# Instruction: How to handle Adverse Events and Serious Adverse Events

ISF/ TMF section 19.1

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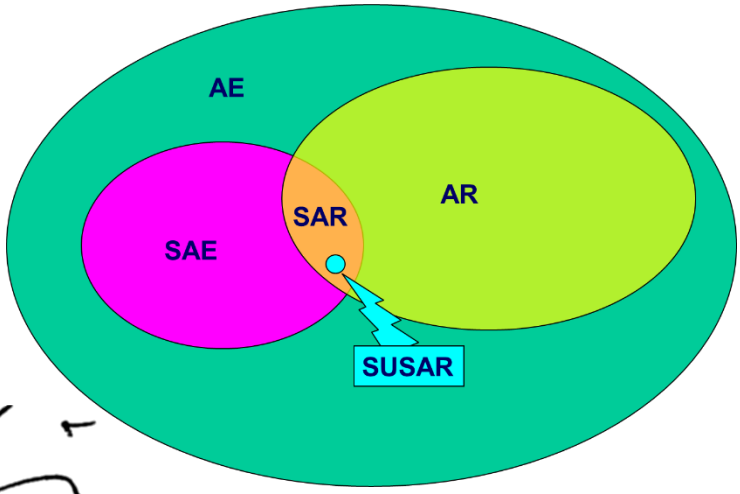



**AE** Adverse Event – any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with the treatment

**AESI** Adverse Event of Special Interest

**SAE** Serious Adverse Event – an untoward medical occurrence or effect that at any dose results in:

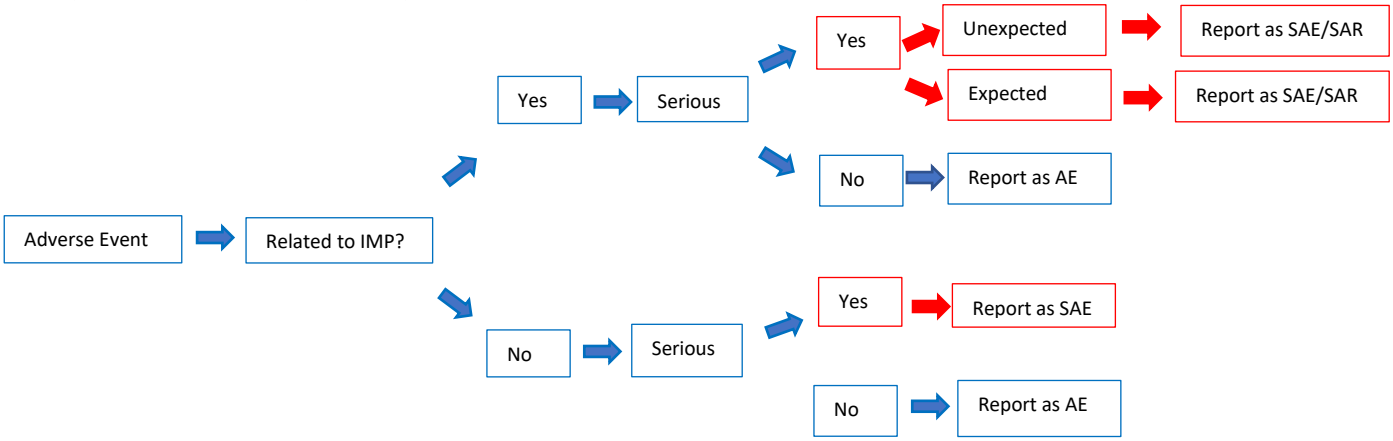
- death
- is life-threatening
- requires hospitalization or prolongation of existing hospitalization
- result in persistent or significant disability or is a congenital anomaly or birth defect
- is an important medical event

**AR** Adverse Reaction – any untoward and unintended response to an investigational medicinal product (IMP) related to any dose administered

**SAR** Serious Adverse Reaction are those AEs of which a reasonable causal relationship to any dose administered of the Investigational medicinal product, and fulfilling the above serious criteria

**SUSAR** Suspected Unexpected Serious Adverse Reaction are adverse reactions, of which the nature or severity is not consistent with the applicable product information (e.g. Investigators Brochure or Summary of Product Characteristics)

## The processes of reporting



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**Please be aware that the detailed information on how to complete of both Adverse Events and Serious Adverse Events are in the following sections of the REDCap e-CRF:**

- **Medical History (incl. infections)/Adverse Events**
- **Serious adverse event**

## Reporting of Adverse Event (AE)

The AE reporting period for this study begins as follows and ends 2 years after first dose of study drug:

| | |
|---|---|
| Treatment group: | When the subject receives the first dose of study drug = Cycle 1 Day 1 (C1D1) |
| Observation group: | Day similar to C1D1 |

Please be aware that only information about AE's **> grade 1** will be collected, unless the AE qualifies as an AESI or a SUSAR.

It is the responsibility of the Investigator to make the classification of the individual AE, i.e. Severity, Action taken and relationship to trial drug.
If access to REDCap is not available at the time the AE is detected the information and classification can be made on a paper copy, signed and dated by the Investigator. All data must as soon as access again is available, be entered in REDCap.

## Adverse Event of Special Interest (AESI)

The following Adverse Events are of special interest in this study and will actively be requested for:

- Atrial fibrillation
- Ventricular arrhythmias
- Tumor Lyses Events (TLS)
- Infections
- Disease progression
- Treatment for CLL
- Malignancies
- Bleeding events

***NB:*** ***Clinical TLS is an important medial event in this trial which must be reported as an SAE***

***All Grade ≥3 infectious events are considered AESIs to be reported along with SAEs within 24 h to sponsor in the phase 2 part***

## Reporting of Serious Adverse Events (SAE)

SAEs must be reported to the sponsor through the eCRF system, which automatically notifies the sponsor, **within 24 hours of awareness**.

Also, for these reports it is the responsibility of the Investigator to make the classification of the event.
If access to REDCap is not available at the time the SAE is detected the information and classification can be made on a paper copy, signed and dated by the Investigator. All data must as soon as access again is available, be entered in REDCap.

A detailed narrative must be included in the SAE report by the Investigator, additional information e.g. laboratory reports and source data may be added as attachments.

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**Reporting of Suspected Unexpected Serious Adverse Reaction (SUSAR)**
Should a SUSAR occur – this should also be reported via the eCRF system as an SAE, which automatically notifies the sponsor, **within 24 hours of awareness.**

The urgency in this kind of event is that the Sponsor must notify the Health Authorities within 7 days at the latest after awareness, if the event has been either fatal or life-threatening.
All other cases must be reported within 15 days at the latest to the Authorities by the Sponsor.

## Definitions for the grading of the severity (intensity) of AEs:

CTCAE (version 5 or higher) will be used, if the AE is not listed in the CTCAE, the following grading system should be used to assess severity:

***Grade 1 (Mild AE)*** *Experience which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities.* ***Not to be reported in this trial.***

**Grade 2 (Moderate AE)** Experience which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

**Grade 3 (Severe AE)** Experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment.

**Grade 4 (Life-threatening or disabling AE)**
Experiences which cause the subject to be in imminent danger of death.
hould always be reported as an SAE/SAR/SUSAR.

**Grade 5 (Death related to AE)**
Experiences which results in subject death.
Should always be reported as an SAE/SAR/SUSAR.