Basic pharmacovigilance principles and rules

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What is Pharmacovigilance

- **According to WHO**, Pharmacovigilance is « the science and activities related to the detection, assessment, understanding and prevention of adverse drug effects or any other possible drug-related problems »
- supervision of medicinal products to ensure the **maximum safety** and the **best possible risk-benefit ratio** of the medicinal product
- pharmacovigilance includes the **collection of information** relevant to the safety of a medicinal product, including information obtained through clinical trials, **its evaluation** and the **implementation of appropriate measures**
- the safety of medicines must be continuously monitored throughout the whole life cycle of the medicine (experiments on animals have limited information value for the human safety, restricted time and number of patients in clinical trials, rare and late serious reactions would probably stay unknown)

Pharmacovigilance in CT – Regulatory requirements

EU

- **Directive 2001/20/EC** on the implementation of good clinical practice in the conduct of clinical trials
- **REGULATION No 536/2014** on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
- **CT- 3** - Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (2011/C 172/01)

ICH

- ICH - E6 - Good Clinical Practice - Consolidated Guideline
- 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 – E2F – DSUR

Local regulatory requirements – country specific (CZE, HUN, POL, SVK)

Abbreviations

- **AE** – Adverse Event
- **AR / ADR** – Adverse Reaction / Adverse Drug Reaction
- **SAE** – Serious Adverse Event
- **SAR / SADR** – Serious Adverse Reaction / Serious Adverse Drug Reaction
- **UADR** - Unexpected Serious Adverse Reaction
- **SUSAR** – Suspected Unexpected Serious Adverse Reaction
- **AESI** - Adverse event of special interest
- **TEAE**- Treatment emergent adverse event
- **DSUR** – Development Safety Update Report
- **ASR** – Annual Safety Report
- **IMP** – Investigational Medicinal Product , **CT** – Clinical Trial, **CA –** Competent Authority, **EMA** – European Medicines Agency, **EV** – EudraVigilance, **CTIS** - Clinical Trials Information System, **ICH** – International Conference on Harmonisation, **SPC, SmPC** – Summary of Product Characteristics, **IB** – Investigator's Brochure, **EC** – Ethic Committee, **RSI**– Reference Safety Information, **CRF** – Case Report Form, **GCP** – Good Clinical Practice

Pharmacovigilance Events - Definitions

Adverse event

- Any untoward medical occurrence in a clinical trial participant to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment *(and /or the experimental procedure)*
- An adverse event can therefore be:
  - any **unfavorable and unintended sign,** including an abnormal finding from an additional examination (lab tests, X-ray, ECG,…)
  - any **symptom** or **disease** temporally associated with the use of a medicinal product,
  - **any worsening** (during the study) **of a symptom or a disease** already present when the participant entered the study (increase in frequency and/or intensity).

Assessment of adverse events –relationship (causality)

Adverse reaction

Any untoward and unintended response to an investigational medicinal product related to any dose administered to the clinical trial participant.

- In general, if a relationship between AE and IMP is at least reasonably possible (i.e. the relationship cannot be ruled out) it is to be considered as "related".
- Assessment usually done by investigator, causality should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both (investigator and sponsor) should be provided.
- AE might be related to clinical trial procedure - usually also causality assessment of AE to study (experimental) procedure is done

Assessment of adverse events – seriousness

Serious adverse event (SAE)

A serious adverse event is any untoward medical occurrence that at any dose:

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

Important medical events - may jeopardize the patient or may require intervention **should also usually be considered serious.** Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

EMA – Important Medical Event list

Assessment of seriousness usually done by investigator, should not be downgraded by the sponsor (can be upgraded in case sponsor has different opinion).

