PARTICIPANT SAFETY AND ADVERSE EFFECTS

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Objectives

Participants will be able to demonstrate an understanding of:

- **Human Subject Protections and Safety Monitoring**
- **Protocol requirements pertaining to safety**
- **Safety and adverse event terminology**
- **Expedited reporting of adverse events**
- **Causality assessment**

Historical perspectives

1961-1962: Thalidomide tragedy Exposed loopholes in Food, Drug and Cosmetic Act of 1938: Companies could distribute unapproved drugs for experimental purposes

- Did not require notification to patients of investigational status
- Did not require companies or doctors to keep track of distribution
- Did not require FDA to be notified of experimental use
- Did not require records to be kept
- Did not require demonstration of drug effectiveness

Current Perspectives

- Subject participation in research is voluntary
  - Placed their faith in the investigators
  - Participation is a gift in the service of the public interest
- Investigators must not betray the public trust
  - Must conduct trials with ethical and scientific integrity
  - Must implement high standards for human subject protections
  - Must assure subject well-being and safety at all times

1995: Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products

- Handbook for Good Clinical Research Practice (GCP) as an adjunct to Guidelines
  - encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies
  - ensures studies are scientifically and ethically sound
  - clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented

1995: Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products

Safety reports

- Immediately report any adverse event that is alarming (e.g. an unexpected event that is serious or life-threatening)
- Record non-serious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol

Legislature to protect participants

Research Involving Human Subjects

Sri Lanka Draft Clinical Trial Act section 12 provides assurance that

- Dignity, rights, safety and well being of all trial subjects are safeguarded by the trial protocol;
- Rights safety and well being of all vulnerable trial subjects participating in clinical trials including prisoners, armed personnel forces, staff and students of medical academic institutions, children, pregnant and lactating mothers, persons who are socially and economically disadvantaged, patients with incurable diseases, refugees and minors are protected by the clinical trial protocol
    1. Research reviewed and approved by IRB accredited by the authority
    2. Subject to continuing review by IRB

Expectations for protecting the rights, safety, and welfare of subjects

- Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society.
- A trial should be initiated and continued only if the anticipated benefits justify the risks.
- Provision of reasonable medical care for issues related to study participation (e.g. to manage an adverse event)
- Facilitation of care for other health issues that might arise during the study
- Avoiding exposure of subjects to unreasonable risks

Protocol development – safety issues

- Written plan for how the drug is to be studied and the procedures to be followed by each investigator
- A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.
- Stopping rules
- Safety monitoring and evaluation
- Safety Reporting
- Case Report Form

Adverse Event

- Protocol specifications for AE
- When to collect, e.g., study visit
- Method of collection, e.g., in person, telephone call
- Duration of collection, e.g., from enrollment to completion
- What to collect, e.g., all AEs, only certain AEs by body system, only certain AEs by severity
- What forms to use, e.g., AE CRF, study CRFs
- Protocol specifications for SAE
- Criteria
- Expedited timeframes
- Reporting form, e.g., SAE

Data and safety monitoring boards

DSMB

- *"An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial."*
- **•ICH–GCP [1.25]**

Data Safety and Monitoring Board (DSMBs)/ Data Monitoring Committees (DMCs)

- **Composition of the DSMB: generally at least three members**
- ideally independent of sponsor and investigators
  - clinicians and biostatisticians relevant expertise
  - clinical trials experience
  - freedom from conflicts of interest

- **Frequency of meeting dependent on: anticipated event level**
- **anticipated subject accrual**

- *Requirement for DSMB is dependent on type of study, level of risk, and duration of study*

Responsibilities of the DSMB

- **Interim monitoring:**
  - efficacy
  - safety
  - study conduct
  - external data

