IOCTB LEARN

EXPEDITED SAFETY REPORTING REQUIREMENTS FOR HSA AUTHORISED/NOTIFIED CLINICAL TRIALS

Presented by:

Innovation Office & Clinical Trials Branch

Health Products Regulation Group

Health Sciences Authority

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Outline

- Key Definitions
- Expedited Safety Reporting Requirements for HSA Authorised or Notified Clinical Trials
- Responsibilities of the Sponsor and the Principal Investigator
- What, When and How to Submit Expedited Safety Reports to the HSA
- Urgent Safety Measures

Learning Objectives

1. Appreciate the importance of continuous safety monitoring and expedited safety reporting in clinical trials
2. Understand the terms used in safety reporting
3. Describe the expedited safety reporting requirements for HSA authorised or notified clinical trials
4. Understand the roles and responsibilities of the Sponsor and the Principal Investigator
5. Describe what, when, and how to submit expedited safety reports to the HSA
6. Understand what urgent safety measures are and how they should be reported to the HSA

Clinical Trial Safety Monitoring and Reporting

- During drug development, safety information about an investigational product may be limited and continues to evolve.
- Important to continuously monitor and evaluate safety during clinical trials.
- New and important information about serious adverse reactions to an investigational product must be promptly reported to all investigators, respective Institutional Review Boards (IRBs) and the HSA.
- Allows prompt actions to be taken, where necessary, to safeguard the safety of trial participants (e.g., revising informed consent documents, increasing participant monitoring, revising eligibility criteria, pausing or stopping a clinical trial).
- Sponsors and investigators play key roles in ensuring these safety requirements are met.

KEY DEFINITIONS

Adverse Event or Adverse Drug Reaction

Adverse Event (AE)

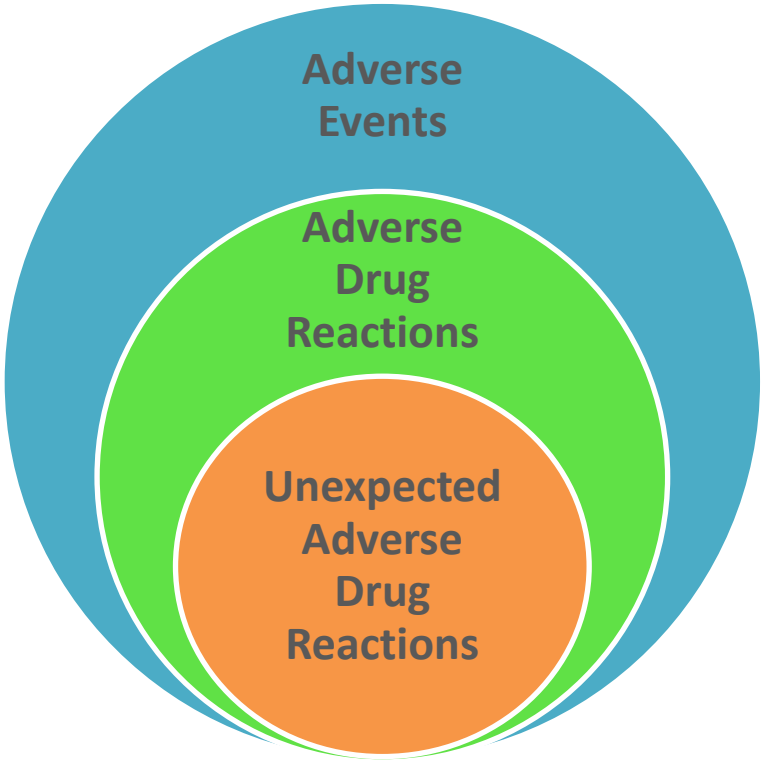
Any untoward medical occurrence in a trial participant administered an investigational product and which does not necessarily have a causal relationship with this treatment.

Adverse Drug Reaction (ADR)

Any adverse event **related** to any dose of the investigational product administered to the trial participant (i.e., reasonable possibility of causality).

