



FDA's Clinical Investigator Course

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U.S. Department of Health and Human Services

Food and Drug Administration





Safety assessment in Clinical Trials and Beyond

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Outline

- Introduction
- Sources of safety information
- Is your patient right for the trial?
- Safety monitoring/ AE ascertainment
- AE Coding
- Safety Reporting
- Postmarketing safety (MedWatch) reporting
- Summary



Evaluation of Safety

- Evolving process
- Available data depend on the stage of development
- Safety information on approved products is reflected in product labeling (Package Insert)
- Up-to-date safety information on the products under investigation is found in the Investigator's Brochure (IB)
 - In vitro testing Nonclinical pharmacology/toxicology studies
 - Clinical safety and pharmacokinetic data if available
 - For products under investigation, IB is equivalent to the Package Insert



Sources of Safety Information

- Clinical trial data for the indication
- Nonclinical data (CMC, in vitro, animals)
- Clinical Pharmacology studies
- Clinical trial safety data for other indications
- Postmarketing experience
- Medical literature
- Safety profile of other drugs in the same class

■ ■ ■ Nonclinical information

- Chemical structure/Drug class
 - Class toxicities
- In vitro toxicity evaluation
 - Genotoxicity
 - Cardiac repolarization
- Pharmacology-Toxicology studies in animals
 - Organ specific toxicities
 - Carcinogenicity
 - Teratogenicity

■ ■ ■ Phase 1/Pharmacokinetic Trials

- Absorption, metabolism, C_{\max} , AUC, $T_{1/2}$
 - in healthy subjects
 - in patients
 - in special populations
- Drug safety profile in dose escalation trials
 - Healthy volunteers
 - Safety signals supporting nonclinical findings
 - New safety signals in humans only

■■■ Is your patient fit for the trial?

Apply IB findings to the protocol and a prospective subject

- Inclusion/Exclusion criteria
 - medical history
 - lab values
 - concomitant medications
- Dosing regimen, duration (examine the potential for drug accumulation/ toxicities) – monitoring implications
 - PK parameters single versus multiple doses
 - Linearity of exposure with dose escalation



Safety Monitoring

Unexpected Adverse Events

Common Adverse Events

Laboratory abnormalities

Adverse Events

Rare Adverse Events

Adverse Events of Special Interest

Serious Adverse Events

Adverse Reactions

■ ■ ■ Ascertainment of Adverse Events

- Spontaneously reported/observed symptoms and signs
- Symptoms/Signs reported as a result of a probe
 - Checklist
 - Questionnaire
- Both

■ ■ ■ Other Safety Assessments/Monitoring

- Vital signs
- Laboratory evaluations
 - CBC
 - LFTs
 - CPK
 - Renal Function Tests
 - Pancreatic enzymes
- Special safety assessments, for example:
 - Visual, Hearing
 - Neurological exam
 - ECG



Adverse Event / Experience

- Any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related (21 CFR 314.80)
 - sign, symptom, or disease
 - abnormal lab, VS, imaging, ECG, etc
 - worsening of the above
 - constellation of the above

ideally, prospectively established case definition (e.g., drug-induced parkinsonism)

■ ■ ■ AE Severity Grading Scales

- Provide general guidance on parameters for monitoring safety in clinical trials
- They are specific to:
 - Study population
 - Phase of product development (1-4)
 - Product evaluated (small molecule, therapeutic biologic, device, vaccine)
- Examples:
 - NCI
 - DAIDS
 - WHO
 - DMID

■ ■ ■ AE Severity Grading Scale (NCI)

- Common Terminology Criteria for Adverse Events (CTCAE) used for oncology drugs, generally not appropriate for otherwise healthy subjects.
- Grade refers to the severity of the AE
 - **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated
 - **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
 - **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
 - **Grade 4** Life-threatening consequences; urgent intervention indicated.
 - **Grade 5** Death related to AE.