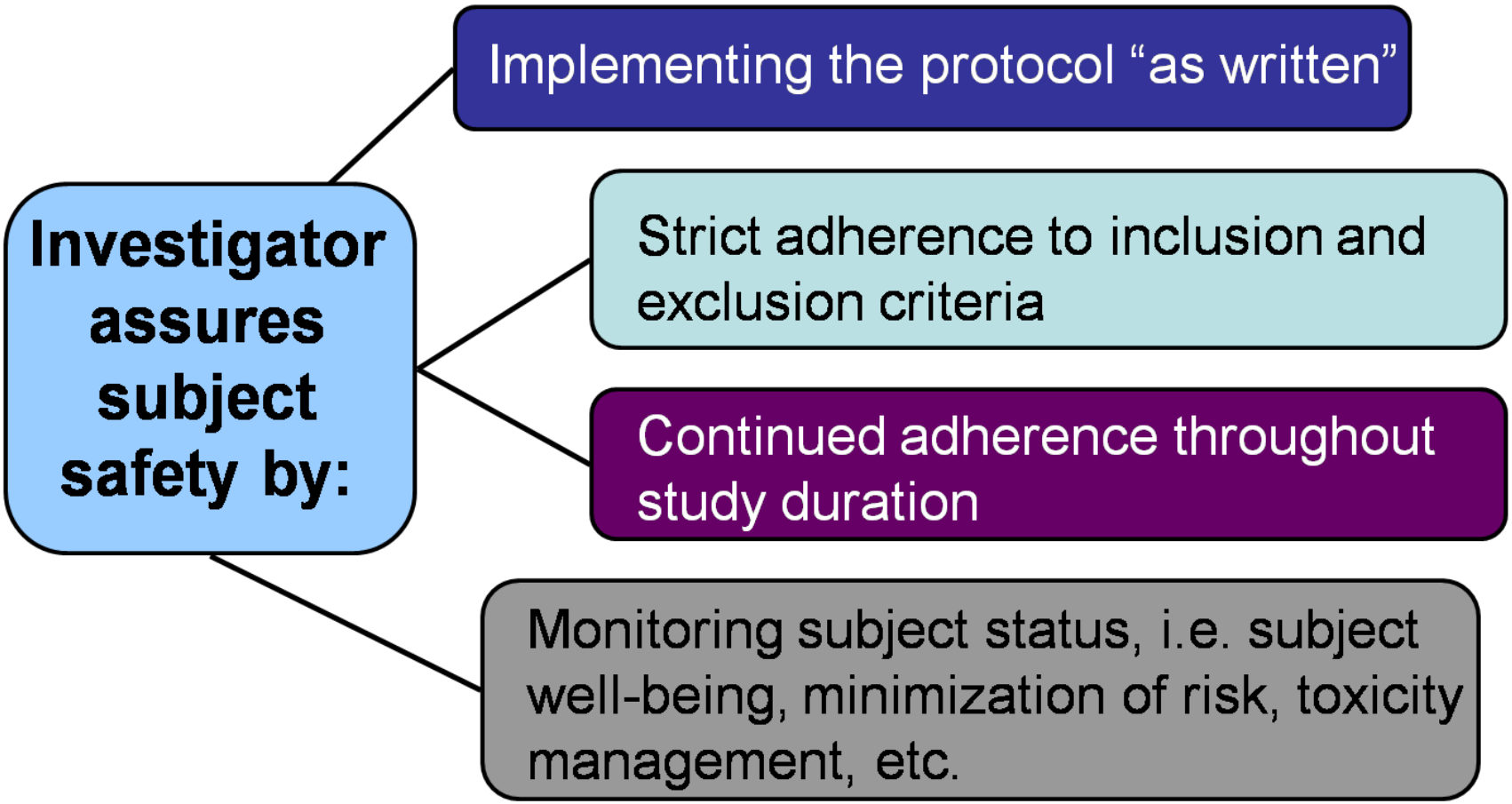
- **Making recommendations:**
  - **termination**
  - protocol changes

