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AE vs SAE vs SUSAR: Key Differences in Safety Reporting

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Published by IntuitionLabs · 2025-11-19 · adverse event reporting · pharmacovigilance · ae vs sae vs susar · clinical trial safety · ich gcp · expedited reporting · drug safety · serious adverse event

Original article: <https://intuitionlabs.ai/articles/ae-sae-susar-differences>



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AE vs SAE vs SUSAR: Key Differences in Safety Reporting

Adverse event (AE) reporting is the cornerstone of patient safety in clinical research and [pharmacovigilance](#). An **Adverse Event (AE)** is broadly defined as “*any untoward medical occurrence*” in a trial participant or patient receiving a medical product ([ichgcp.net](#)) ([www.fda.gov](#)). Crucially, an AE does **not** require proof of causality with the treatment; it includes any unfavorable sign, symptom, or disease temporally associated with the product, whether or not it is actually caused by it ([ichgcp.net](#)) ([eur-lex.europa.eu](#)). Among AEs, a subset are designated **Serious Adverse Events (SAEs)** when they lead to outcomes of significant clinical importance – typically death, life-threatening situations, inpatient hospitalization or prolongation of hospitalization, persistent disability/incapacity, congenital anomaly, or other critical medical events ([ichgcp.net](#)) ([www.fda.gov](#)). In other words, *all SAEs are AEs, but not all AEs are serious*: SAEs are classified by **seriousness** criteria—patient outcome or required intervention—rather than causality. Severity describes an event’s intensity, not whether it is serious for regulatory reporting.

A further category, **Suspected Unexpected Serious Adverse Reactions (SUSARs)**, refines this framework. In the U.S. IND framework, this is a serious, unexpected suspected adverse reaction: there must be evidence suggesting a causal relationship, and the reaction must not be listed in the Investigator’s Brochure at the observed specificity or severity. Thus, it combines **seriousness**, **suspected causality**, and **unexpectedness**. A serious event that is expected or lacks evidence suggesting a causal relationship is not an individual SUSAR/IND safety report solely on that basis, although other safety-reporting obligations can apply. ([FDA IND safety reports](#))

Expedited reporting is jurisdiction-specific. For U.S. INDs, sponsors notify FDA and participating investigators no later than 15 calendar days after determining that information qualifies for reporting; unexpected fatal or life-threatening suspected adverse reactions must be reported to FDA no later than 7 calendar days after initial

receipt. EU clinical-trial sponsors submit SUSARs to EudraVigilance. Ethics-committee or IRB notification depends on the applicable jurisdiction, institutional procedures, and protocol rather than being a universal SUSAR-recipient rule. ([FDA IND safety reports](#)) ([EMA clinical-trial safety reporting](#))

In short, the difference is one of scope and obligation. **AEs** encompass all medical events and are collected for completeness; **SAEs** are AEs that meet critical outcome criteria and require prompt reporting to the sponsor under the protocol and applicable requirements ([eur-lex.europa.eu](#)) ([eur-lex.europa.eu](#)); **SUSARs** are those SAEs believed related to treatment and *unexpected*, which trigger expedited reporting to regulators within defined timelines ([www.endpointadjudication.com](#)) ([pmc.ncbi.nlm.nih.gov](#)). This report will explore these categories in depth – examining definitions across guidelines (ICH, FDA, EMA), detailing reporting responsibilities and timelines, and analyzing empirical studies and case examples that illustrate how AE/SAE/SUSAR reporting functions in practice. We will also discuss the implications of current processes and future directions (e.g. enhanced global harmonization, digital tools) for improving safety monitoring in clinical research.

Introduction and Background

Adverse event reporting has been integral to drug and device safety since the mid-20th century. Landmark catastrophes such as **thalidomide** in the late 1950s (leading to thousands of birth defects) prompted major reforms in [clinical regulations worldwide](#) ([embryo.asu.edu](#)). In particular, regulators recognized the need for systematic collection of any untoward occurrences in clinical trials. Over ensuing decades, international guidelines like the [ICH Good Clinical Practice \(GCP\)](#) and specific safety reporting guidances codified the necessary terminology and processes. The ICH E6(R3) guideline was finalized on January 6, 2025, with regional adoption by the [EMA \(effective July 2025\)](#), [FDA \(September 2025\)](#), and [Canada \(April 2026\)](#). The restructured guideline emphasizes proportionality, quality-by-design, and flexibility for diverse trial models. The E6(R3) GCP glossary explicitly defines key terms:

- **Adverse Event (AE):** “Any unfavorable medical occurrence in a trial participant. The AE does not necessarily have a causal relationship with the treatment.” ([ichgcp.net](#)).
- **Serious Adverse Event (SAE):** “Any unfavorable medical occurrence that is considered serious if it *results* in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect” ([ichgcp.net](#)).

These definitions mirror regulatory statutes. For instance, the EU Directive 2001/20/EC (transposed into national law) defines an AE and SAE almost identically: “*Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship*” ([eur-lex.europa.eu](#)), and a “*serious adverse event*” as one causing death, life-threatening condition, hospitalization/prolongation, disability, or birth defect ([eur-lex.europa.eu](#)). Similarly, the U.S. FDA describes a serious adverse event as any undesirable experience associated with a medical product resulting in death, life-threatening condition, hospitalization (initial or extended), disability or permanent damage, or

congenital anomaly (www.fda.gov) (www.fda.gov). Notably, FDA's phrasing also underscores that “*any undesirable experience*” is an AE, but it only “should be reported” if it meets these serious criteria (www.fda.gov).