AE Severity Grading Scale (FDA/CBER)

- Healthy adult and adolescent volunteers in vaccine trials
 - Grade 1 Mild
 - Grade 2 Moderate
 - Grade 3 Severe
 - Grade 4 Potentially Life-threatening

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf>



Serious Adverse Event (21 CFR 312.32(a))

- Any Adverse Event that results in the opinion of the Investigator or Sponsor in:
 - Death or is life-threatening (immediate risk of death)
 - Hospitalization or prolongation of existing hospitalization
 - Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (aka disability)
 - Congenital anomaly / birth defect



Uncommon Serious AEs


- Anaphylaxis
- Aplastic anemia
- Blindness
- Deafness
- Bone marrow suppression/pancytopenia
- DIC
- Hemolytic anemia
- Liver failure
- Liver necrosis
- Liver transplant
- Renal failure
- Seizure
- Stevens-Johnson/TEN
- Sudden death
- Torsades
- TTP
- Vfib



Evaluation of a Serious Adverse Event

- Is it of common occurrence in the population under study?
- Was it “treatment-emergent”?
- Did it respond to de-challenge?
- Did it recur on re-challenge?
- Were there concomitant medications?
- Were pertinent labs/other tests done?
- Was there an obvious alternative cause?
- Is SAE a study endpoint?

Note to Investigators: provide enough relevant information in CRF to allow for good quality narratives



AE Reporting requirements for the Investigator to the Sponsor (21 CFR 312.64(b))

- All Serious Adverse Events with causality assessment
- Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations.

Note to Investigators: Report all SAEs regardless of causality. Include in your report results of relevant lab tests performed outside protocol scheduled visits

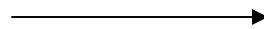
■ ■ ■ Coding of Adverse Events

- Process of converting investigators' "verbatim" terms to standardized "Preferred Terms" (PT)
 - Standardization allows sorting of AEs and grouping of like events
 - PT used to calculate incidence of AE
- Currently most used: MedDRA (Medical Dictionary for Regulatory Activities)



MedDRA Structure – Hierarchy

Highest level of terminology, least specific

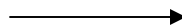


SOC - System Organ Class (26)

HLGT - High Level Group Term (335)

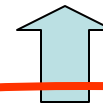
HLT - High Level Term (1,709)

Represents a single specific medical concept



PT - Preferred Term (18,786)

LLT - Lowest Level Term (68,258)



**AE as reported on CRF
“Verbatim”**





Coding Problems

- Coding problems may lead to missing safety signals
 - Splitting same AE among similar PTs
 - Hypertension, high blood pressure, etc.
 - Lumping different terms to same PT
 - Leg edema, face edema, etc.
 - Lack of adequate term/definition
 - Drug hypersensitivity, Metabolic syndrome, Serotonin syndrome

Note to Investigators: Be consistent and use scientific terminology when reporting AEs

