occur following treatment
  – any event that in the judgment of the reporter may require intervention to prevent a listed outcome.

• Serious AE’s may exclude:
  – adverse events that are defined in the protocol as non-reportable SAE
  – adverse events that are study endpoint (unless unusual)*

*21 CFR 312.32(c)(5)
Unexpected Adverse Events

- The specificity or severity of which is not consistent with the current investigator brochure; or the general investigational plan or elsewhere in the current application (IND)

  - Hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis.
  - Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents.
Unexpected ≠ not being anticipated

*Unexpected* = has not been previously observed (i.e., not included in the investigator brochure),

IN CONTRAST TO

An un-anticipated effect based on the drugs pharmacology or reports from a similar drug in this class

Ref: (21 CFR 312.32(a))
Other Common Safety Terms

SUSAR
Serious Unexpected Suspected Adverse Reaction

Triggers an Expedited IND Safety Report
From Sponsors to FDA and to Investigators

HOWEVER, DO NOT CONFUSE SUSAR’s with….
Other Common Safety Terms

Unanticipated Problems Involving Risks to Subjects and Others (UPIRTSO)

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Unanticipated
Related to study
Risk represents a problem for the study

-FDA Draft Guidance Sep 2010

Other Common Safety Terms

When does a Risk represent a Problem for the Study?

Event places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
Goal #2

Contrast the safety event reporting requirements for investigators and sponsors
SELF - ASSESSMENT

Which of the following is (are) true?

1. Sponsors must report each SAE to the FDA in an expedited manner (via IND safety report)
2. Investigators should not report an SAE to the sponsor when the causality is unlikely.
3. Sponsors and investigators share equal responsibility for determining the causal relationship between the drug and the SAE.
ADVERSE EVENTS
(A deeper dive....)

• IND regulations:
  – do not require sponsors to report SAE’s to the FDA in an expedited manner if they are “unlikely or remotely related to the product”.
  – the causal relationship must be at least reasonably possible.
  – The SAE must also be unexpected.

• The IND regulations require Investigators to report SAE’s to the sponsor regardless of causality.
  – A causality assessment must accompany the report
ADVERSE EVENTS (A deeper dive....)

- IND regulations specify that
  - if either the sponsor or investigator believes that the event is serious (or life-threatening), the event must be considered as such and evaluated by the sponsor for expedited reporting

- the sponsor is responsible for determining causality of an event to the drug (with consideration of input from the investigator)

  • NB: differs from ICH which allows the sponsor or investigator to determine causality
ADVERSE EVENTS
(A deeper dive....)

• Causality assessment for an individual case-report is different from the assessment of overall relatedness of a new event.

• While an individual AE reports may have a possible, probable or definite causality assessment, the overall causality assessment may be indeterminate.

WHY?

• The individual AE assessment lacks a scientific basis for causation....lacks an analysis against a larger dataset.
ADVERSE EVENTS  
(A deeper dive....)

• Appropriately deciding whether the adverse event meets the definition of a suspected adverse reaction is not easy.

• The sponsor should evaluate the available information and decide if there is a reasonable possibility that the drug caused the adverse event and, therefore, meets the definition of a suspected adverse reaction.
ADVERSE EVENTS
(A deeper dive....)

• Sponsors are to report to FDA only if there is evidence to suggest a causal relationship.

• The decision about when a Sponsor should report to the FDA is a matter of judgment based on a variety of factors including the study population, the nature and seriousness of the reaction, and the magnitude of the observed increase in the rate.
Protocol violations and deviations

How are these different?

and

What needs to be reported?
SELF - ASSESSMENT

Which of the following is (are) true?

1. The sponsor needs to report all protocol violations and deviations to the FDA.
2. Single patient exemptions to inclusion criteria must be prior-approved by the FDA and IRB.
3. Violations or deviations that involve a new or increased risk must be reported to the IRB and FDA.
Protocol violations and deviations

- The terms “protocol deviation and violation” are not defined by either HHS (45 CFR 46) or FDA (21 CFR 50).
- ICH 4.5 Compliance with Protocol
  - 4.5.2 …do not deviate from the protocol without prior agreement by the sponsor and the IRB….
  - 4.5.3 …document and explain any deviation from the approved protocol.
  - 4.5.4 …a deviation is allowable to eliminate an immediate hazard to trial subjects without prior IRB approval….and, if appropriate, the proposed protocol amendment(s) should be submitted: (a) to the IRB for review, (b) to the sponsor for agreement and, if required, (c) to the regulatory authorities
Protocol violations and deviations
DUHS Definitions

• Violations - means an intentional act … in which the protocol is not followed.

• Deviations - means an inadvertent act … in which the protocol is not followed. (a mistake)

• “Reportable Event” means a protocol deviation or violation that is likely to adversely affect the rights and welfare of the research subjects, the safety of the research subjects, or the integrity of the research data.
 Protocol violations and deviations

• Reporting to the FDA
  – Report protocol violations and deviations that result in new risks or increased risks
  – Report changes to protocol via amendment
    • (e.g. changes to inclusion/exclusion criteria)
Protocol violations and deviations

• Reporting to the IRB
  – Generally, violations/deviations will be reported to the IRB, but the requirements and reporting time frame differs based on risk
  – Planned deviations usually require prior IRB approval
    • e.g., altered inclusion/exclusion criteria
    • provisions for use prior to IRB approval exist for emergencies
  – New or increased risks require prompt reporting
    • e.g. unanticipated problems
SAE’s and Unanticipated Problems

How are these different?

What are differences in the reporting requirements?
AE’s are relatively infrequent events ....
AE’s are relatively infrequent events and study related AE’s are even less common....
AE’s are relatively infrequent events and SAE’s are even less common....

