U.S. FOOD & DRUG ADMINISTRATION

Safety Assessment in Clinical Trials and Beyond

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Clinical Investigator Training Course

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Clinical Reviewer

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Learning Objectives

- To understand the sources of safety information available to investigator
- To learn the limitations of the clinical trials for safety assessment and use of safety outcome trials
- To determine what is necessary to report a safety event and which events are reported to the sponsor and/or FDA

Outline

- Introduction
- Sources of safety information
- Limitations in clinical trials
- Safety monitoring/Reporting
- Safety outcome trials
- Summary

Evaluation of Safety

- Evolving process
- Available data depend on the stage of development
- Safety information for approved products is reflected in product labeling (Prescribing Information)
- Up-to-date safety information on the investigational product is found in the Investigator Brochure (IB)

Sources of Safety Information

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

Clinical Studies/Trials

- Healthy subjects
- Patients
- Special populations
  - Renal impairment
  - Hepatic impairment
  - Pediatric and geriatric
  - Pregnant and lactating women

Limitations in Clinical Trials

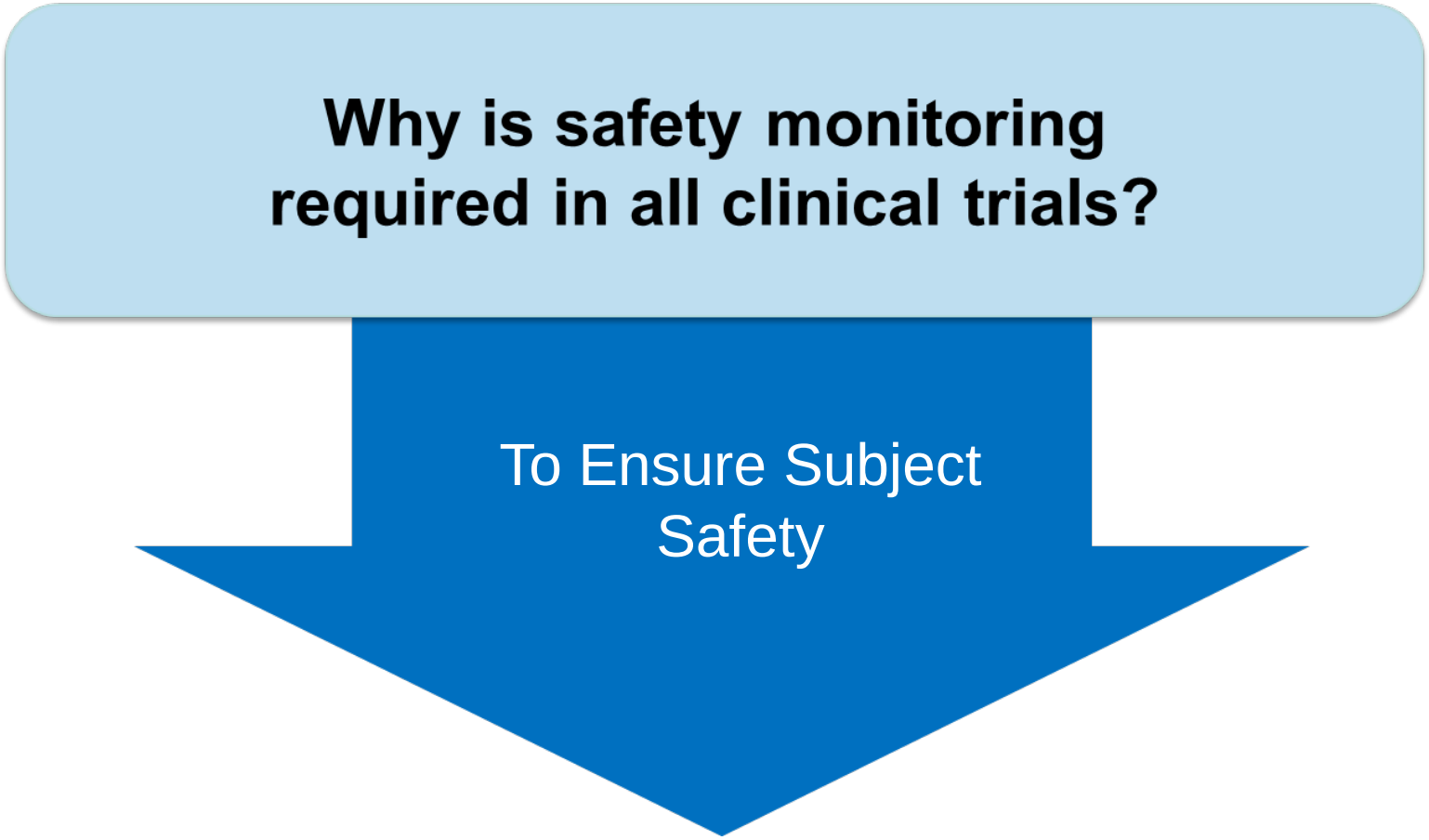
- Generally, designed to test a hypothesis for demonstration of efficacy
- Can be limited with regard to safety
  - Number of subjects exposed
  - Length of follow-up
- Size of safety database should characterize and quantify safety profile of a drug over a reasonable duration of time
  - Size depends on drug's novelty, available of alternative therapy, intended population and condition being treated, and intended duration of use