Safety Monitoring

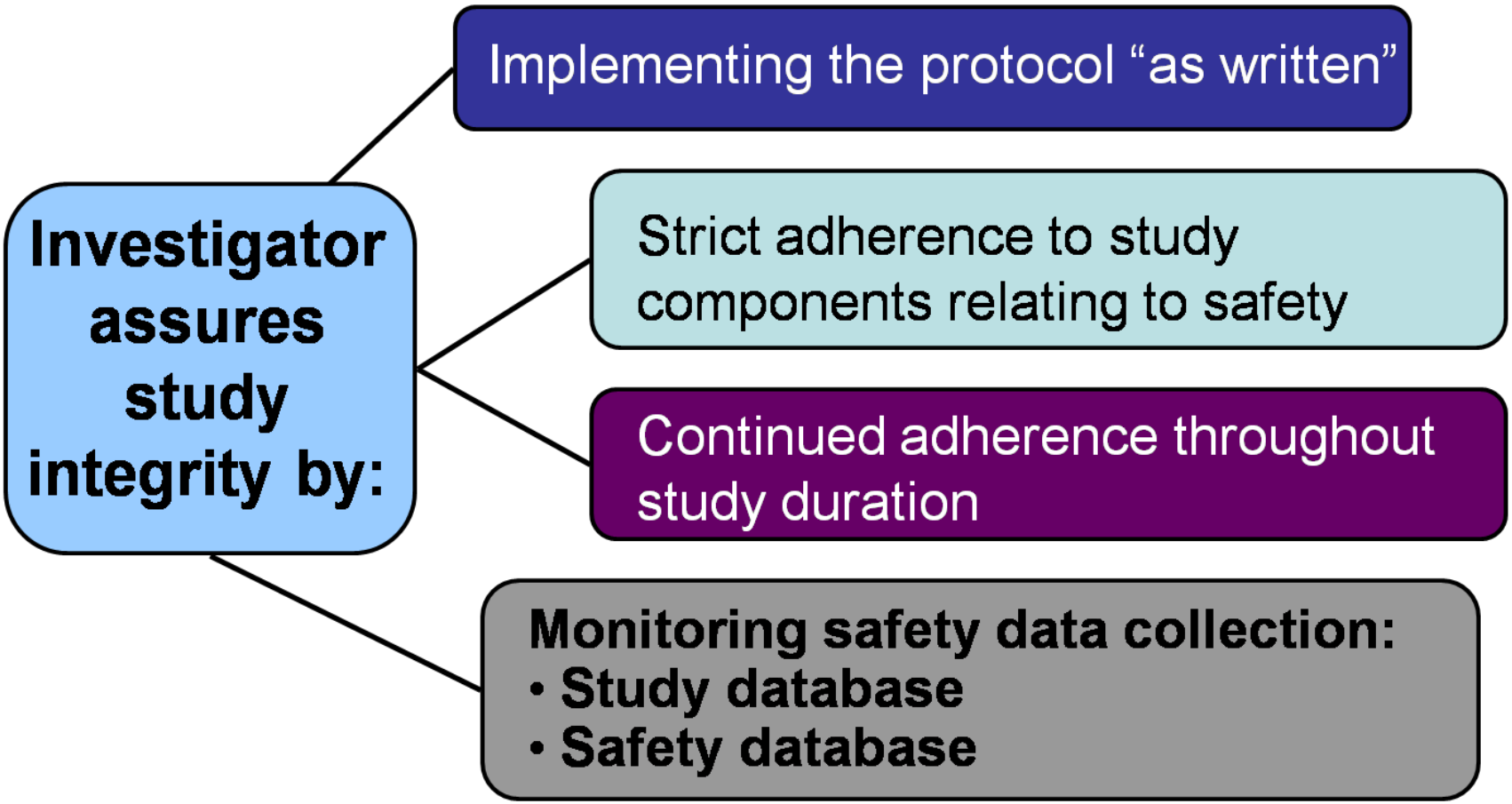
Why is safety monitoring required in all clinical trials?