Unexpected Adverse Drug Reaction

Any adverse drug reaction, the **nature or severity** of which is **not consistent with the applicable product information** (e.g., Reference Safety Information in Investigator's Brochure or approved product label).



Causality or Relatedness

- A judgment about the likelihood that the investigational product caused the adverse event
- Made by both the Sponsor and the Investigator
- When determining causality, considerations may include:
  - Available safety information about the investigational product
  - Nature of adverse event (AE), e.g., uncommon event known to be strongly associated with drug exposure, such as Stevens-Johnson syndrome or hepatic injury, would typically suggest causality
  - Temporal relationship
  - Response to de-challenge / rechallenge
  - Alternative causes, e.g., patient's underlying disease, medical history, background medications
- Determines the need for expedited safety reporting to the HSA

Expectedness

Expected

- Previously observed and described in the Investigator Brochure (e.g., Reference Safety Information) or Product Information Leaflet

Unexpected

- Not previously observed or described in the Investigator Brochure or Product Information
- Not listed at the specificity or severity that has been observed

Example: If the Investigator Brochure referred only to "elevated hepatic enzymes" or "hepatitis", occurrence of "hepatic necrosis" would be unexpected by virtue of its greater severity.

Note: The term "expected" should not be taken to mean "anticipated" for the disease being treated or population being studied, or from the pharmacological properties of the product.

Serious Adverse Event or Drug Reaction

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR)

Any adverse event or adverse drug reaction that:

- results in **death**;
- is **life-threatening**;
- requires inpatient **hospitalisation** or prolongation of existing hospitalisation;
- results in **persistent or significant disability or incapacity**; or
- is a **congenital anomaly or birth defect**.

***Important medical events** that may not be immediately life-threatening, result in death, or require hospitalisation, may be considered serious when, based upon appropriate medical judgment, they may jeopardise the trial participant or require medical or surgical intervention to prevent one of the outcomes listed above.

Examples:

- *Allergic bronchospasm requiring intensive treatment in an emergency room*
- *Convulsions that do not result in hospitalisation*
- *Development of drug dependency*

“Serious” versus “Severe”

Serious ≠ Severe

- The terms “serious” and “severe” are not synonymous.
- The term “severe” is often used to describe the intensity (severity) of a specific event, e.g., mild, moderate, severe, or CTCAE grades 1 (mild) to 5 (fatal).
  - A severe event (e.g., severe headache) may be of relatively minor medical significance
- This is not the same as “serious”, which is based on patient outcomes usually associated with events that pose a threat to a participant’s life or functioning.
- It is the seriousness (not severity) of an event that determines expedited safety reporting requirements.

CTCAE – Common Terminology Criteria for Adverse Events

Unexpected Serious Adverse Drug Reactions (USADRs)

Any adverse drug reaction, the **nature or severity** of which is **not consistent with** applicable product information, and that:

- results in **death**;
- is **life-threatening**;
- requires inpatient **hospitalisation** or prolongation of existing hospitalisation;
- results in **persistent or significant disability or incapacity**; or
- is a **congenital anomaly or birth defect**

USADRs must be reported to the HSA expeditiously in accordance with regulatory requirements (i.e., expedited safety reporting).

Schematic Overview

Expedited Safety Reporting

Adverse Event (AE)

- Is it a **SERIOUS** adverse event or an important medical event for which expedited reporting is appropriate?

Yes

Serious Adverse Event (SAE)

- Is there a reasonable possibility that the serious adverse event is **RELATED** to the investigational product?