Size of Safety Database

- For products intended for long-term treatment of non-life threatening conditions > 6 months
  - ICH recommends 1500 subjects exposed: 300-600 exposed for 6 months, 100 exposed for 1 year (at doses in the therapeutic range, multiple dose studies)
- For products intended for short-term treatment < 6 months
  - Difficult to provide general guidance on size (depends on indication and disease state
  - Sponsors encouraged to discuss with FDA

E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions

Safety Monitoring



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, vital signs, imaging, ECG, etc
  – worsening of the above
  – constellation of the above

Ascertainment of Adverse Events

- Spontaneously reported/observed symptoms and signs
- Symptoms/Signs reported as a result of a probe (checklist or questionnaire)
- Testing
  - Vital signs
  - Laboratory tests
  - Special safety assessments (visual, hearing)

AE Severity Grading Tables

- 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, DMID, FDA/CBER

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
- Hospitalization
- Disability
- Congenital anomaly / birth defect
- Important medical events

Uncommon Serious AEs

- Anaphylaxis
- Aplastic anemia
- Blindness
- Deafness
- Bone marrow suppression
- Disseminated Intravascular Coagulation
- Hemolytic anemia
- Liver failure
- Liver necrosis
- Liver transplant
- Renal failure
- Seizure
- Stevens-Johnson Syndrome
- Sudden death
- Torsades
- Thrombotic Thrombocytopenic Purpura
- Ventricular fibrillation

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?

AE Reporting Requirements Investigator to Sponsor (21 CFR 312.64(b))

- All Serious Adverse Events (SAE) regardless of causality
- Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations
- Study endpoints that are SAEs ONLY if there is evidence of causal relationship to the drug
- Investigators provide causality assessment in the report

Discussion Case 1

You are the investigator for a clinical study evaluating whether antihypertensive Drug A is associated with a reduced risk of death, MI, or stroke. A 75 years old white male patient died in the study.

Do you have to report this case to the sponsor?

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)

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
  - Edema: leg edema, face edema, etc.
- Lack of adequate term/definition
  - Drug hypersensitivity, Metabolic syndrome, Serotonin syndrome
    - May need prospective case definition if syndrome not well characterized by a single term

Unexpected Adverse Event (21 CFR 312.32(a))

- Not listed in the Investigator 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

Discussion Case 2

You are the investigator for a clinical trial evaluating a new quinolone antibacterial Drug B for the treatment of pneumonia.

Investigator brochure lists a number of serious adverse events associated with use of quinolone drugs, including neurotoxicity.

Is a seizure in this trial considered an expected adverse event?

