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Safety Reporting

Reporting of Adverse Events and Serious Adverse Events in Clinical Trials for Investigator Site Staff

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Presentation Topics

1. Definitions
2. Legal Framework
3. General Expectations
4. AE Reporting: Expectations and Common Inspection Findings
5. SAE Reporting: Expectations and Common Inspection Findings
6. Sponsor Responsibilities

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References

- Note for Guidance on Good Clinical Practice: Consolidated Guideline (ICH Topic E6, Step 5, CPMP/ICH/135/95)
- European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004 to 2009 (SI No.190 of 2004, as amended)
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001
- EudraLex - Volume 10, Clinical Trial Guidelines

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Definitions (Ref: SI No.190 of 2004)

- **Adverse Event**: Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences that do not necessarily have a causal relationship with treatment

- **Adverse Reaction**: Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject

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Definitions (Ref: SI No.190 of 2004)

- **Serious Adverse Event/Serious Adverse Reaction**: Any adverse event or adverse reaction that, at any dose,
  a) Results in death,
  b) Is life-threatening
  c) Requires hospitalisation or prolonged hospitalisation
  d) Results in persistent or significant disability or incapacity
  e) Consists of a congenital anomaly or birth defect

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Definitions (Ref: SI No.190 of 2004)

- **Unexpected Adverse Reaction**: In respect of an investigational Medicinal Product, an adverse reaction, the nature or severity of which is not consistent with the information about that medicinal product as set out
  a) In the case of a product which is the subject of a marketing authorisation, in the summary of product characteristics for that product
  b) In the case of any other investigational medicinal product, in the Investigators brochure relating to the particular clinical trial.

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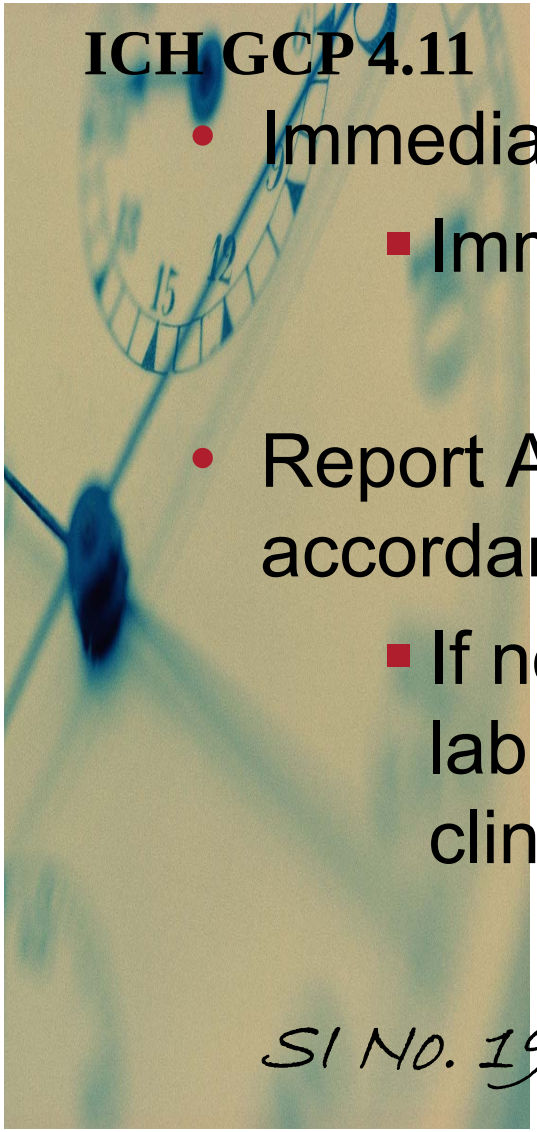
Legal Framework



ICH GCP 4.11

- Immediate reporting of SAE to the Sponsor
  - Immediate = within 24 hours
- Report AE and laboratory abnormalities in accordance with protocol requirements
  - If no instruction in protocol regarding lab abnormalities → report as AE if clinically significant

SI No. 190 of 2004: Regulation 29

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General Expectations

- Adequate training of staff in safety reporting requirements
- Understand what constitutes a Serious Adverse Event
- Appropriate delegation of duties
- Reference in medical records of participation in a clinical trial
- Encourage Subjects to always remind GP or other treating Physician of participation in a clinical trial

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Expectations for Adverse Event Reporting

- As required by the protocol
- Complete and accurate source documentation
- Assessment of event documented in real time
  - Include: Mild, Moderate, Severe and/or Grade 1, 2, 3, 4, 5
- Investigator assessment of causality
  - Relationship to trial medication: Probable, Possible or Unrelated
- Documentation of treatment (if any)

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Expectations for Adverse Event Reporting

- Seriousness Assessment of each event
- Adequate review of medical records for events
- Accurate and timely completion of event in CRF
- Concomitant Medication ⟶ Corresponding AE