Yes

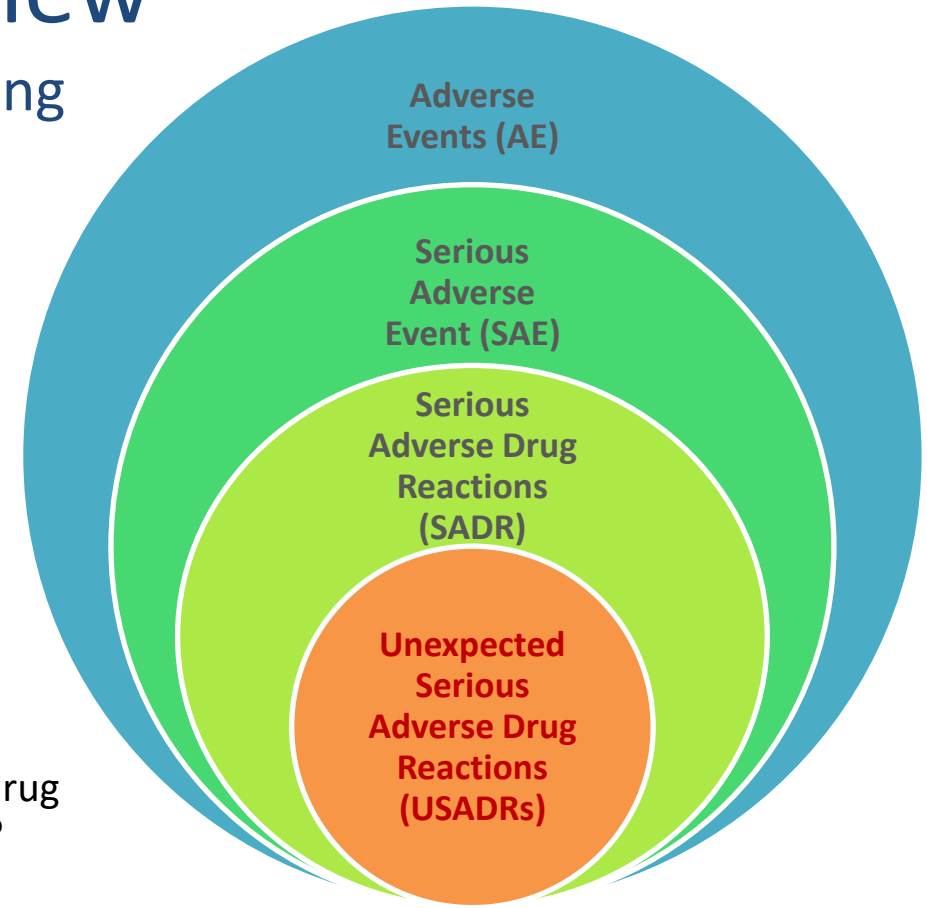
Serious Adverse Drug Reaction (SADR)

- Is the serious adverse drug reaction **UNEXPECTED**?

Yes

Unexpected Serious Adverse Drug Reaction (USADR)

Expedited Safety Reporting to the HSA



SAFETY REPORTING REQUIREMENTS FOR HSA AUTHORISED OR NOTIFIED CLINICAL TRIALS

Scope

Regulatory requirements on expedited safety reporting

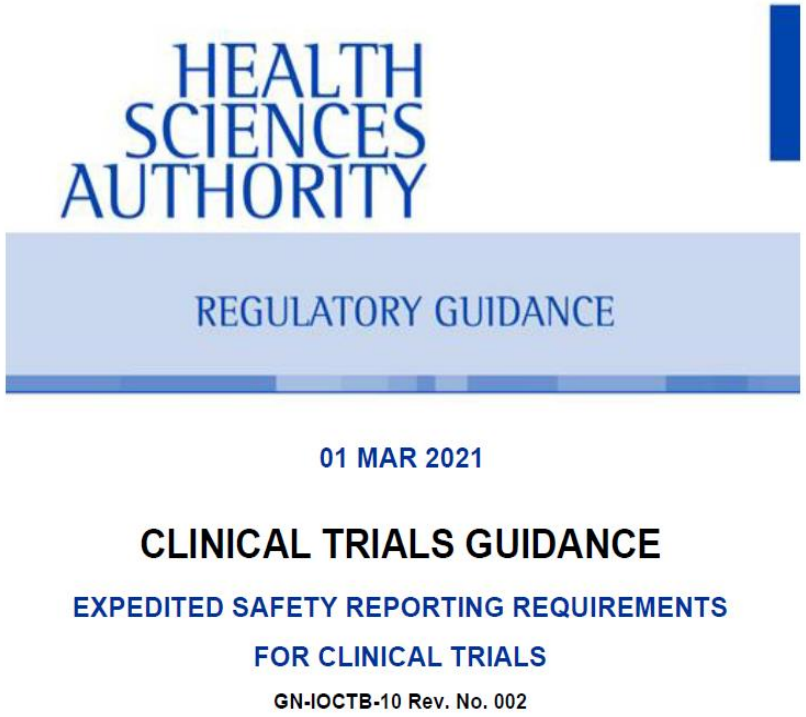
- Health Products (Clinical Trials) Regulations (henceforth referred to as “Clinical Trials Regulations”)

