"Try falling down and scraping your knee. Then you can talk to me about pain."
Adverse event and safety monitoring in clinical trials

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Objectives

• Purpose
• Identifying
• Reviewing
• Coding
• Reporting
Purpose

• To identify safety concerns
• To exclude safety concerns
• To contextualize risk
• To comply with regulations

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events

FDA Guidance: Adverse Event Reporting to IRBs – Improving Human Subject Protection 2009

Safety Reporting Requirements for INDs and BA/BE Studies 2012

Safety Assessment for IND Safety Reporting, DRAFT 2015
Purpose

To separate the wheat from the chaff... or...

to see the dog and the soldier
Ways of Measuring Safety

• On the primary outcome measure…
  – i.e. “Negative efficacy”

• On other pre-defined safety outcomes…

• Through monitoring of adverse events…
Ways of Measuring Safety

• Pre-defined safety outcomes...
  – AE’s of special interest
  – Practical
  – Objective
  – Using available information
  – Communicable
AE Regulations and Guidelines

• Similar (but not identical) terms are defined similarly (but not identically) in multiple places:
  – 21 CFR 312 (IND) and 314 (NDA)
  – 21 CFR 812 (IDE) and 814 (Premarket approval)
  – FDA guidance(s)
  – ICH GCP E6 and E2A and E9
  – ISO 14155 GCP for devices
  – NIH/NCI
AE Regulations and Guidelines

- Adverse event terms are not defined or described in...
  - 45 CFR 46  The Common Rule
  - 21 CFR 50  FDA HSP Regulations
  - 21 CFR 56  IRB Regulations
  - ICH E2B  Clinical Safety Data Management
AE Regulations and Guidelines

• Synonyms of adverse “event” include:
  - Effect
  - Experience
  - Health Consequence
  - Outcome
  - Occurrence
  - Reaction (to a drug)
Quiz

Select the most accurate statement

A. FDA guidance suggests that all AE be reported expeditiously to the IRB

B. The Common Rule distinguishes between Adverse Events and Adverse Occurrences

C. Safety outcomes should be predefined.
What is an adverse event?

“any UNTOWARD medical occurrence in a subject”

- Syndromes/diagnoses preferably
- Symptoms if necessary
- Report separate events individually
What are not adverse events?

- Outcomes (death, surgery, intubation, etc.)
- Pre-existing conditions (unless worsening)
- Abnormal results of tests if not considered by the investigator to be clinically significant
- Other people’s problems and near misses
Unanticipated Problems

Do not report A,
Do report B and C

A = Adverse Events that are not Unanticipated Problems
B = AE that are unanticipated problems
C = Unanticipated problems that are not AE
Properties of an AE

- Seriousness
- Expectedness
- Relatedness
- Severity
- Treatment, Resolution, Outcome
Seriousness

• Fatal
• Life-Threatening
• Causes or prolongs hospitalization
• Result in disability/congenital anomaly, or
• Require intervention to prevent permanent impairment or damage
Expectedness

• **Expected**
  – adverse reactions anticipated with the study intervention and pre-defined in the investigator brochure or protocol
  – (controversial?) adverse events commonly seen in subject’s clinical scenario

• **Unexpected**
  – events not anticipated from the intervention or the subject’s clinical scenario
  – aggregate imbalance of anticipated or common event at interval analysis
Relatedness

Sample Algorithm

**Not Related**
- The timing is wrong and there was clearly another cause

**Unlikely** (one or both)
- Another cause is possible
- Not something the intervention is known to cause

**Possibly** (2 of 3)
- Timing is suggestive.
- No other likely causes.
- This is something the intervention is known to cause.

**Probably** (must have all 3)
- Timing is suggestive.
- No other likely causes.
- This is something the intervention is known to cause.

**Definitely** (must have all 3)
- Timing is suggestive.
- No other possible cause.
- This is something the intervention is known to cause.
Severity

• Unrelated to Seriousness (sort of)

NCI Common Terminology Criteria for Adverse Events (CTCAE)

0 No AE (or within normal limits).

1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

2 Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL).

3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

4 Life-threatening consequences; urgent intervention indicated.

5 Death related to AE.
Treatment, Resolution, Outcome

- Date of onset, date resolved
- Action (none, discontinued, other…)
- Outcome
Quiz

Which of these cannot be an adverse event?

A. Vomiting
B. Motor vehicle crash
C. Death
D. Pneumonia
Identifying AE

• Over what period will events be collected?
• When will you look?
• Where will you look?
Identifying AE

- Naming of events
  - Disambiguate

- Narrative description
  - Enough but not too much
  - Templates?
“I just have to create a few loose ends for other people to clear up, and then I can out of here.”
Reviewing AE

• Internal review
  – Administrative errors
  – Completeness
  – Consistency
Reviewing AE

• Independent review/adjudication
  – Source material provided
  – Determinations to be made
  – Workloads and timelines
Coding AE

• Lumping versus splitting
Coding AE

• Available systems
  – MedDRA
  – WHO-ART
  – COSTART
  – ICD-10
  – SNOMED CT
Coding AE

- Hierarchy imposed
- Multiaxiality
Coding AE

• Completeness: AE “GOLD” requires clarification

• Accuracy: AE “COLD” might mean … Clarification or study specific plan required

• Verbatim: Coder cannot interpret 3 events (polydipsia, high blood sugar, polyuria = diabetes)

• Judgment: “Convulsions on drug withdrawal” codes to… “convulsions” or “drug withdrawal”?

Qureshi S, J Clin Res Best Pract 2012;8(3)
Coding AE

• Consistency (in systematic review)
  – Coding agreement 88%
  – Accuracy 92%

Reporting AE

• To whom
  – IRB
  – FDA
  – DSMB
Reporting AE

• When
  – Reporting schedules
  – MedWatch
  – Individual reports
  – Aggregate reports
Reporting AE

• Future directions
Other elements of a safety plan

- Emergency unblinding
Thank you

Questions?