HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Pharmacovigilance Systems

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HPRA Information Day – GCP for IMP clinical trials

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What we will cover

Pharmacovigilance and Clinical Trials

- What is Pharmacovigilance?
- Key Legislation and Guidance
- Key Definitions

Case Processing (AEs/SAEs)

- Data Collection
- Record Keeping
- Data Evaluation
- SUSAR Reporting

Other PV Processes

- Reference Safety Information
- Annual Reporting

What is Pharmacovigilance?

HPRA
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'The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem'

Ref. WHO definition

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***

(Principle 2.2, ICH GCP E6)

Key Legislation and Guidelines

EU: Directive 2001/20/EC and 2005/28/EC, as amended

S.I. No. 190 of 2004, as amended

EudraLex Volume 10 Clinical Trial Guidelines – Chapter I ‘CT-1’ and Chapter II ‘CT-3’

ICH E6: GCP, ICH E2A – E2F: Pharmacovigilance

HPRA Guide to Clinical Trial Applications

HPRA Guide to Electronic Transmission of SUSARs Associated with the Use of Human Medicines

Definitions

An **adverse event (AE)** is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which **does not necessarily have a causal relationship** with this treatment

An **adverse reaction (AR)** is all untoward and unintended responses to an investigational medicinal product **related** to any dose administered

Ref: Article 2 (m), (n) of Directive 2001/20/EC

Definitions

A **serious adverse event (SAE)/serious adverse reaction (SAR)** is an AE/AR which;

- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect,
- + *an important medical event/medically significant*

SUSAR: **S**uspected **Unexpected** **S**erious **A**dverse **R**eaction requires expedited reporting

Ref: Article 2 (o) of Directive 2001/20/EC, 3(15) of 'CT-3'