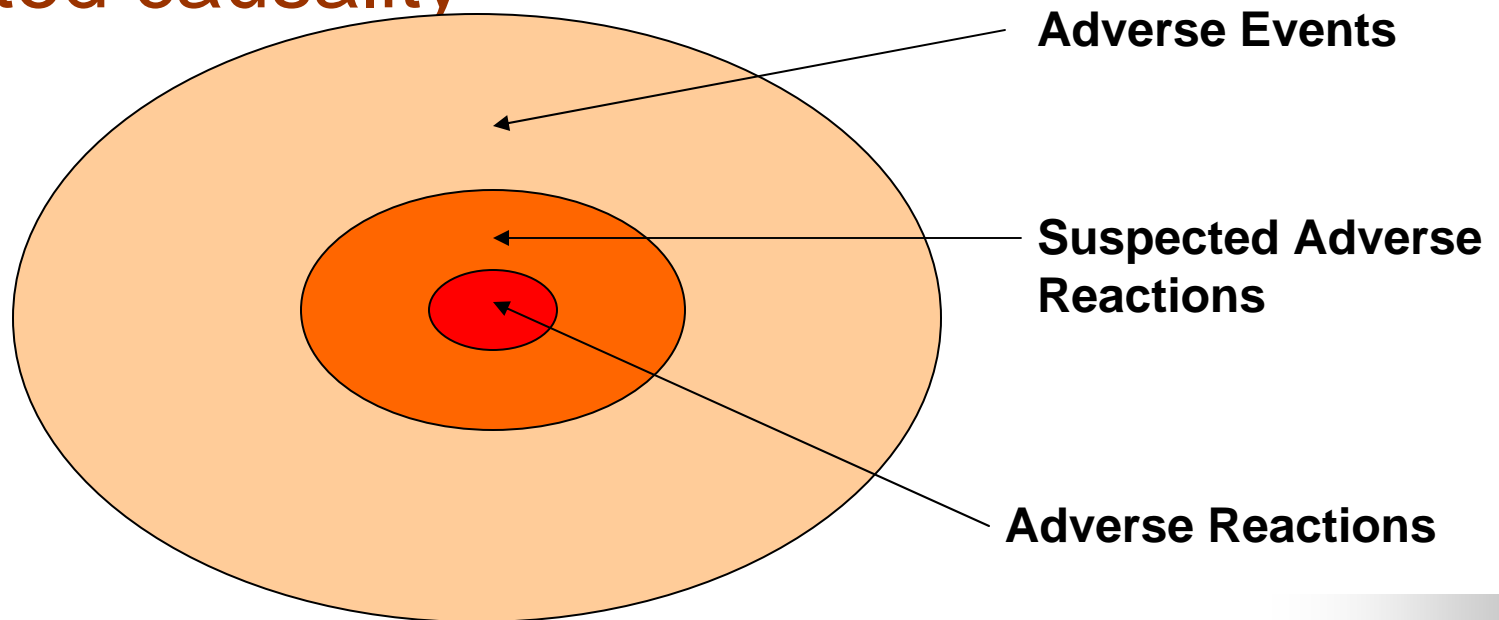


Unexpected Adverse Event (21 CFR 312.32(a))

- Not listed in the Investigator's Brochure (IB) or if IB not available or required
- Not listed at the specificity or severity observed
- Mentioned in IB as anticipated due to pharmacokinetic properties of the drug or occurred with other drugs in this class, but not with the study drug

Suspected Adverse Reaction (21 CFR 312.32; 21 CFR 314.80)

- Suspected Adverse Reaction : an Adverse Event with a **reasonable possibility of drug related causality**





Expedited Safety Reporting to FDA by Sponsor (New Safety Reporting Rule) (21 CFR 312.32(c)(1)(i))

- Adverse Events that meet all three criteria are reported to FDA (SUSAR):
 - Serious (S)
 - Unexpected (U)
 - Suspected Adverse Reactions (SAR)
- Fatal or life-threatening SUSAR should be reported to FDA no later than 7 days
- Others SUSAR should be reported to FDA no later than 15 days

■ ■ ■ Expedited reporting by Sponsor (2) 21 CFR 312.32(c)

- (C)(1)(ii) Findings from other studies
- (C)(1)(iii) Findings from animal or in vitro testing
- (C)(1)(iv) Increased rate of occurrence of serious suspected adverse reactions
- Report not later than 15 days of you becoming aware of the finding



Causality Assessment for Common AEs, Sponsor/FDA

- Individual assessment unlikely to help determine attribution for common AEs, i.e. headache, nausea, MI in elderly
- Such AEs require aggregate analyses using a population approach (risk or rate with study drug vs. control)
 - Placebo or active control
 - Other doses in multiple dose studies

■■■ Postmarketing Safety

- Postmarketing studies
 - Nonclinical studies
 - Clinical trials
 - Observational studies
 - Registries
- FDA AERS (Adverse Event Reporting System repository) through MedWatch
- VAERS (Vaccine Adverse Event Reporting System)
- Sentinel Initiative
 - Active surveillance system to query diverse automated healthcare data

■ ■ ■ MedWatch

- FDA's reporting system for AE founded in 1993
- Voluntary reporting of any SAE regardless of causality
 - Healthcare professionals, consumers, patients
 - 1 page form
 - Online, by phone, mail or fax
- Also, provides subscribers with potential safety signals alerts



Summary

- Evaluation of safety spans drug's life time
- Investigators play an integral part in assuring quality safety assessments
 - Provide relevant/complete AE information
 - Use the most scientific term when reporting
 - Report clinical and lab AEs from unscheduled tests/visits
 - Continue to report SAE once drug approved

■ ■ ■ References

- 21 CFR 312.32, 21 CFR 314.80
- New Safety Reporting Rule

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm226358.htm>

- Guidance
- Final rule
- NEJM perspective

(<http://www.nejm.org/doi/pdf/10.1056/NEJMp1103464>)

- FDA /CBER toxicity grading guidance

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf>

- MedWatch

<http://www.fda.gov/Safety/MedWatch/default.htm>