Apply to HSA authorised or notified clinical trials of

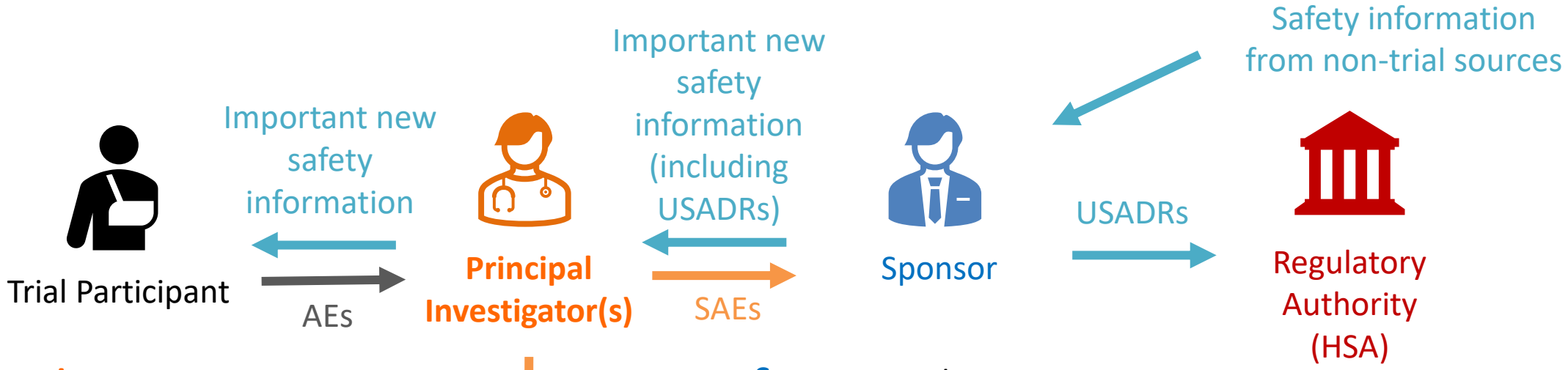
- Therapeutic Products (TPs), and
- Class 2 Cell, Tissue and Gene Therapy Products (CTGTPs)

Regulatory Guidance & ICH Guideline

- HSA Clinical Trials Guidance (GN-IOCTB-10): Expedited Safety Reporting Requirements for Clinical Trials
- ICH E2A Guideline on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
- ICH E6(R3) Good Clinical Practice (GCP) Guideline



Overview of Safety Reporting Requirements



Principal Investigator must

- Immediately report all Serious Adverse Events* to the **Sponsor**, followed by detailed report thereafter
- Report SAEs to the **IRB(s)** in accordance with **IRB** requirements

**except events specified in the protocol as not requiring immediate reporting (e.g., study endpoints/outcomes)*

Sponsor must

- Evaluate safety of investigational product on an ongoing basis
- Report USADRs to **HSA** as soon as possible, within prescribed timeframes
- Promptly notify all **investigators** of safety information or findings that could affect participant safety, including USADRs
- Promptly communicate to trial participants any important new safety information relevant to participant's decision to participate in the trial