Assessment of adverse events – severity

- **Severity –** The severity of AE describes its intensity which is graded.

grading: mild – moderate – severe

Grade 1 – Grade 5 (event: mild – moderate – severe - life-threatening – death)

CT in oncology- guideline for AE severity assessment : CTCAE (Common Terminology Criteria for Adverse Events , Version 5.0 Published: November 27, 2017)

!!! Severity ≠ Seriousness (regulatory definition for regulatory reporting obligations, based on patient/event outcome or action criteria)**!!!**

Assessment of adverse events – expectedness

- **Expectedness**

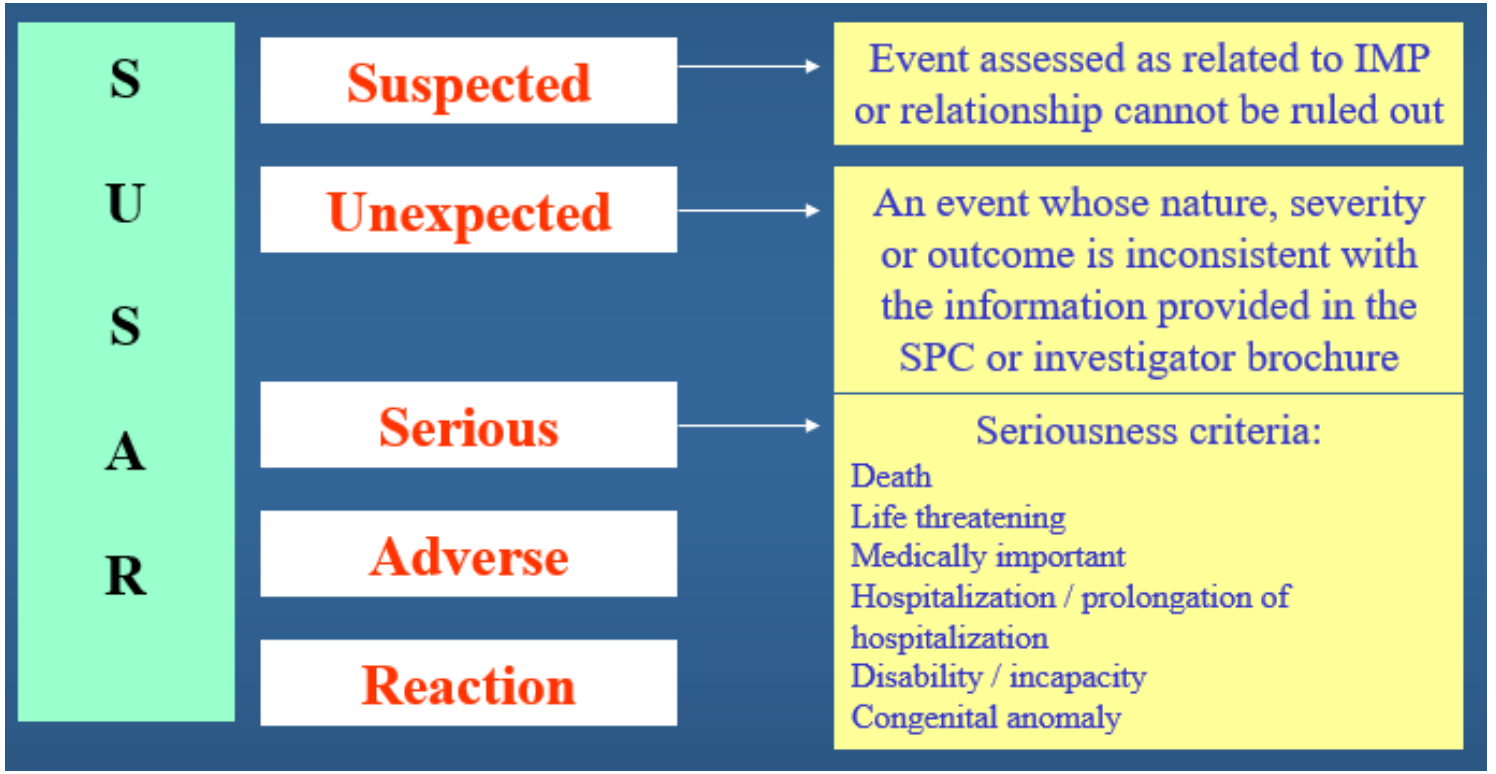
An AE/AR should be considered as unexpected if its nature, severity or outcome is not consistent with the reference safety information (RSI):