- All AE’s
- AE’s-related to study
- SAE

Investigators to sponsor regardless of causality

Sponsor to FDA if related to the study and unexpected (Expedited report)
AE’s and SAE’s are relatively infrequent events and UaP’s are even less common....

*UaP = unanticipated problems involve risk to subjects/others

ExpEDITEd (aka “prompt”) reports: sponsor to FDA if related to the study and unexpected and to the IRB if a new or increased risk!
AE’s and SAE’s are relatively infrequent events and UaP’s are even less common.

*UaP = unanticipated problem involve risk but may not result in an AE

**Expedit**ed (aka “prompt”) reports: sponsor to FDA if related to the study and unexpected and to the IRB if a new or increased risk!
Unanticipated Problem Involving Risks to Subjects or Others

• In the judgment of the investigator, any problem or event:
  – related to the research, and
  – unexpected, and
  – new or greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
FDA Guidance for reporting adverse events and unanticipated problems*

(A deeper dive....)

With few exceptions, FDA believes that an individual adverse event report cannot be readily concluded to represent an unanticipated problem, even if the event is not addressed in the investigator’s brochure, protocol, or informed consent documents....and sponsors should not report these to the IRB in the absence of relevance.

*21 CFR 56.108(b)(1)
Subject Safety and Systems of Care (moving beyond the regs)

• Safety Events that are **patient care-related problems** (e.g., medications/devices) should also be reported to the DUHS System Safety Reporting System*

*DUHS Policy and consistent with GCP and Ethical Principles, but NOT a Federal Regulation or Requirement
Subject Safety and Systems of Care (moving beyond the regs)

• Along with the report of the safety event, the PI is required to report to the IRB:
  – 1. What actions were taken to address/correct/resolve the event?
  – 2. What actions are being implemented to minimize the likelihood of recurrence of the event in the future?
Corrective Action and Quality Improvement Plans

- Actions taken to minimize the likelihood of recurrence of the event in the future should be based on the systems failures that may have led to the problem.
- The IRB will review all proposed actions for their appropriateness and likelihood to reduce the risk in the system.
- Action plans, primarily based on education, counseling, discipline, posters, emails, and other temporal measures may be rejected by the IRB as insufficient to prevent future events.
Case Study

• The first 5 subjects enrolled in a multi-center cancer trial, experience blood counts that are significantly lower than expected, resulting in delays in subsequent cycles. The site PI contacts colleagues at several other centers. No other clinical center has experienced this adverse event.

What is your next action?
Goal #3

Identify which adverse events are reportable to the DUHS IRB (and those which are not!)
DUHS Policy

Reportable adverse events

Serious
Related to the research
Unexpected

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All other AE’s are **Not Reportable** to the IRB unless they meet the definition of a UPIRTSO
DUHS POLICY
Protocol violations and deviations

DUHS HRPP policy requires reports if the event:
(i) affects subject rights and welfare, or
(ii) affects subject safety; or
(iii) affects the integrity of study data; or
(iv) affects the subject's willingness to continue in the study; or
(v) is specifically requested by a government agency, internal/external auditor, medical monitor, or the IRB.
DUHS Policy

Unanticipated Problems and Prompt Reporting

• Within 24 hours (immediately) - unanticipated study related death

• Within 5 business days - reportable SAE (i.e., related, serious and unexpected)

• Within 10 business days - any other problem or event requiring prompt reporting
You are not in this alone!

Contact an IRB Chair for guidance on DUHS and Federal reporting requirements

919.668.5111
Supplemental Information
Examples of study drug-related violations and deviations

- Altered dose or dose schedule or route of administration
- Altered dosage form
- Wrong dose, time, route or dosage form
- Wrong patient/subject
- Failure to avoid interactions (drug or food)
- Use of expired or contaminated drug
- Use of commercial inventory instead of study inventory
- Accountability (e.g., lost drug, un-returned supplies)
Examples of study drug-related violations and deviations

- Consumption by family member or pet
- Storage violations by subject
- Preparation errors (e.g., shaking proteins, filtration)
- Un-authorized prescriber
- Un-authorized person administers study drug
- Record-keeping and administrative errors
- Criminal, fraudulent, and misconduct
Summary: Reporting responsibilities*

Investigator

- AE’s to sponsor 21CFR312.64(b)
- SAE’s to sponsor 21CFR312.64(b)
- SAE’s to IRB (“reportable” SAE’s per local policy)

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- UaP’s to IRB (21 CFR 312.53(c)(1)(vii), 312.66, and 21 CFR 56.108(b)(1))
- Deviations & Violations to IRB (per IRB policy)
- Deviations & Violations to sponsor (per protocol)

*Local IRB policies and special contractual agreements may also apply
**Summary:**

**Reporting responsibilities***

**Sponsor**

- AE’s and SAE’s to FDA 21CFR312.64(b)
- SAE’s to IRB when risk is unreasonable and significant 21CFR312.56(d)
- SAE’s with analyses to Investigator 21CFR312.55(b) and 312.32(c)(1)(ii)

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- UADE’s for devices to FDA, IRB and Investigators 21CFR812.150(a)(1), 812.150(b)(1), 812.46(b)
- UaP’s for drugs to IRB 21CFR312.53(c)(1)(vii)

*Local IRB policies and special contractual agreements may also apply*
Summary:

Reporting responsibilities*

IRB (more specifically…”institutional officials”)

- UaP’s to OHRP 45 CFR 46.103(a), (45 CFR 46.103(b)(5)
- Assure via written procedure that UaP’s are reported to FDA 21CFR56.108(b)(1)

*Local IRB policies and special contractual agreements may also apply
Selected References

- FDA Regulations: Monitoring Device Studies - 21CFR812.46
- FDA Regulations: Reporting Device Events - 21CFR812.150
- OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events. January 15, 2007