Active IND
Sponsor's responsibilities

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Active IND
Sponsor's responsibilities

- Protocol amendments
  - New Protocol
  - Change in Protocol
  - New Investigator
- Information amendments
- Safety Reporting
- Annual Reports
- Inactivation of an IND
- Withdrawal of an IND

Protocol Amendments

21 CFR 312.30

- **New Protocol**
  - FDA Form 1571 (Protocol Amendment/New Protocol)
  - Copy of the new protocol
  - Brief description of the most clinically significant differences between the new and previous protocols
- Study may begin provided that
  - The Sponsor has submitted the New Protocol to FDA
  - The Protocol has been approved by the Institutional Review Board (IRB)

Protocol Amendment
Change in Protocol

- **Changes in Protocol**
  - Phase 1-Any change that significantly affects the safety of the subjects
  - Phase 2 and 3- Any change that significantly affects the safety of the subjects, the scope of the investigation, and/or the scientific quality of the study

Protocol Amendment
Change in Protocol (2)

- **Change in Protocol**
  - FDA Form 1571 (Protocol Amendment/Change in Protocol)
  - Brief description of the change and reference (date and number) to the submission that contained the original protocol
    - Track changes and clean version of the protocol change
  - Reference to specific technical information previously submitted or included in the protocol change

Protocol Amendment
Change in Protocol (3)

- Increase in drug dosage or duration of exposure
- Any significant increase in the number of subjects under the study
- Any significant change in the design of the protocol (control group)
- Addition of a new test or procedure intended to improve the monitoring or reduce the risk of a side effect or adverse event

Protocol Amendment
Change in Protocol (4)

- Change may be implemented when
  - The Sponsor has submitted the revised Protocol to FDA
  - The Protocol has been approved by the Institutional Review Board (IRB)
- A protocol change intended to eliminate and apparent immediate hazard to subjects may be implemented immediately provided that
  - FDA is subsequently notified by protocol amendment
  - IRB is notified according 21 CFR 56.104 (c)

Protocol Amendment
New Investigator

- FDA Form 1571 (Protocol Amendment/New Investigator)
- Once the Investigator is added, the investigational drug can be shipped and the investigator may begin participating in the study
- Notification to FDA shall be made within 30 days of the investigator being added to the study

Protocol Amendment
New Investigator

- Investigators name
- Qualification to conduct the investigation
- Reference to previously submitted protocols
- Other information as requested by 21 CFR 312.23 (a) (6)(iii)(b)
- Information Sheet Guidance for Sponsor's, Clinical Investigators, and IRBs
  - https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf

Protocol Amendments Timelines

- **New Protocol and Protocol Change** submitted before implementation
- **New Investigator and/or Update information on investigator** can be submitted at 30-day intervals

Information Amendments

21 CFR 312.31

- The Sponsor shall submit any essential information not within the scope of a protocol amendment, IND safety report or annual report
- FDA Form 1571 (Information amendment)
- Statement of the nature and purpose of the submission
  - New toxicology, chemistry or other technical information
  - Discontinuation of investigation

Information Amendments (2)

- Request for comment
- Specific questions

IND Safety Reporting Regulations

- IND Safety Reporting (21 CFR 312.32)
  - Requirements for expedited reporting under an IND
- Investigator Reports (21 CFR 312.64)
  - Reporting requirements from investigators to sponsors
- Applicability of requirements regarding an IND application (21 CFR 320.31)
  - Requirements for bioavailability/bioequivalence expedited reporting

IND Safety Reports

- **S**erious
- **U**nexpected
- **S**uspected
- **A**dverse
- **R**eactions

Adverse event

21 CFR 312.32 (a)

- Any untoward medical occurrence associated with the use of a drug in humans, *whether or not considered drug related*
  - Unfavorable sign (e.g. abnormal lab finding)
  - Symptom or disease temporarily associated with the use of the drug
  - Does not imply any judgment about causality

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.
  - For FDA reporting, the Investigator is responsible for making the causality judgment and provide this assessment to the Sponsor (21 CFR 312.64 (b))
  - The Sponsor assessment determines the reportability regardless the investigator's assessment

Adverse Reaction

- Any adverse event caused by a drug.
  - Unexpected
  - Serious
  - Life-Threatening