- Investigator's brochure for an unauthorised IMP
- Summary of product characteristics for an authorised IMP

= Unexpected Adverse Drug Reaction (UADR)

Usually assessed by Sponsor, in some clinical trials (e.g. academic) assessment can be done also by the investigator

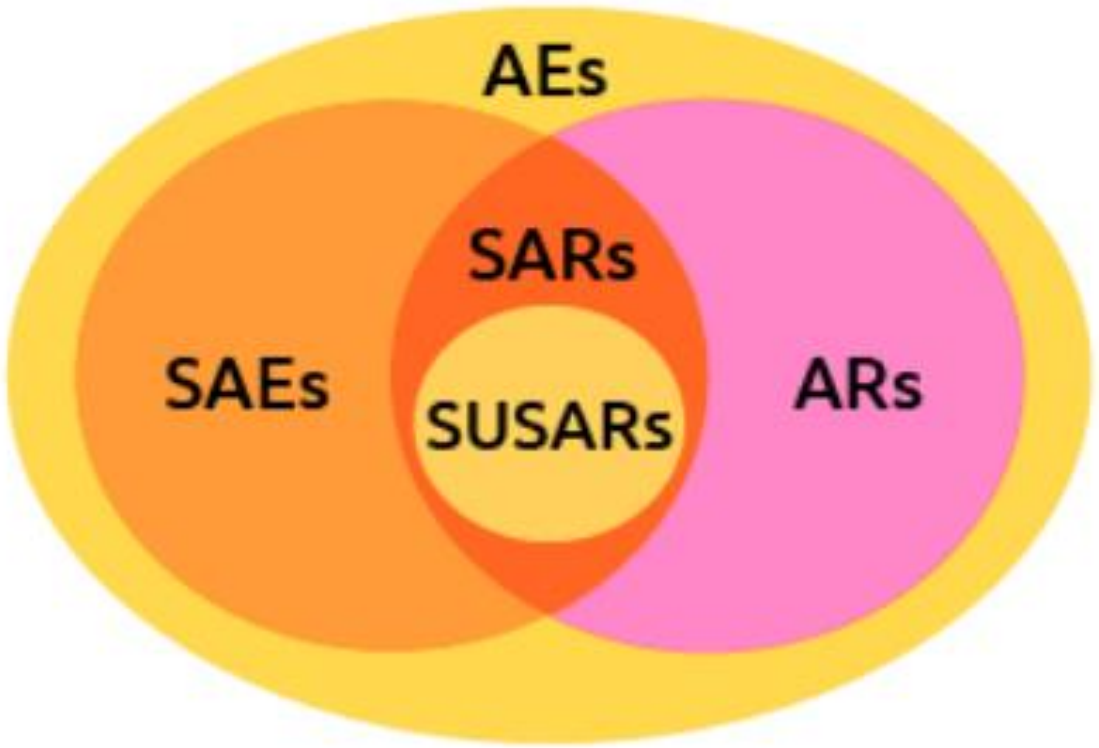
SUSAR - definition



AESI, TEAE

- **AESI - Adverse event of special interest** - is one of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such an event may require further investigation in order to characterize and understand it (example: increase of transaminases during administration of potentially hepatotoxic drug)
- **TEAE- Treatment emergent adverse event** - any event that occurs or worsens (in intensity or frequency) after the first administration of the IMP

AEs - summary



RESPONSIBILITY of **INVESTIGATOR**

- recording of all adverse events (continuously)
  - in the medical file (source documentation)
  - in the Case Report Form (CRF): AE form as soon as the investigator is informed about the event
- **reporting to SPONSOR**
  - immediately (within 24 hours)
    - all **SAE**s – exception – events defined by protocol – SAE which are not subject of expedited (immediate) reporting (e.g. Hospitalization due to planned surgery, expected toxicities..)
    - All other events which require immediate notification per protocol (e.g. Pregnancy, Overdose, AESI)