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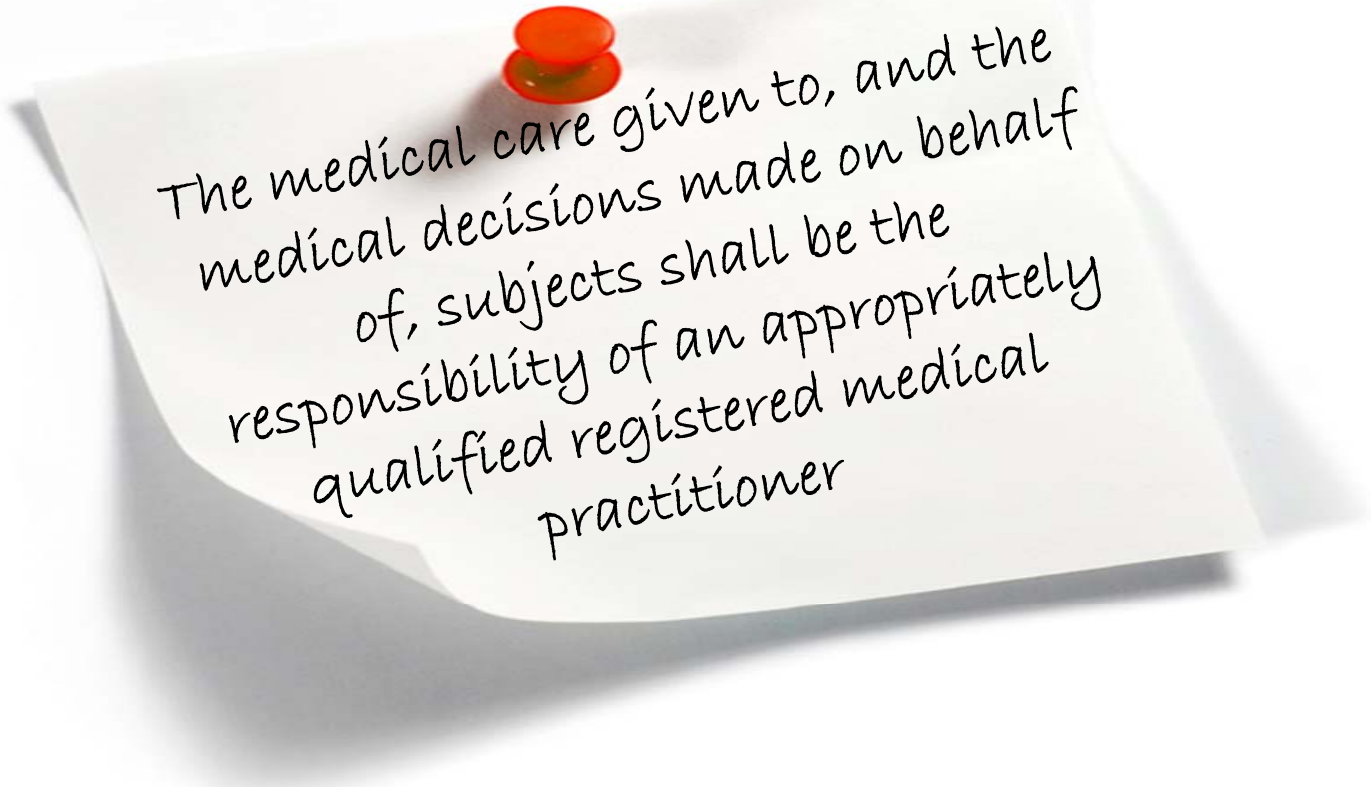
Remember

SI No. 190 of 2004, Schedule 1, Part 2:



Note: "Registered Medical Practitioner" means a person registered in the register established under the Medical Practitioners Act 1978

Common Deficiencies

- Unreported AE
- AE not recorded in CRF in timely manner
- No assessment/documented Investigator assessment of AE
- Inadequate source documentation
- Poor quality CRF data
- Concomitant Medication ➡ No corresponding AE
- Laboratory abnormalities not reported (where required)

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Use of Worksheets

- Mainly Oncology trials
- Worksheets used by Research Nurses to record events (eg. common chemo toxicities)
- Physicians documenting events in medical records
- Duplicate recording of events
  → inconsistencies between both
- Which is source

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Reminder

Serious Adverse Event/Serious Adverse Reaction: Any adverse event or adverse reaction that, at any dose:

- ✓ Results in death,
- ✓ Is life-threatening
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- ✓ Results in persistent or significant disability or incapacity
- ✓ Consists of a congenital anomaly or birth defect

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Expectations for SAE Reporting