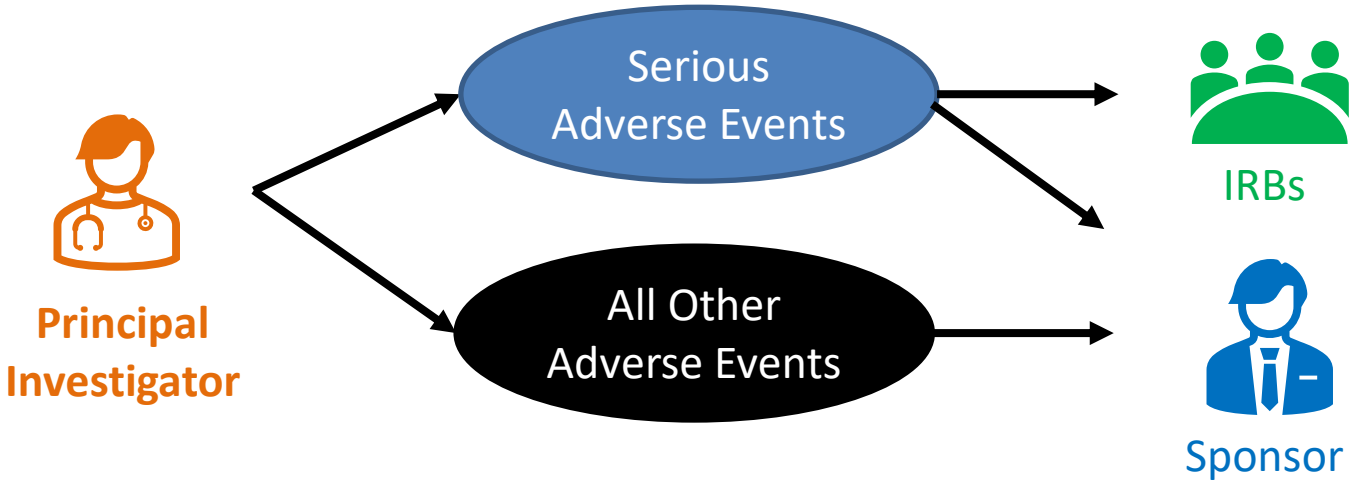
RESPONSIBILITIES OF THE SPONSOR AND THE PRINCIPAL INVESTIGATOR

Responsibilities of the Principal Investigator

The **Principal Investigator** should:

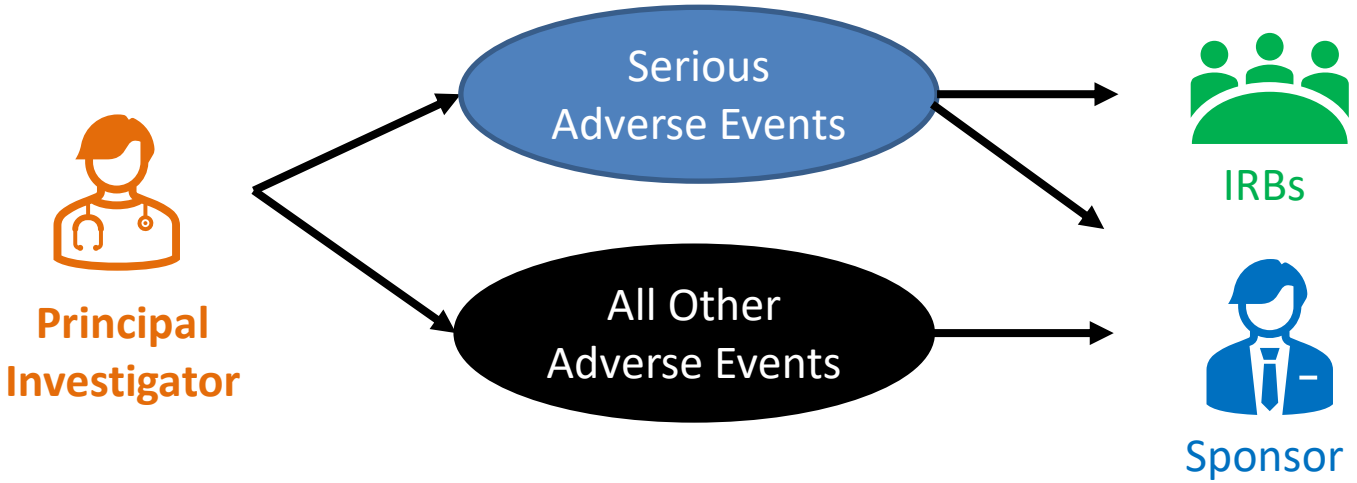
- Discuss potential adverse events (AEs) with trial participants during the informed consent process
- Communicate the importance of prompt AE reporting by trial participants
- Guide participants on AE documentation (e.g., signs and symptoms, onset date, duration, severity, treatments received)
- Instruct trial participants to inform other doctors about their trial participation during any medical consultations
- Establish and review safety reporting processes with all study team members, ensuring clear understanding of roles, responsibilities, and procedures for timely documentation, assessment, and follow-up of reported AEs.