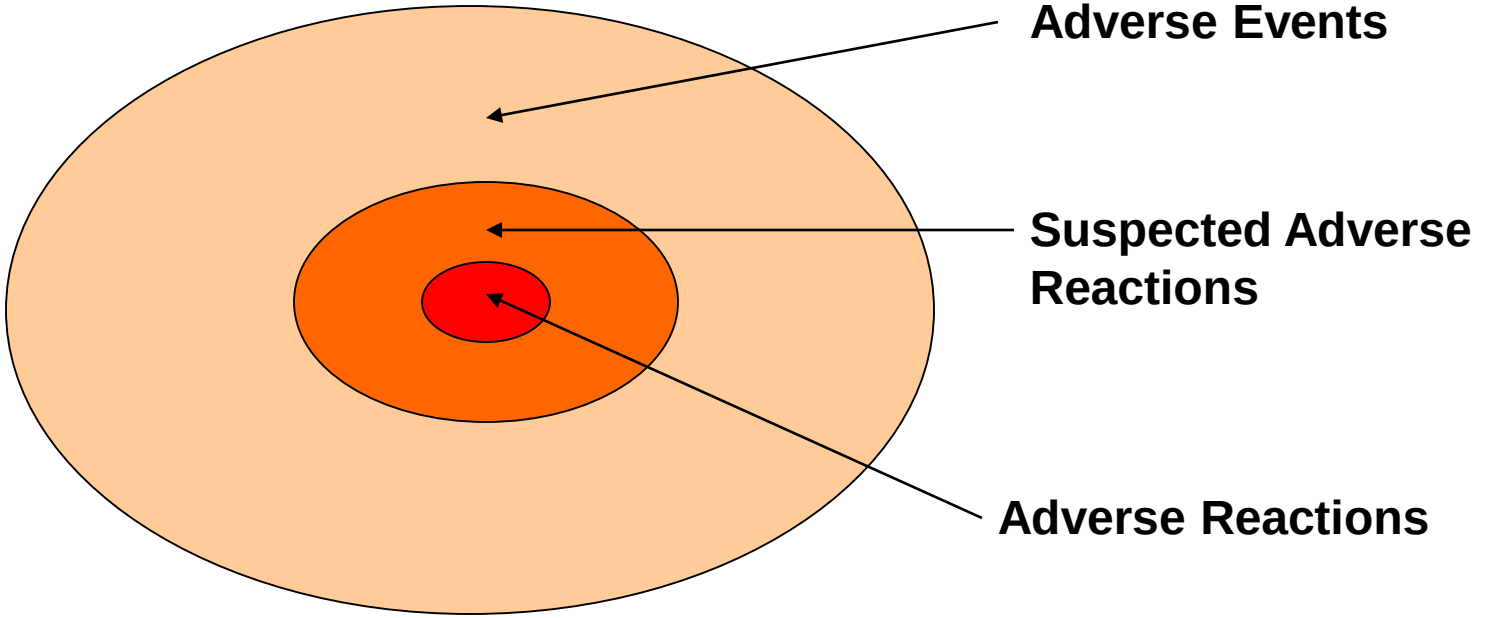
Suspected Adverse Reaction (21 CFR 312.32(a))

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

- A single occurrence of an uncommon event that is known to be strongly associated with drug exposure (SJS, angioedema, hepatic injury)
- ≥1 occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the exposed population (neutropenia in healthy subjects, heart valve lesions in young adults)
- An aggregate analysis of specific events observed in a clinical trial indicates that those events occur more frequently in the drug treatment group than in a concurrent or historical control group (acute MI in long-duration trial with elderly cancer patients)

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 (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 reported to FDA no later than 7 days
- Others SUSARs -- no later than 15 days

Discussion Case 3

In a study of a marketed HIV Drug C, an 8 month old infant enrolled at 1 month of age was noted at study month 4 to have a moderate hearing loss in clinic progress notes.

Should this event have been reported to the sponsor expeditiously?

Discussion Case 3 cont'd

The drugs used in the study are not labeled for ototoxicity based on adult trials.