Adverse Reactions (1)

- Serious
  - In the view of the Sponsor or Investigator results in
    - Death
    - A life-threatening adverse event
    - Inpatient hospitalization or prolongation of existing hospitalization
    - Persistent or significant incapacity
    - Substantial disruption of the ability to conduct normal life functions
    - A congenital anomaly/birth defect

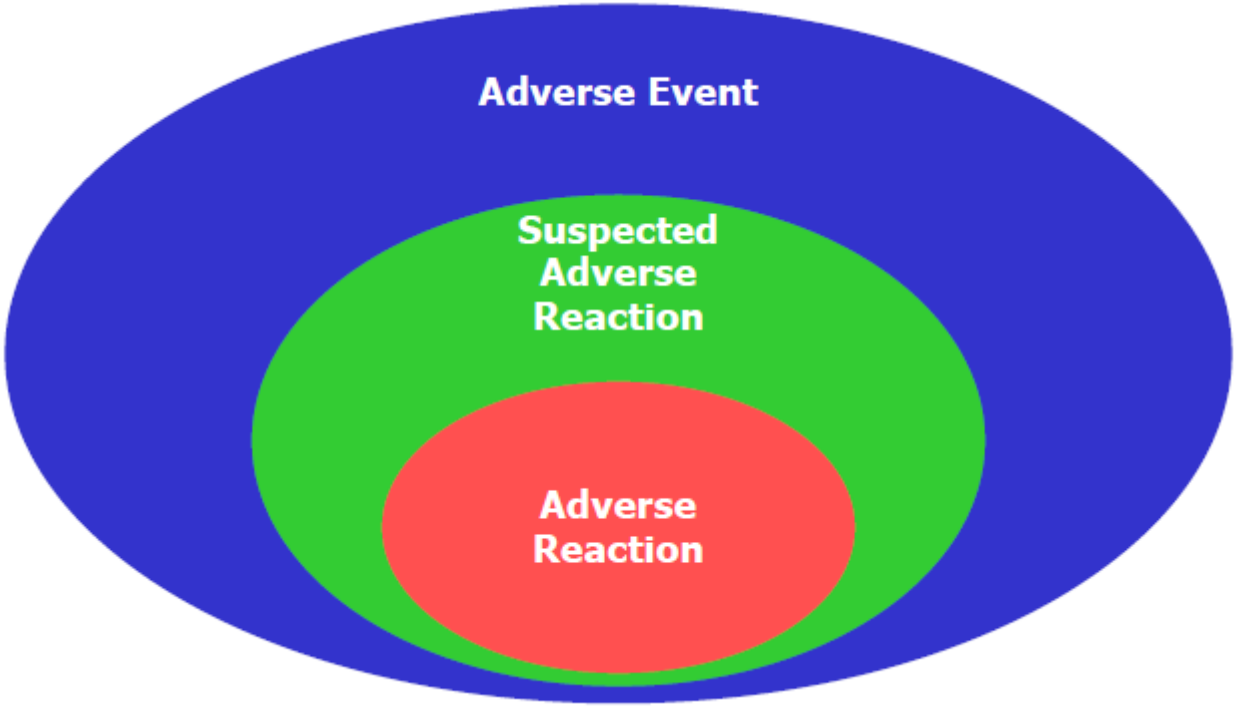
Adverse Reactions (2)

- Unexpected
  - Not listed in the Investigator Brochure (IB) or Package Insert (PI)
  - Not listed at the specificity or severity that has been observed
  - Not consistent with the risk information described in the Investigational Plan or elsewhere in the application

Adverse Reactions (3)

- Life Threatening
  - In the view of the Sponsor or Investigator places the patient or subject at immediate risk of death

Relationship between AE, SAR, and AR



7-day IND safety reports

Sponsor must report within 7 days:

- Unexpected and related fatal or life threatening events
  - Notification by telephone, fax, or e-mail
  - A 7-day report is usually followed by a 15-day IND safety report

15-day IND safety report

Sponsor must report no later than 15-days:

- All serious, unexpected and suspected AR that are
  - A single event that is uncommon and know to be strongly associated with drug exposure
  - One or more occurrences of an event that is not commonly associated with drug exposure, but is uncommon in the population exposed to the drug
  - An aggregate analysis of specific events observed in a clinical trial that indicates that those events occur more frequently in the drug treatment group than in a control group
- Observations from animal or *in-vitro* studies suggesting significant risk to human subjects

Mandatory Safety Reporting (1)

- Initial Reporting
  - As soon as possible but no later than 7 calendar days following receipt of the information
    - Unexpected or life threatening adverse reactions
  - As soon as possible but no later than 15 calendar days following receipt of the information
    - **S**erious, **U**nexpected and **S**uspected **A**dverse **R**eactions
    - Observations from animal or *in-vitro* studies suggesting significant risk to human subjects

Mandatory Safety Reporting (2)

- Follow-up reporting
  - Any relevant information obtained by the Sponsor that pertains to a previously submitted IND Safety Report
  - Submitted without delay, but no later than 15 calendar days after the information is received

IND Safety Reports

- Submitted in Form 3500 A (MedWatch) if from clinical trials or narrative format if from animal or epidemiological studies to the appropriate FDA Division
- Must be accompanied by the FDA Form 1571
- Type of report identified in both forms
- Submission must be identified as:
  - "7-day IND Safety Report" for unexpected fatal or life-threatening suspected adverse reaction reports or
  - IND Safety Report" for 15-day reports or
  - "Follow-up IND Safety Report" for follow-up information

Additional IND Safety Reports

21 CFR 312.32 (c)(1)(ii-iv)

- Findings from other studies (ii)
- Findings from animal or in vitro testing (iii)
- Increased rate of occurrence of serious, suspected, adverse reactions (iv)
- Suggests a *significant risk* in humans exposed to the drug
  - Safety-related changes in the conduct of the investigation (e.g., revisions to the study protocol, ICF and/or IB)

Safety Reporting

- Safety Reporting Requirements for INDs and BA/BE Studies-Small Entity Compliance Guidance
  - https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm332846.pdf
- Safety Reporting Requirements for INDs and BA/BE (Bioavailability/Bioequivalence)
  - https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm227351.pdf

Annual Report

21 CFR 312.33

- Report of the progress of the investigation
  - Individual Study Information-Summary of the status of each study in progress during the previous year
    - Title of the Study, its purpose, brief description of the patient population and indication if the study is complete
    - Total number of subjects initially planned for inclusion, number of subjects included to date, number of subjects who dropped from the study, etc.
    - If study has been completed, a summary of interim results or description of results

Annual Report (2)

- Summary Information obtained in the previous year's clinical and non clinical investigations
  - Narrative or tabular summary showing most frequent and serious adverse experiences by body system
  - Summary of all IND safety reports submitted the past year
  - List of subjects who died, with cause of death
  - List of subjects who dropped out in association with any adverse events

Annual Report (3)

- Brief description of any information deemed to further understanding of the drug's actions
- List of preclinical studies completed or in progress
- A summary of any significant manufacturing or microbiological changes during past year

Annual Report (4)

- A description of the general investigational plan for the coming year
- Change made to a Phase 1 study not yet reported to the IND
- Summary of significant foreign marketing
- Log of outstanding issues for which the sponsor expects a reply, comment or meeting (not mandatory)

Annual Report (5)

- Submitted within 60 days of the anniversary date that the application went into effect.
- Submitted annually
- Include FDA Form 1571
- Development Safety Update Report (DSUR) can be submitted to meet IND application annual report requirements
  - https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073109.pdf

IND Inactivation

21 CFR 312.45

- May be inactivated at the Sponsor's or FDA's request
  - No subjects entered in clinical trial(s) for 2 years or longer
  - The IND application is on hold for 1 year or longer
- No requirement to submit IND annual reports
- An IND that remains on inactive status for 5 years may be terminated by FDA

IND Withdrawal

21 CFR 312. 38

- Requested at any time
  - Notify FDA
  - All clinical investigations conducted under the IND are ended
  - All investigators are notified
  - All stocks of the drug returned to the Sponsor or disposed
  - Provide reasons if withdrawn for safety reasons

Questions?

Please complete the session survey:
surveymonkey.com/r/DRG-D2S03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