Responsibilities of the Principal Investigator



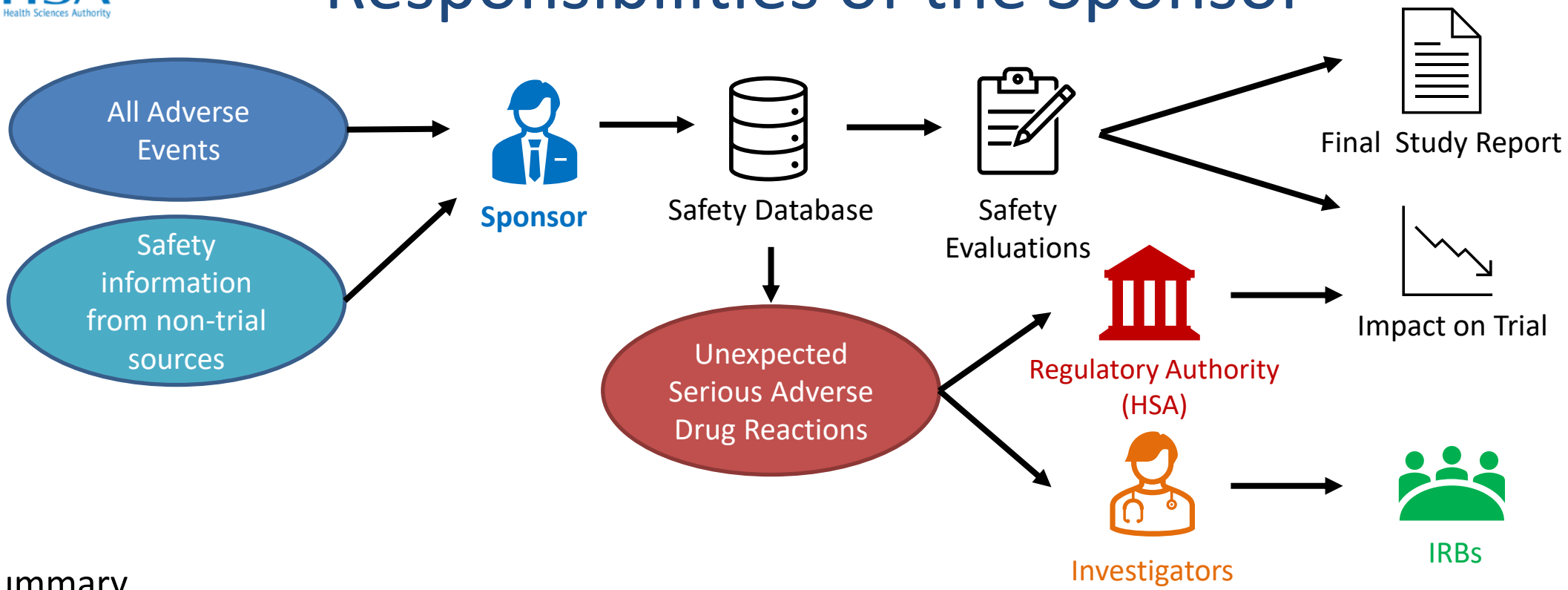
- The **Principal Investigator** should report adverse events and/or abnormal test results required for safety evaluations (as outlined in the protocol) to the **Sponsor**, according to the reporting requirements and within the time periods specified in the protocol.
- The **Principal Investigator** must report all serious adverse events (SAEs) to the **Sponsor** immediately after becoming aware of the event.
  - Except those events identified in the protocol as not requiring immediate reporting, e.g., deaths or other events that are study endpoints.
  - Include an assessment of causality.
  - Subsequent information on the SAE should be submitted as a follow-up report, as necessary.

