Transforming Clinical Trial Safety: Regulatory Expectations & Inspection Findings for Site Notifications for SUSARs

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US-FDA (United States Food and Drug Administration)

The sponsor must notify all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting as follows:

- **(c)(1)(i)**: Serious and unexpected suspected adverse reaction.
- **(c)(1)(ii)**: Findings from other studies (other than those reported under paragraph (c)(1)(i) whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- **(c)(1)(iii):** Findings from animal or in vitro testing: that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure
- **(c)(1)(iv):** Increased rate of occurrence of serious suspected adverse reactions.

HEALTH CANADA

- Sponsors should refer to ICH Guidance Documents E6: Guideline for Good Clinical Practice and E2A: Clinical Safety Data Management for safety reporting requirements to Qualified Investigator(s) and their Research Ethics Board(s).

- The reporting of SUSARs to investigator(s)/institutions(s) and to the IRB(s)/IEC(s) should be undertaken 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. Reporting of SUSARs to the investigators/institutions should be made in accordance with regulatory requirements.
- Urgent safety issues requiring immediate attention or action should be reported to the IRB/IEC and/or regulatory authority/(ies) and investigators without undue delay and as specified in regulatory requirements.
- Investigator Responsibility: Specifying that the investigator/institution should promptly report to the IRB/IEC:
  - deviations from the protocol to eliminate immediate hazards to the trial participants
  - changes increasing the risk to participants and/or significantly affecting the conduct of the trial
  - all suspected unexpected serious adverse reactions (SUSARs) in line with applicable regulatory requirements;
  - new information that may affect adversely the safety of the participants or the conduct of the trial.

European Medicines Agency

- Article 17(1)(d) of Directive 2001/20/EC provides that 'the sponsor shall also inform all investigators'. The information should be concise and practical. Therefore, whenever practicable the information on SUSARs should be aggregated in a line listing of SUSARs in periods as warranted by the nature of the research project/clinical development project and the volume of SUSARs generated. This line listing should be accompanied by a concise summary of the evolving safety profile of the IMP.
- Sponsor responsibilities: Reporting of suspected unexpected serious adverse reactions (SUSARs) to the Ethics Committee.
- The purpose of the reporting obligation towards the Ethics Committee is to make the Ethics Committee aware of SUSARs that have occurred in the territory of the Member State concerned

Medicines & Healthcare products Regulatory Agency

1. **SUSAR 7/15 Day Reports** Sponsor should report to the relevant ethics committee Fatal or Life Threatening SUSARs within 7 days and any other SUSARs within 15 days of first awareness of the reaction.
2. A sponsor shall ensure that, in relation to each clinical trial in the United Kingdom for which he is the sponsor, the investigators responsible for the conduct of a trial are informed of any suspected unexpected serious adverse reaction which occurs in relation to an investigational medicinal product used in that trial, whether that reaction occurs during the course of that trial or another trial for which the sponsor is responsible.
3. **Annual list of suspected serious adverse reactions and safety report** As soon as practicable after the end of the reporting year, a sponsor shall, in relation to each investigational medicinal product tested in clinical trials in the United Kingdom for which he is the sponsor furnish the licensing authority and the relevant ethics committees with a list of all the suspected serious adverse reactions which have occurred during that year and a report on the safety of the subjects of those trials.

Inspection Findings - USFDA

Program Area: Bioresearch Monitoring

- **2022:** Failure to provide all participating investigators with a written IND safety report
- **2017:** Failure to provide FDA and all participating investigators with an adequate written IND safety report

Challenges in Manual process of SUSAR Notifications

- Excel-based tracking prone to data integrity issues
- Maintenance of contact information on Excel prone to error
- Institutional policies block email delivery notifications
- Multiple emails for 1 SUSAR in case of multiple studies at a Site.
- Super busy Sites and Investigators do not respond.
- Lack of regulatory-compliant audit trails.

Selected References

1. 21CFR312.32 Investigational New Drug Application
2. ICH Guidance Documents E6: Guideline for Good Clinical Practice
3. E2A: Clinical Safety Data Management
4. EU CT-3 (2011/C 172/01)
5. REGULATION (EU) No 536/2014
6. The Medicines for Human Use (Clinical Trials) Regulations, 2004

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