To Ensure
Subject Safety and
Study Integrity

Purpose of Safety Monitoring

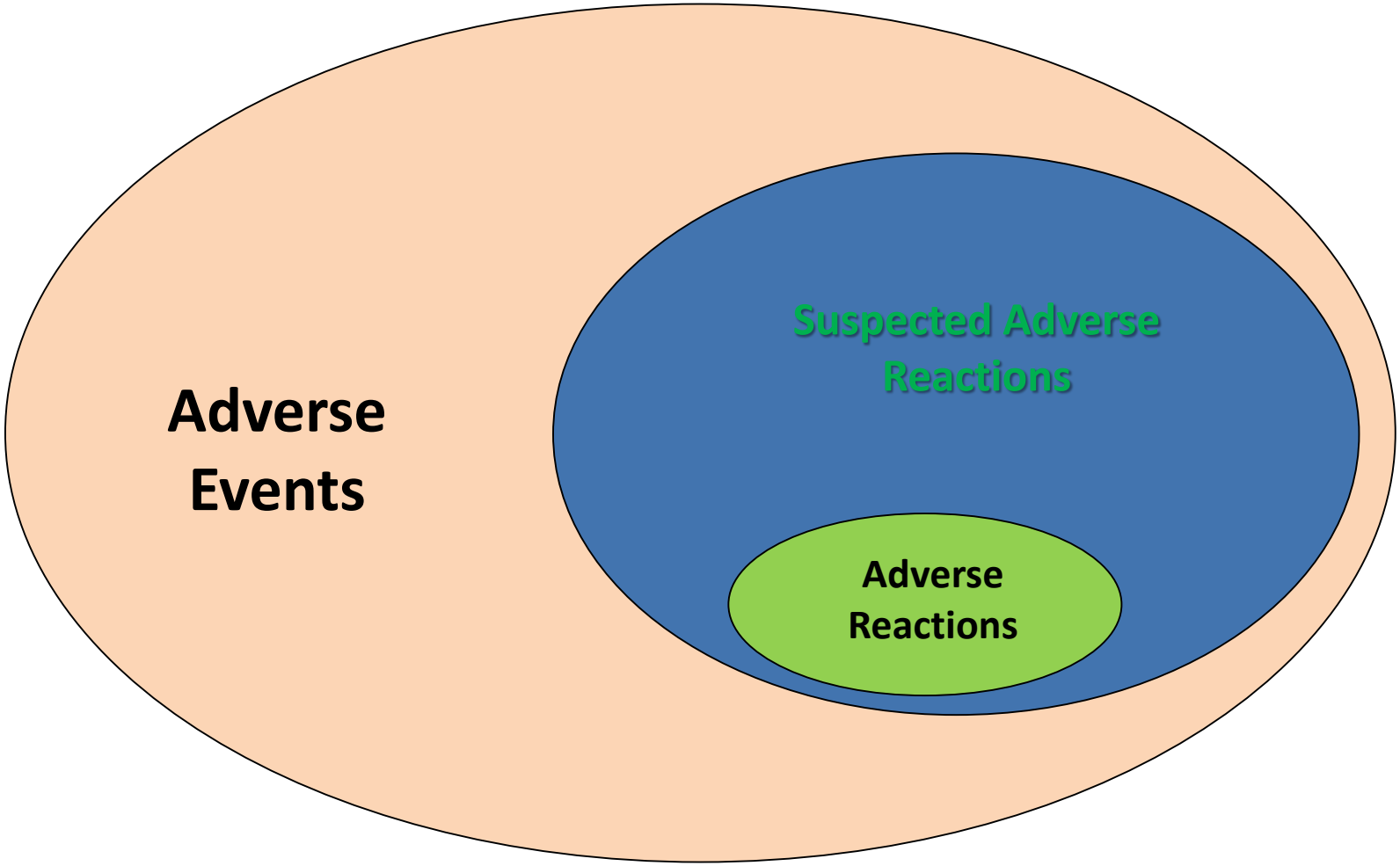


Purpose of Safety Monitoring



Definitions and Terminology

The Universe of Adverse Events



Adverse Event (or Adverse Experience)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Thus:

- any unintended / unfavorable sign, symptom or disease
- temporarily associated with drug
- whether or not causally related

Adverse drug reactions

Pre-approval Clinical Phase:

- All noxious and unintended responses to a medicinal product* related to any dose should be considered adverse drug reactions.
- *"responses to a medicinal product": a causal relationship is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Marketed Medicinal Products:

- A noxious and unintended response which occurs at a dose normally used in man for prophylaxis, diagnosis or therapy or for modification of physiological function.