Responsibilities of the Principal Investigator



- The **Principal Investigator** must report all SAEs to the relevant **IRB** in accordance with **IRB** requirements.
- The **Principal Investigator** may delegate activities for safety reporting to qualified investigator site staff but retains overall responsibility for the safety of trial participants.

Responsibilities of the Sponsor



In summary,

- The **Sponsor** is responsible for the ongoing safety evaluation of the investigational product(s).
- The **Sponsor** should aggregate, as appropriate, and review relevant safety information in a timely manner.
  - This may result in the update of safety information in the protocol, Investigator's Brochure, informed consent documents and related documents.
- The **Sponsor** must expedite the reporting of USADRs to the **HSA** and promptly notify **Investigators** of USADRs, who should report these to **IRBs** accordingly.

Responsibilities of the Sponsor

- The **Sponsor** should review the available emerging safety information to assess whether there is any new data that may affect the participant's willingness to continue in the trial, impact the conduct of the trial, or alter the approval/favourable opinion of the **IRB** or the **HSA**. Such information should be communicated to the participants, the **Investigators**, the **IRB** and the **HSA** in a timely manner.
- The **Sponsor** should submit safety updates and periodic reports, including changes to the Investigator's Brochure to the **HSA**.
- The **Sponsor** must expedite the reporting of all unexpected, serious adverse drug reactions (i.e., USADRs) to the **HSA** within prescribed reporting timeframes.
  - Undertaken by assessing the expectedness of the reaction in relation to the applicable product information (e.g., the reference safety information in the Investigator's Brochure).

Responsibilities of the Sponsor

- The **Sponsor** should report USADRs to the **Investigators** and **IRBs** in a manner that reflects the urgency of action required and should take into consideration the evolving knowledge of the safety profile of the product.
- Urgent safety issues requiring immediate attention or action should be reported to the **IRBs** and **Investigators** without undue delay and to the **HSA** within prescribed reporting timeframes.
- Alternative arrangements for safety reporting to **HSA**, **IRBs** and the **Investigators,** and for reporting by the **Investigators** to the **Sponsor**, should be prospectively agreed upon with the **HSA** and, if applicable, the **IRB**, and described in the clinical trial protocol.

WHAT, WHEN AND HOW TO SUBMIT EXPEDITED SAFETY REPORTS TO HSA

What Should Be Reported to HSA

- For an investigational product (i.e., therapeutic product or CTGTP) being studied in a clinical trial in Singapore, report all USADRs:
  - From the same clinical trial (whether occurring in local or overseas trial sites)
  - From other local or overseas clinical trials of the same investigational product
  - From other non-trial sources (e.g., spontaneous reports)
- Report other observations that may materially influence the benefit-risk assessment of an investigational product, e.g.,
  - An increase in the rate of occurrence of an expected, serious adverse drug reaction judged to be clinically important
  - A significant hazard to the study population, such as lack of efficacy with an investigational product used in treating a life-threatening disease
  - A major safety finding from a newly completed animal study, such as carcinogenicity

What Should Not Be Reported to HSA

- Serious adverse drug reactions that are expected, unless clinically important increase in rate of occurrence
- SAEs not considered to be related to the investigational product, whether expected or not
- Non-serious adverse drug reactions, whether expected or not
- Adverse events associated with placebo

Expedited Safety Reporting Timelines

- **Fatal or Life-threatening USADRs**
  - As soon as possible and no later than 7 calendar days after the sponsor first becomes aware of the event
  - Follow-up report: within the next 8 calendar days
    - Include assessment of the importance and implications of the findings, including any previous experience with the same or similar products.