Unblinded review of the safety data identified 3 cases of hearing loss in Drug C arm and 1 on the comparator.

Is this event reportable to FDA?

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 sponsor 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
  - Dose response in dose-ranging studies

Safety Outcomes Trial (SOT)

- Prospective, randomized, controlled trials designed to test safety hypothesis
  - Uses a clinical outcome such as mortality as primary endpoint
  - Designed to assess rate of commonly occurring AE not readily interpretable as drug-related in absence of a control group
  - In contrast to relatively rare events (agranulocytosis or SJS) that would be interpretable as single event in absence of control group

SOTs

- Depending on the degree of concern about a drug-related signal, can be required prior to approval or post-marketing (issued as a PMR under section 505(o)(3) of FD&C Act)
- Requires study population with high risk of event of interest
- Generally large, expensive, long-term studies
  - Should be evaluated by FDA review division and SOT subcommittee
- Examples: CAST for anti-arrhythmia, PROMISE for heart failure

SOT Example: Diabetes Drug Development

- Early suspicion that anti-diabetic drug cause increased cardiovascular (CV) risk
- DB, PC, RCT: Empaglifozin vs. placebo on CV events in adults with Type 2 DM at high CV risk
  - 7020 total patients observed over median of 3.1 years
  - Primary composite outcome - death from CV source, non-fatal MI or stroke
  - Significant lower rate of death in empaglifozin group; no significant difference in rate of MI or stroke
- SOT helped rule out excess risk of adverse CV outcomes

Safety Assessment Committee (SAC)

- Group of clinical trial experts
- Assesses whether AE(s) in an ongoing trial need to be reported to FDA in real time taking into account safety data for the whole IND
- Follows predefined Safety Surveillance Plan (SSP)
- Identifies anticipated SAEs, lists previously reported SUSARs, identifies roles for members, outlines principles of unblinded review of aggregate data, available to FDA for review

SAC: monitoring

- Whether a single occurrence of an SAE needs to be reported (did patient(s) received the drug)
- Whether an event needs to be reported based on an aggregate analysis
  - Data form the ongoing trial
  - Data from all trials under IND
- Whether study needs to be terminated or modified based on new safety finding
  - Enrollment criteria, informed consent, etc

Safety Reporting After Drug Approval

- Clinical trials for new indications
- Postmarketing safety trials
- Observational studies
- New nonclinical safety studies
- FAERS (FDA Adverse Event Reporting System repository) through MedWatch
- NDA safety reporting
  - Periodic Adverse Event Reporting (PADER)
  - Annual Reporting

Summary

- Evaluation of safety spans drug's life cycle
- Size of safety database should be adequate to assess risk
- Investigators play an integral part in assuring quality safety assessments by reporting:
  - relevant/complete AE information using the most scientific terms
  - clinical and lab AEs from unscheduled tests/visits
  - SAEs once drug approved
  - Safety outcome trials can test specific safety hypothesis
- Sponsor with help of SAC report expeditiously

Question 1

Expedited IND safety reporting to FDA by the Sponsor is required for which of the following events?

A). Serious and unexpected adverse events

B). Nonserious adverse reactions

C). Adverse events not listed in the IB

D). Serious and unexpected suspected adverse reactions

Question 2

True or False?

A sponsor would not have to report a case of hepatic failure if the investigator brochure listed elevated hepatic enzymes or hepatitis.

References

- 21 CFR 312.32, 21 CFR 314.80
- Safety Reporting Rule (Final Rule)

  http://www.gpo.gov/fdsys/pkg/FR-2010-09-29/pdf/2010-24296.pdf

  – Safety Reporting Requirements for INDs and BA/BE Studies

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

  -- Draft guidance safety assessment for safety reporting

  https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm477584.pdf
- E1A The Extent of Population Exposure to Assess Clinical Safety

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e1a-extent-population-exposure-assess-clinical-safety-drugs-intended-long-term-treatment-non-life
- Toxicity grading

  – FDA /CBER guidance

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