Serious adverse event (experience)

Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability / incapacity
- is a congenital anomaly / birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Unexpected Adverse Drug Reaction

- An adverse reaction, the nature or severity of which is not consistent with the applicable product information. e.g., for investigational products - the Investigator's Brochure

- Not based on what might be anticipated from the pharmacological properties of the medicinal product

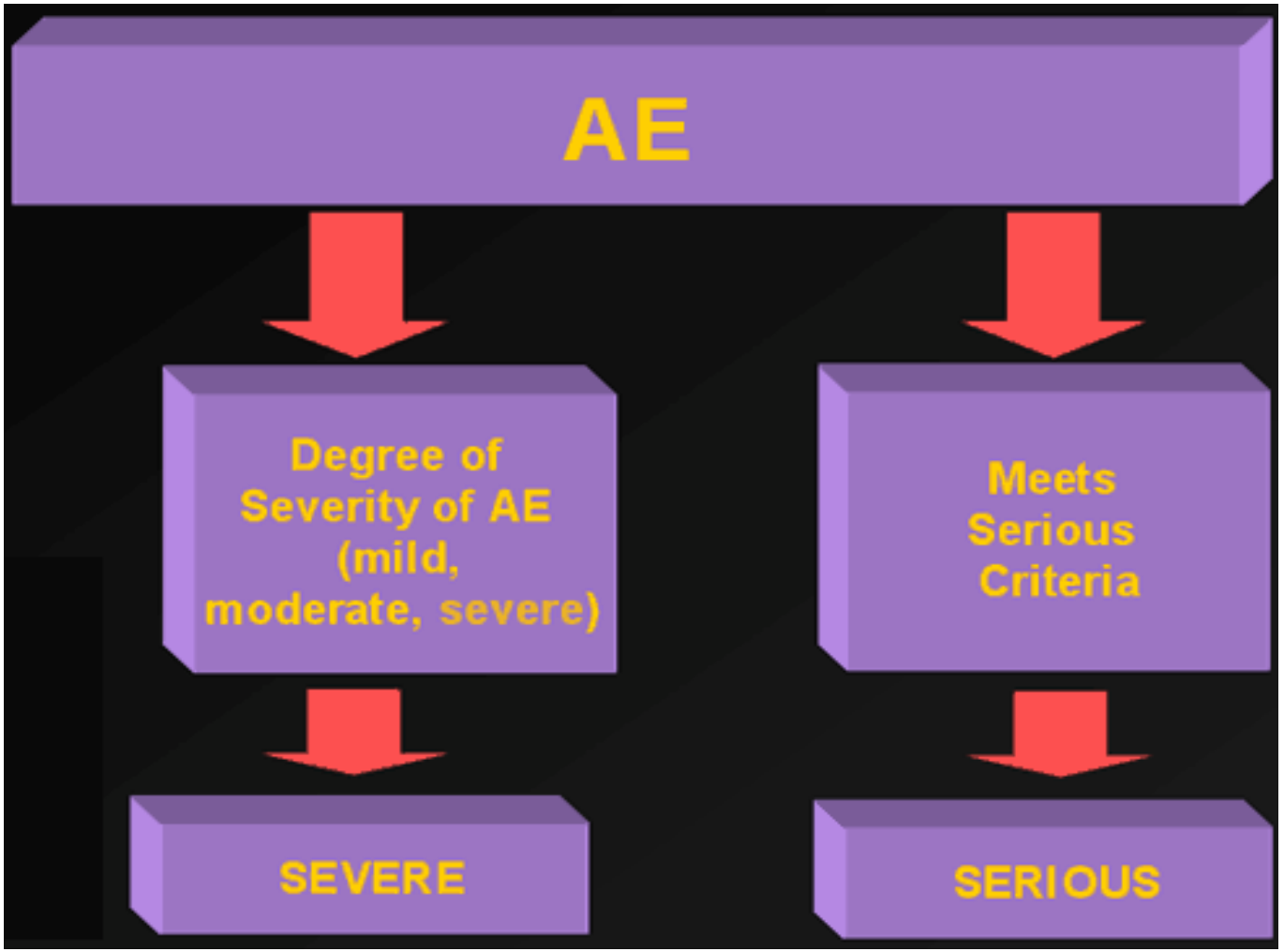
What Qualifies for Expedited Reporting to Regulatory Authorities?

