

"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”

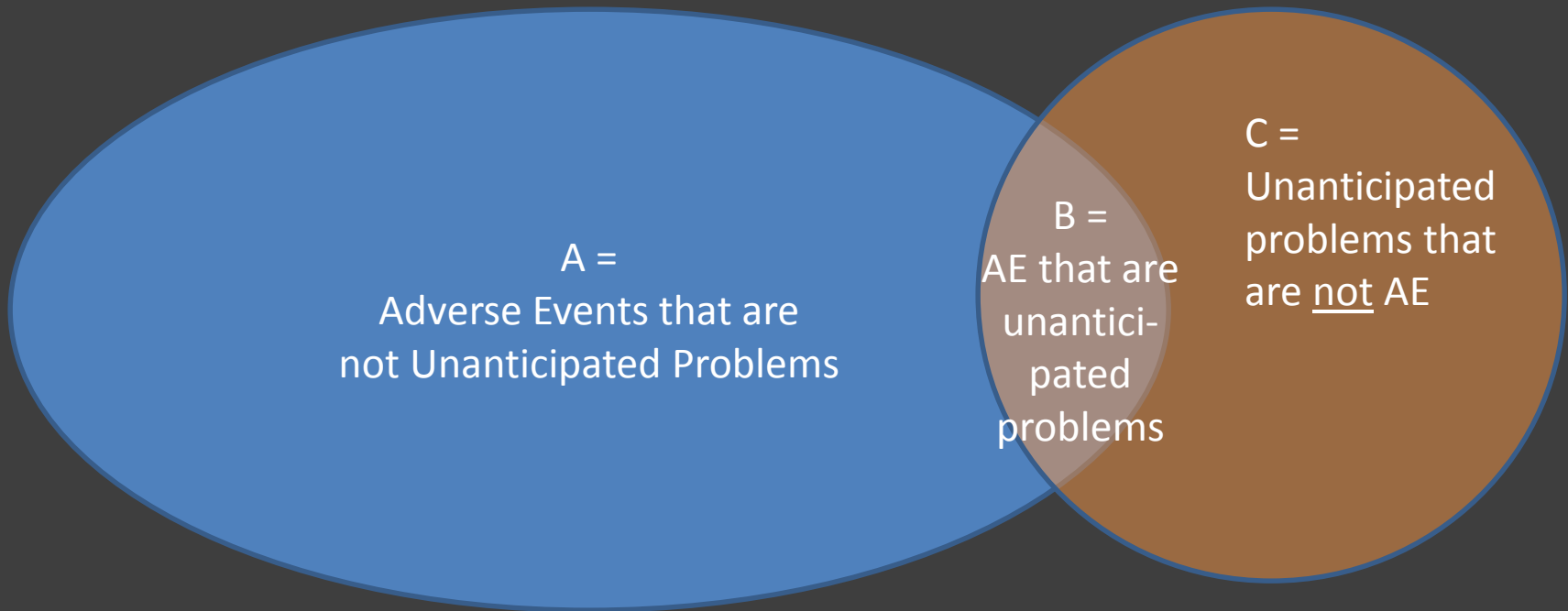
- Syndromes/diagnoses preferably
- Symptoms if necessary

- 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

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)

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). | 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. |
| 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. | 4 Life-threatening consequences; urgent intervention indicated. |
| 2 Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL). | 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

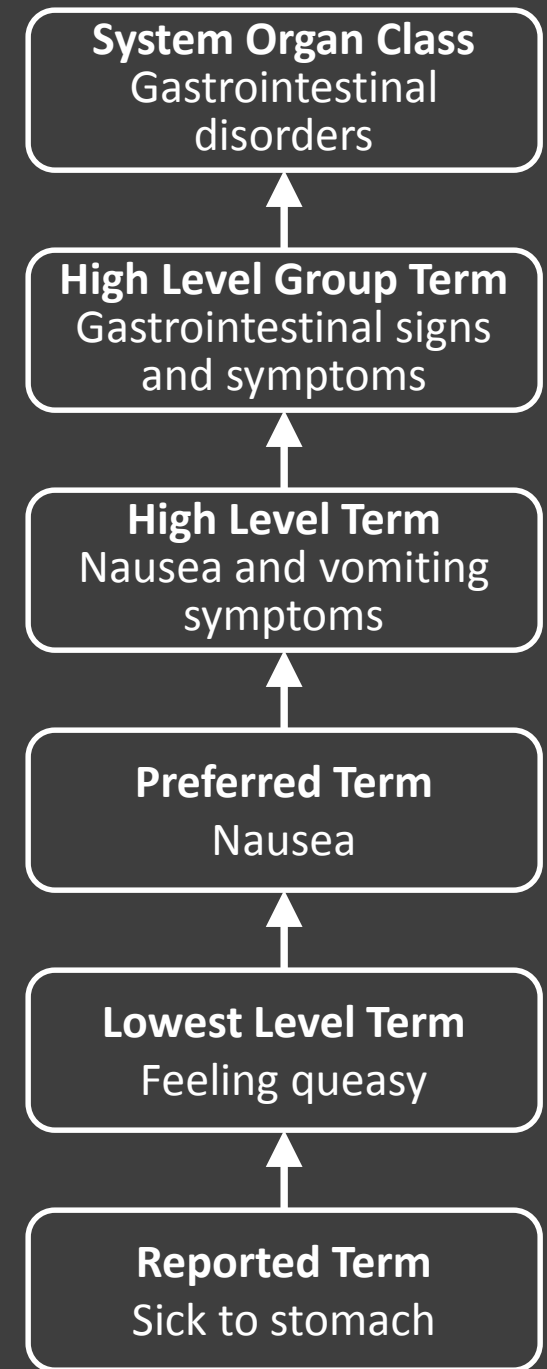


Coding AE

- 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%

Schroll JB et al. Challenges in Coding Adverse Events in Clinical Trials: A Systematic Review. PLoS ONE 2012;7(7):e41174

Reporting AE

- To whom
 - IRB
 - FDA
 - DSMB

Reporting AE

- When
 - Reporting schedules
 - MedWatch
 - Individual reports
 - Aggregate reports

Reporting AE

- Future directions
 - Harmonization: the Safety Reporting Portal, MedWatchPlus, FAERS or BAER format.
(Initiated 2004, implemented in 2010 for NIH gene transfer trials, and non-investigational purposes)

Other elements of a safety plan

- Emergency unblinding

Thank you

Questions?