- **All other USADRs**
  - As soon as possible and no later than 15 calendar days after the sponsor first becomes aware of the event

Initial Expedited Safety Report

Minimum Criteria

- An identifiable patient
- A suspect therapeutic product or cell, tissue and gene therapy product
- An identifiable reporting source
- An event or outcome that meets the following three criteria:
  - It is serious
  - It is unexpected
  - There is a reasonable suspected causal relationship

How to Report

- CIOMS-I form widely accepted for expedited safety reports
- Data elements to include in expedited safety reports to HSA:
  - Refer to HSA Clinical Trials Guidance (GN-IOCTB-10): Expedited Safety Reporting Requirements for Clinical Trials, Appendix 2
- Describe USADR using MedDRA terminology
- Submit expedited safety reports through PRISM

9.1. Appendix 1: CIOMS-I Format

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

Managing Blinded Treatment Assignments

- The Sponsor and Investigator may be blinded to individual trial participants' treatment assignments
- Recommend that the Sponsor break the blind for that specific participant when a USADR occurs that requires expedited reporting
- Knowledge of treatment necessary for interpreting the event and meaningful safety communication
- Minimal impact to study integrity (unblinding infrequent, exclude serious events that are key study endpoints, e.g., death, stroke, myocardial infarction)
- Expedited safety reports should not be submitted if participant was receiving placebo

Locally Registered and Auxiliary Products

Risk-based Approach

USADR associated with	Product Registration Status in Singapore	Expedited Safety Reporting Requirements
Investigational Product (IP)	Unregistered	All USADRs from: • The same clinical trial ongoing in SG (whether occurring locally or overseas) • Other local or overseas clinical trials of the same IP • Other non-trial sources (e.g., spontaneous reports)
	Registered	Only USADRs relevant to the new indication or use being studied in Singapore (whether occurring locally or overseas). Example: USADRs from the same clinical trial assessing the new indication or use in SG (whether occurring locally or overseas).
Auxiliary Product (AP)	Registered or unregistered	Only local USADRs from the same clinical trial ongoing in SG.

Investigational Product (IP) – TP/CTGTP or a placebo that is to be tested or used as a reference in a clinical trial
Auxiliary Product (AP) – TP/CTGTP used for the needs of a clinical trial but not as an investigational product
USADR – Unexpected, Serious Adverse Drug Reaction

URGENT SAFETY MEASURES

Urgent Safety Measures

Urgent Safety Measures

- The Sponsor and any Investigator of a clinical trial may take any urgent safety measures to avoid an immediate hazard to the health or safety of trial participants, without prior regulatory approval.

Notifications of Urgent Safety Measures

- The sponsor must, as soon as possible and in any event not later than 7 days after the date any urgent safety measures have been taken, notify HSA of the measures taken and the circumstances giving rise to the measure.
- Notifications of urgent safety measures should be submitted through PRISM.

Summary

- Continuous safety evaluation and expedited reporting are crucial to ensure prompt identification and management of new and emerging safety signals in clinical trials.
- Ensures prompt actions taken, where necessary, to safeguard safety of trial participants.
- Understand key terms used in safety reporting and regulatory requirements for expedited safety reporting.
- The Sponsor and the Principal Investigator have important responsibilities to ensure
  - SAEs are immediately reported to the sponsor, and IRB(s) as per IRB requirements
  - Ongoing safety evaluation
  - Expedited safety reporting to the HSA within prescribed timeframes
  - Timely communication of new and important safety information to participating investigators and trial participants
- When, what and how to submit expedited reports to HSA.
- How to notify HSA of urgent safety measures taken to protect participants.

References

- Health Products (Clinical Trials) Regulations
- HSA Regulatory Guidance (GN-IOCTB-10): Expedited Safety Reporting Requirements for Clinical Trials
- ICH E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
- ICH E6 (R3) Good Clinical Practice (GCP) Guideline

We welcome your enquiries and feedback!

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THANK YOU!