Events which are serious, unexpected and have a reasonable causal relationship to study drug in the investigational phase

Important Medical Events - examples:

- Allergic bronchospasm requiring intensive treatment in an ER or at home
- Blood dyscrasias or convulsions that do not result in inpatient hospitalization
- Development of drug dependency or drug abuse

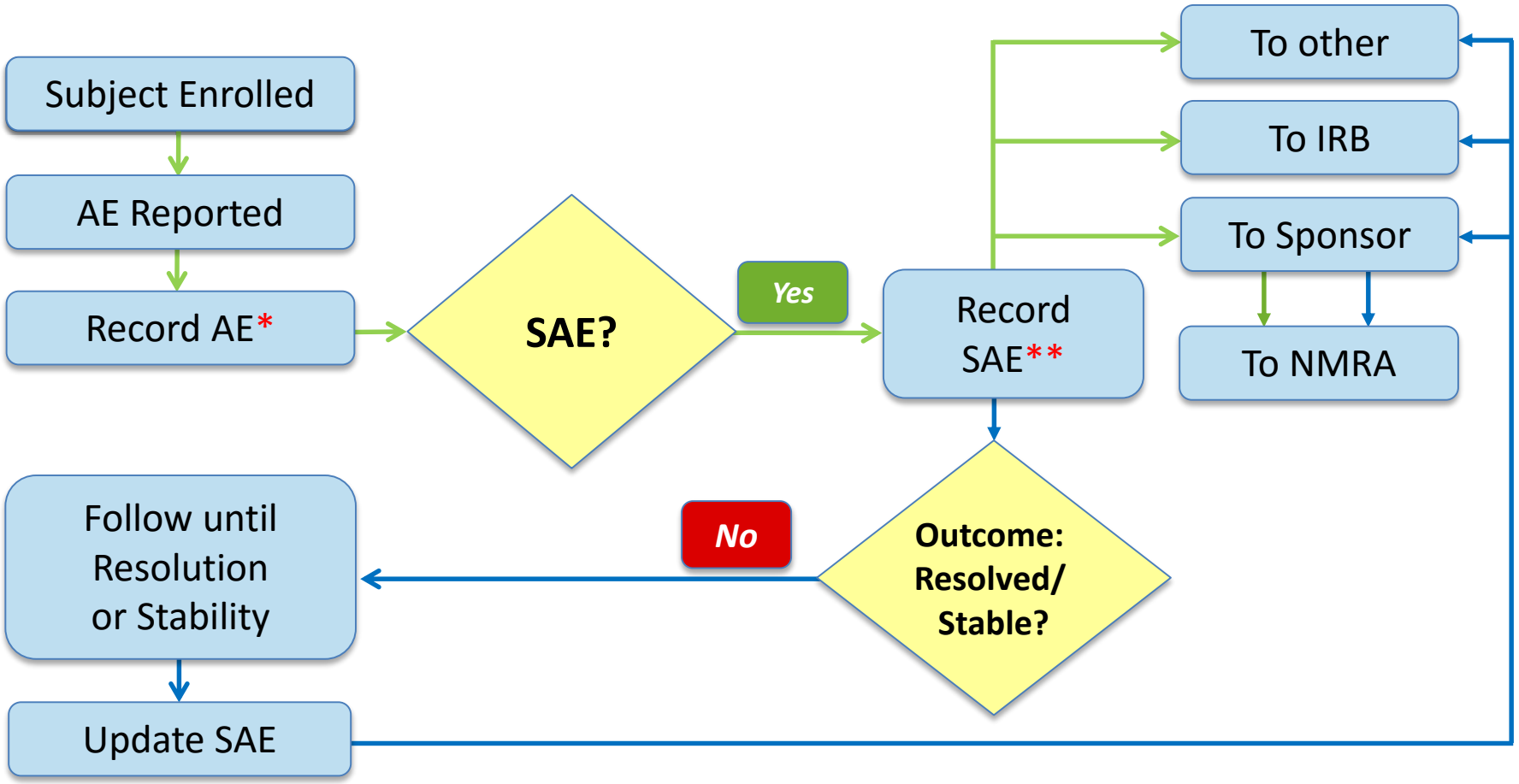
Serious vs. Severe



Severity

- Describes the intensity of the event
- Events are graded on a severity scale
  - Mild, Moderate, Severe
  - Numeric Scale, e.g., 1 to 5
- Severity grading must match the clinical picture
  - Presenting AE is Grade 1
  - AE progressed to SAE (hospitalization)
  - The expedited report should have the grade of the SAE, not the AE

Adverse Event Flowchart



Expedited Reporting Timeframes to Regulatory Authorities

- Fatal or Life-Threatening Unexpected ADRs: As soon as possible but no later than 7 calendar days (of first knowledge by sponsor that case meets expedited reporting criteria)
- Followed by a complete report within 8 additional calendar days
- All other SUSARs - as soon as possible but no later than 15 calendar days

Causality

ICH E2A

- Conveys that a "causal relationship" between the study product and the adverse event is "at least a reasonable possibility"
  - Facts (evidence) exist to suggest the relationship
  - Information on SAEs generally incomplete when first received
  - Follow-up information actively pursued
- Assessed by:
  - Reporting health professional
  - Sponsor

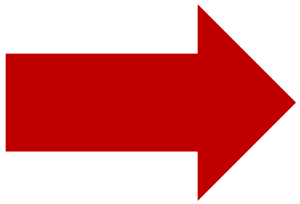
Determination of Causality

- Standard determinations include:
  - Is there [Drug Exposure] and [Temporal Association]?
  - Is there [Dechallenge/Rechallenge] or [Dose relationship]?
  - Any known association per [Investigator's Brochure] or [Package Insert]?
  - Is there [Pharmacological Plausibility]?
  - Any other possible [Etiology : underlying disease : concurrent condition; other medications]?