Responsibilities of the Investigator & Sponsor

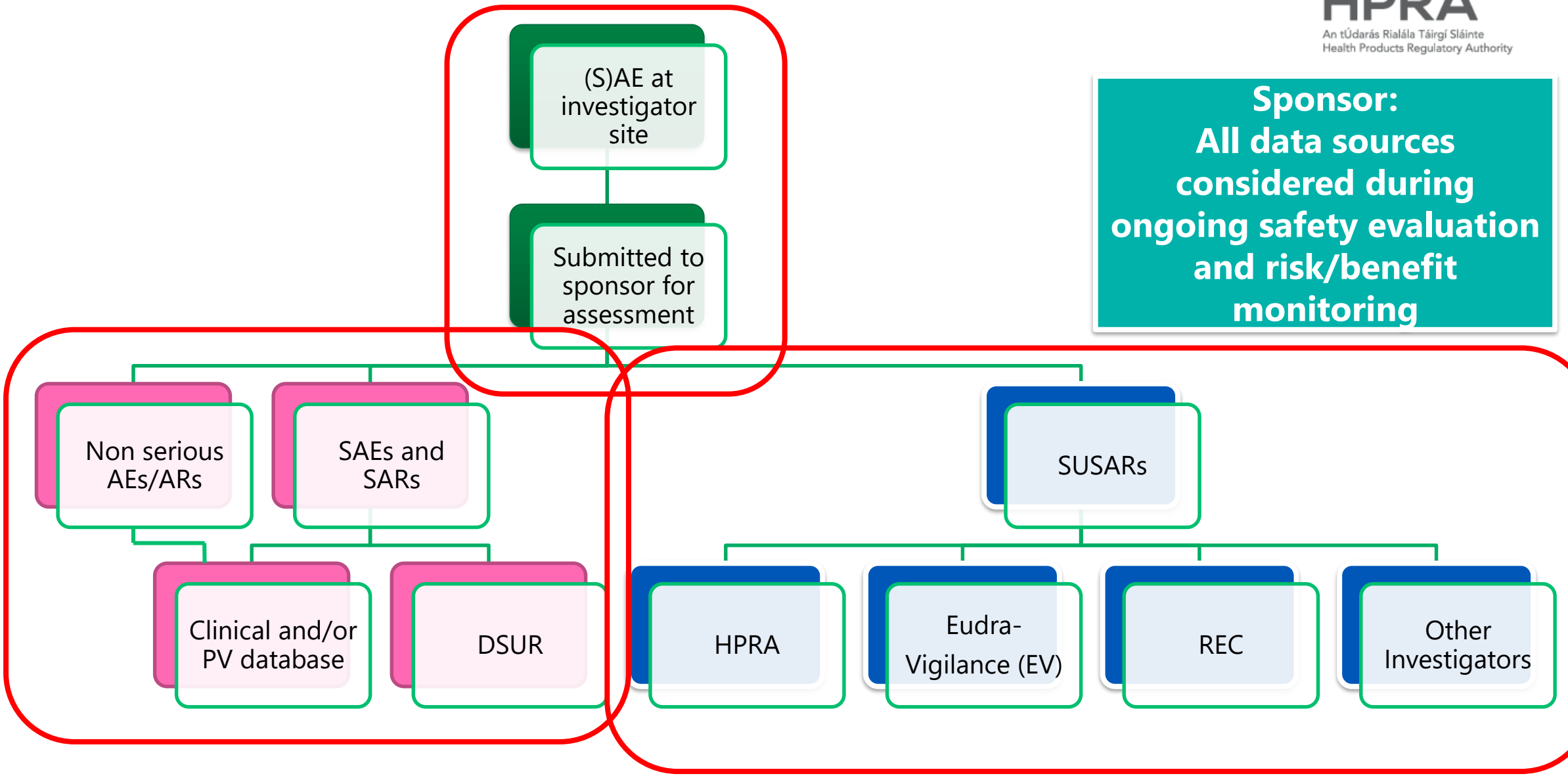
Investigator

- Reporting SAEs to sponsor
- Reporting of non-serious AEs and/or laboratory abnormalities to sponsor

Sponsor

- Recording of AEs
- Expedited reporting of SUSARs
- Informing investigators
- Development Safety Update Report (DSUR) reporting
- Ongoing safety evaluation

Ref: 3(14) and 3(15) of 'CT-3'



Sponsor:
All data sources considered during ongoing safety evaluation and risk/benefit monitoring

Sponsor Systems & Procedures

The sponsor should arrange for systems and written procedures covering all stages of pharmacovigilance to ensure compliance

- Following processes, at a minimum: case documentation, data collection, validation, evaluation, archiving, reporting and following-up.

All actions undertaken should be documented

Delegation of tasks does not remove the ultimate responsibility of the sponsor or investigator for the conduct of the clinical trial

Ref: 3(17) of 'CT-3'

Experience: Non-Commercial Sponsor Inspections

Medical expertise available, with a network of investigators who had contributed to trial design/protocol writing & providing ongoing medical advice

Observations/deficiencies:

- Sponsor systems & procedures: deficiencies in key areas, in particular, SAE case processing
- Lack of resource to support development of systems/written procedures
- Distribution of tasks, including to investigators, not clearly documented

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Data collection: Key Requirements

SAEs to be reported immediately by investigator to sponsor (within 24 hours)

- With exception of SAEs that the protocol/IB identifies as not requiring immediate reporting

Immediate report to be followed by detailed, written reports

AEs and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the protocol

Ref: Article 16(2) of Dir 2001/20/EC (as amended), 4.3 (28) (29) (31), 5(34) of 'CT-3'

Data collection: Key Sponsor Systems & Procedures

The protocol should contain sufficient detail on investigators' responsibilities, including process for SAE identification and reporting

- Definition of SAE
- Instruction regarding any SAEs that do not require immediate reporting
- Clear instruction that those SAEs still require reporting and how i.e. via the clinical database
- Clear instruction for any other safety events to be collected e.g. AEs of special interest, pregnancy reports
- Timeline for immediate reporting defined (e.g. within 24 hours of awareness)
- Time period for collection (start and stop)

Data collection: Key Sponsor Systems & Procedures

- Reporting tools e.g. SAE report form with sufficient data fields (consider CIOMS I format)
- Reporting process defined e.g. fax, email, eCRF
- Standardised causality grading scheme
- Data protection – e.g. pseudoanonymisation
- Training of investigators and delegated staff
- Sufficient monitoring plan to verify investigator compliance

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Record keeping: Key Requirements

The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators

All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification

Quality control (QC) should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly

Ref: Article 16(4) of Dir 2001/20/EC (as amended), 2.10 and 5.1.3 of ICH GCP E6

Record Keeping: Key Sponsor Systems & Procedures

Detailed written procedures should be in place, specifying the handling of data at each step, as well as QC controls. Key components include;

- **SAE receipt;** record of date of receipt – clock start for SUSAR regulatory reporting
- **SAE case identification;** method to assign unique identifier to an SAE case, including for initial and follow up reports
- **SAE assessment;** 'database' to capture pertinent SAE information
- **SAE case file;** collate all records for an SAE case, including investigator reports, sponsor assessment, QC checks, evidence of regulatory reporting
- **QC;** internal checks to ensure all of above correct, including any data communicated to regulators/ethics committees

Record keeping: Key Sponsor Systems & Procedures

PV/Safety database:

- Location where SAE data are 'collated'
- Typically a computerised system (specialist database or spreadsheet)
- May be used as a source form which SUSAR reports and line listings for DSURs/continuous monitoring are generated

Non commercial setting: Microsoft Excel® spreadsheets commonly used

- Need to comply with ICH GCP E6 5.5.3 and 5.5.4 on Data handling
- Consider suitability relative to the size of the trial/amount of data
- Strict process for controlling data entered into the spreadsheet
- Audit trial; need to record changes

Record Keeping: Other Aspects to Consider

Inspectors typically ask:

- How does the sponsor verify information received is correct?
- Is it checked for minimum reporting criteria?
- Is there a check for duplicate reports?
- Is a follow-up process defined, including timelines and number of attempts?
- Is there a cross check with site monitoring?
- Is there a periodic reconciliation with clinical database, and follow up on any inconsistencies?