- Minimum criteria for initial SAE Report:
  - Identifiable subject
  - Identifiable reporter
  - Event description
  - Product
- Report within 24 hours: Verbally/Written
  - If verbal, then immediate follow-up in writing
- Investigator assessment of causality/relationship
- Investigator sign-of of event
- Adequate Follow-up

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Common Deficiencies

- Unreported SAE
- Late reporting of SAE
- Poor quality reports
- Inadequate/Inaccurate source records
- No Investigator assessment of causality
- Inadequate Follow-up

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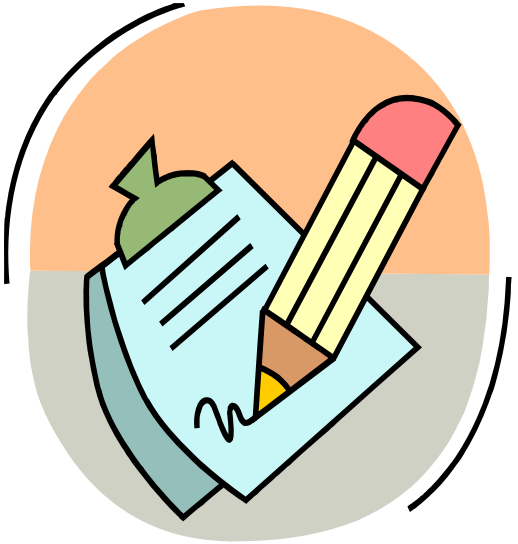
Expectations for Follow-up

- Monitor event until resolution
- Provide follow-up information to Sponsor as soon as it becomes available, e.g.
  - Discharge records
  - Laboratory reports/Other reports
  - Autopsy reports for deaths
- Don’t wait for Sponsor requests for FU
- Clear and accurate data
- Answer all queries from Sponsor in timely manner



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Sponsor Responsibilities

- Expectedness assessment → recognised adverse effect of the medication or is it unexpected
  - SPC
  - Investigator Brochure
- Onward SUSAR reporting to Competent Authorities
- Continuous evaluation of safety data:
  - Facilitate identification of new safety concerns
  - Establish safety profiles of medicinal substances
  - Ensure timely and appropriate regulatory action
  - Support prompt communication of any safety concerns as necessary

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Summary

- Timely reporting of SAE and AE
- Adequate & accurate source records
- Clear & accurate reports
- Investigator assessment of causality
- Adequate Follow-up

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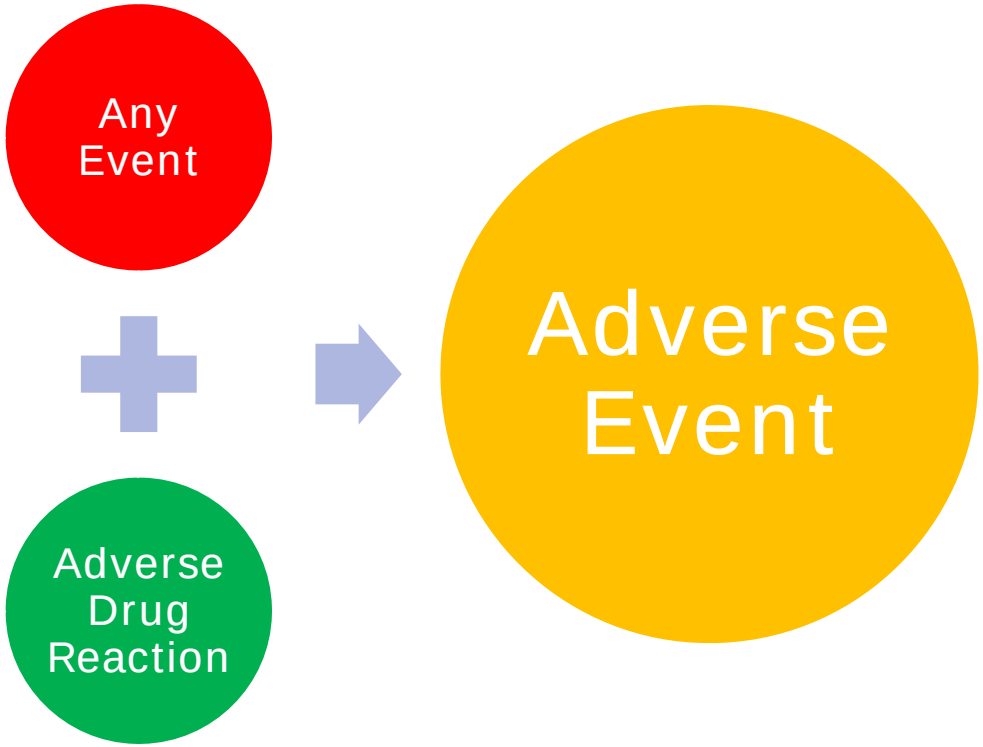
And Finally



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Thank You

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Abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
AR	Adverse Reaction
CRF	Case Report Form
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction

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