Examples of Reasonable Possibility

Individual occurrence

- a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure



Angiodema	**Anaphylaxis**
Hepatic Injury	**Blood Dyscrasias**
Stevens-Johnson Syndrome	**Rhabdomyolysis**

Causality Determinations

WHO-UMC	ICH E2A	CIOMS WG VI	DAIDS Manual 2.0
Certain	Related	Related	Related
Probable/Likely	Possibly	Not Related	Not Related
Possible	Unlikely		
Unlikely	Not		
Conditional/ Unclassified			
Unassessable/ Unclassifiable			

Narrative Template

- Provide details of [Treatment] and [Treatment Rationale] on basis of [Findings/Test Result(s)]. Describe [Treatment Response].
- If hospitalization, provide [Dates Hospitalization], describe relevant [Hospital Course], [Diagnostic Work-up], [Procedures/Tests and Results], [Treatment], [Treatment Response].
- Provide [Discharge Diagnosis], and any [Follow-up Information]. List [Discharge Meds].
- Provide pertinent [Past Medical Hx], [Family Hx], [Concomitant Meds], [Alcohol/Tobacco/Substance Use] and any previous similar [AEs].

Suspected Adverse Reaction / Adverse Reaction

- **Suspected Adverse Reaction**: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event

- **Adverse Reaction**: Any adverse event caused by a drug

Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction

ICH: E Documents on Safety

Clinical Safety

- **ICH E1** – *The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions*
- **ICH E2A** – *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*
- **ICH E2B** – *Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports*
- **ICH E2C** – *Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs*
- **ICH E2D** – *Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting*
- **ICH E2E** – *Pharmacovigilance Planning*
- **ICH E2F** – *Development Safety Update Report*

Good Clinical Practice

- **ICH E6** – *Good Clinical Practice*

http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html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Questions ?