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Key Requirements: Data evaluation

Ongoing safety evaluation of IMPs

i.e. benefit/risk monitoring (3 (16) 'CT-3')

Evaluation to identify SARs & SUSARs

(7.4 'CT-3')

Evaluation to identification of safety issues not falling within the definition of SUSAR (7.11.4 'CT-3')

SAE Assessment: Key Responsibilities

Investigator:

- Seriousness
- Causality

Sponsor:

- Completeness of information
- Expectedness
  - An unexpected AR is an AR, the nature or severity of which is not consistent with the applicable product information (ref: Article 2(p) of Dir 2001/20/EC)
- Classification as SAE, SAR, SUSAR

SAE assessment: Key Sponsor Systems & Procedures

Seriousness

- Check on receipt of SAE that seriousness criteria are met, and are consistent throughout the report

Causality

- Check on receipt investigator causality given, and if not, timely follow up
- Sponsor may also undertake assessment but **should not downgrade**

Expectedness determination

- Clearly defined process, whereby, expectedness is determined according to the CT-3 definition and against the RSI
- Regulatory assessment: based on what events are listed as having been previously observed, and not on the basis of what might be anticipated

Ref: 7.3 (57 - 62) of 'CT-3'

SAE assessment: Key Sponsor Systems & Procedures

Coding of events/terms

- MedDRA terminology may be used

Classification

- Determine if SAE, SAR, SUSAR
- Important to undertake this in a timely manner to meet reporting timelines

Medical review

- Typical in non-commercial trials for Chief investigator to be involved in medical review
- May be risk proportionate e.g. review of SUSAR reports, reviewing of periodic SAE line listings
- May advise on follow up, causality and expectedness

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Key Requirements: SUSAR Reporting

Fatal and life-threatening SUSARs to be reported to the regulatory authority/REC immediately, and no later than **7 days** after knowledge by the sponsor

- Follow-up information to be reported by day 8

All other SUSARs to be reported to the regulatory authority/REC as soon as possible but within a maximum of **15 days** of first knowledge by sponsor

Clock for reporting starts as soon as information containing minimum criteria is received (day 0)

- Minimum criteria includes; valid EudraCT no., sponsor study no., one identifiable coded subject, one identifiable reporter, one SUSAR, one suspect IMP and a causality assessment

Ref: 17 (1) (a), (b) and (d) of Dir 2001/20/EC as amended and 7.1 (27) and 7.7.2 (93) of 'CT-3'

Key Requirements: SUSAR Reporting

Regulatory reporting via the EudraVigilance database

- HPRA may report for non-commercial sponsors without access to EV, contact medsafety@hpra.ie before commencing the trial

As a general rule only SUSARs on which the treatment allocation of the subject is unblinded should be reported to the regulatory authority/REC

The sponsor should inform investigators of SUSARs, however, this information should not be unblinded unless judged necessary for safety reasons

Ref: 7.11.1 (111) and (112) of 'CT-3'

SUSAR reporting: Key Sponsor Systems & Procedures

Procedure in place covering reporting

- Reporting mechanism, reporting requirements, timelines, QC check

Staff involved in reporting trained on requirements and procedures

Regulatory unblinding

- 'Firewall' to personnel involved in trial conduct
- Process should be clearly defined in written procedures
- Note: Separate mechanism to emergency unblinding

System to monitor reporting compliance

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Key Requirements: Reference Safety Information

Primary purpose is to serve as the basis for expectedness assessment of suspected SARs by the sponsor for expedited reporting of SUSARs

RSI may be Investigator's brochure (IB) or SmPC (if IMP has a marketing authorisation)

Annual validation and update (if required)

Clinical Trials Facilitation Group (CTFG) Q and A document (November 2017) on RSI

- http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf

Ref: 43A of SI 190/2004 (as amended)

RSI: Key Sponsor Systems & Procedures

Procedure covering identification, maintenance and updates to RSI

- Identification of RSI
- Inclusion in the clinical trial application
- Annual validation of IB/periodic review for updates to SmPC by respective marketing authorisation holder
- Handling of amendments to HPRA and REC trial approvals (e.g. substantial amendment)
- Training of personnel in how to perform an expectedness assessment

Annual Reporting: Key Requirements

Development Safety Update Reports (DSURs)

- A sponsor shall, in relation to each investigational medicinal product tested in clinical trials in the State for which he or she is the sponsor, furnish the HPRA and the relevant ethics committee with an annual report
- Listing of all SARs which have occurred over the period
- ICH E2F, DSUR
- Sponsor is responsible for the preparation, content, format and submission of the DSUR

Ref: S.I no. 190 of 2004 (Reg 32), ICH E2F

Annual Reporting: Key Sponsor Systems & Procedures

Procedure describing DSUR preparation, including template, timelines for gathering data, for submission, for QC and for review and finalisation

DSUR benefit-risk assessment: medical review

Compliance monitoring of submission timelines

Control of bias: for any unblinded/comparative information e.g. line listings, SUSARs

Thank you!