RESPONSIBILITY of **INVESTIGATOR**

- For SAEs and other events requiring immediate notification per protocol: usually relevant medical documentation should be provided to sponsor (anonymized copies of any documents providing additional information – hospital reports, laboratory results,..)
- Follow-up of AEs until their resolution (recovery or stabilization of the clinical state of CT participant), any additional information to be recorded/reported
- Timeframes for recording/reporting of AEs during the study (usually, if not specified otherwise by protocol):
  - all adverse events throughout the whole CT duration
  - after the participant´s last study visit:
    - up to 30 calendar days all SAEs
    - irrespective of the time of onset after the end of the study in case of SAE related to the research

RESPONSIBILITY of **SPONSOR**

Expedited reporting

For both clinical trials authorized under the **Clinical Trials Regulation** or **Clinical Trials Directive:**

SUSAR must be reported Immediately (without a delay) to EudraVigilance

- Within a max of 7 days upon first knowledge (+ 8 days for additional information) for SUSAR being life-threatening or leading to death
- Within a max of 15 days upon first knowledge - all other SUSAR

to ECs and investigators according to local regulatory requirements

- the other new important safety information ("Urgent Safety Restriction" or "Urgent Safety Measure") - immediate notification to CAs/ ECs / investigators

RESPONSIBILITY of **SPONSOR**

Periodic reporting

- **DSUR** (Development Safety Update Report)/**ASR** (Annual Safety Report) – annual review and evaluation of relevant safety information collected during the reporting period concerning IMP
  - ✓to CAs / ECs according to regulatory requirements – CTs under CTD
  - ✓To CTIS – CTs under CTR
- **SUSAR line listings –** to investigators (usually 6 monthly reports), for CTs under CTD according to local regulatory requirements
- **Investigator´s brochure** with RSI – yearly update and notification to CAs/ ECs/INV

RESPONSIBILITY of **SPONSOR (CTR vs. CTD rules applicable since 31.01.2022)**

For clinical trials authorized under the **Clinical Trials Regulation**:

Reporting to CTIS (Clinical Trials Information System):

- Unexpected events (other then SUSARs, e.g. an unexpected increase in the incidence of expected SAR)
- Urgent safety measures (measures taken to protect subjects due to an unexpected event that is likely to seriously affect the benefit-risk balance)
- Serious breaches (are likely to significantly affect the safety and rights of a subject or the reliability and robustness of the data generated in the CTs)
- Annual safety reports (yearly updates on the safety of IMPs)

For clinical trials authorized under the **Clinical Trials Directive**:

All other safety related information should be reported to the national CAs, ECs and investigators via national processes

Checking of understanding

During clinical trial, Investigator should report AE to Sponsor:

- ❑ Only if the event is related to the IMP
- ❑ Always (unless no exceptions specified by protocol)
- ❑ Just in case of serious adverse event

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Checking of understanding

What should investigator do in case CT participant experiences SAE:

- ❑ To report SAE to sponsor immediately (within 24 hours)
- ❑ In case the event is not related to the IMP it is not necessary to report it to the sponsor

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Checking of understanding

Which one of following events is SAE:

- ❑ death of CT participant
- ❑ any event related to IMP
- ❑ any event related to study procedure
- ❑ life-threatening event

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- ✓ life-threatening event

Checking of understanding

CT participant with a medical history of arterial hypertension experiences worsening of arterial hypertension which requires hospitalization. Will the investigator report this event?

- ❑ yes, as adverse event
- ❑ yes, as serious adverse event
- ❑ no reporting is necessary if the event is not related to the IMP

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Checking of understanding

CT participant who is administered IMP experiences significant increase of hepatic transaminases, however without clinical symptoms. Will the investigator report this event?

- ❑ yes
- ❑ no

Checking of understanding

CT participant who is administered IMP experiences significant increase of hepatic transaminases, however without clinical symptoms. Will the investigator report this event?

- ✓ yes (it is AE)
- ❑ no

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Thank you for your attention ☺

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