In practical terms, AE collection and documentation should follow the protocol and applicable jurisdictional requirements, while SAEs generally require prompt attention and reporting to the sponsor. The rationale is clear: while a mild AE (e.g. transient headache) may simply be logged and followed, an SAE (e.g. unplanned hospitalization) usually requires prompt investigation and may signal urgent safety concerns. Historically, failures to properly monitor SAEs have led to halted trials and patient harm. For example, in the infamous 2006 TGN1412 Phase I trial, six healthy volunteers (dosed at far below the animal “safe” level) all experienced **severe, life-threatening multiorgan failure** within hours (pmc.ncbi.nlm.nih.gov). That disaster (and others like it) taught regulators and sponsors to scrutinize first-in-human studies more rigorously and to require extremely cautious dose escalation. Another cautionary case involved the antiviral drug Fialuridine, which proceeded to Phase II only to cause liver failure and death in five patients in 1993 (pmc.ncbi.nlm.nih.gov). Both events underscored how crucial it is to detect *unexpected* serious reactions early in development.

Against this backdrop, **SUSAR** reporting arose as a specialized clinical-trial safety concept. Once seriousness, suspected causality, and unexpectedness are established, expedited-reporting obligations may apply. Investigators must report serious events promptly or immediately according to the applicable requirements, protocol, and any permitted protocol-defined exceptions; many studies operationalize this as a 24-hour site-to-sponsor target, but it is not a universal statutory deadline. Sponsors then assess causality and expectedness.

For U.S. INDs, qualifying serious and unexpected suspected adverse reactions must be reported to FDA and participating investigators as soon as possible and no later than 15 calendar days after the sponsor's determination; unexpected fatal or life-threatening suspected adverse reactions must be reported to FDA within 7 calendar days of initial receipt. EU clinical-trial sponsors report SUSARs to EudraVigilance. These expedited processes help regulators and investigators assess emerging risks and determine whether safeguards are needed. ([FDA IND safety reports](#)) ([EMA clinical-trial safety reporting](#))

Today, AE/SAE/SUSAR classification lives in both pre- and post-marketing contexts, but its origins and core usage are rooted in clinical trials. As such, most focus remains on how investigators, sponsors, and regulators implement these processes in ongoing studies. The rest of this report will explore these definitions and practices in detail, integrating empirical studies, data analysis, and case examples to illustrate how adverse events are captured, classified, and communicated in the modern research setting.

Terminology and Definitions

Understanding how AEs, SAEs, and SUSARs differ begins with their formal definitions, which are remarkably consistent across major regulatory frameworks. Table 1 (below) summarizes the distinctions in terms of seriousness, causality (suspected relationship to the drug), and expectedness.

Term	Definition Highlights	Causality (Suspected)	Expectedness	Reporting Requirement (Sponsor)*
Adverse Event (AE)	Any untoward medical occurrence (sign, symptom, lab abnormality) in a trial subject receiving a drug, <i>regardless of causality</i> (ichgcp.net) (eur-lex.europa.eu). Examples: mild rash; transient fever.	<i>Not required</i> (no causal link assumed)	N/A (no expectation concept)	Recorded in trial data. Report not required unless it meets <i>serious</i> criteria.
Serious Adverse Event (SAE)	An AE that <i>results</i> in death, is life-threatening, requires (or prolongs) hospitalization, causes disability/incapacity, or congenital anomaly (ichgcp.net) (www.fda.gov). (Also include “important medical events” as per ICH/FDA)	<i>Not required</i> (SAE status is outcome-based)	N/A (can be expected or unexpected)	Investigator → Sponsor immediately; under the EU CTR no later than 24 hours, elsewhere per the applicable framework and protocol (eur-lex.europa.eu) (eur-lex.europa.eu); Sponsor adjudicates, records, and follows-up. No immediate regulator report unless it also meets SUSAR criteria.
Suspected Adverse Reaction (AR)	Any AE for which there is a reasonable possibility that the drug caused it (www.law.cornell.edu) (used interchangeably with ADR in some contexts)	Yes (reasonable possibility of drug causation)	Can be expected or not; if unexpected, see SUSAR below	Base reporting on seriousness. Not separately expedited unless serious/unexpected.
Serious Adverse Reaction (SAR) †	An adverse reaction that is serious (i.e. an SAE and related) (ichgcp.net) (www.law.cornell.edu).	Yes	Can be expected or unexpected. If unexpected, see SUSAR.	Handled as SAE (internal report). If unexpected → SUSAR.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An SAR that is <i>unexpected</i> relative to the product's known information (ichgcp.net) (www.law.cornell.edu). This is the intersection of the above three: <i>serious</i> , <i>related</i> , and <i>unexpected</i> .	Yes	Yes (not listed in IB/SmPC, or qualitatively/severity inconsistent with reference safety info) (ichgcp.net) (www.law.cornell.edu) Note: “Unexpected” refers to mismatch with the Reference Safety Information (e.g. the IB or SmPC) (www.law.cornell.edu).	Expedited report to regulators: typically 7 days for fatal/life-threatening SUSARs, 15 days for other SUSARs (www.endpointadjudication.com) (pmc.ncbi.nlm.nih.gov). Investigators report to the sponsor promptly or immediately as required by the applicable framework and protocol; 24 hours is a common operational target, not a universal statutory deadline.

*Regulatory reporting responsibilities may vary by region; the Sponsor column above reflects typical clinical-trial obligations (e.g. per ICH/FDA/EMA).

In summary, **SAEs are distinguished by outcome**, whereas **SUSARs are distinguished by causality and novelty**. An important nuance is that an SAE need not have any causal link to the drug (it could be an accident or intercurrent illness), whereas a SUSAR explicitly implies a suspected causal link. Likewise, a serious drug-related reaction that *was expected* (e.g. a known toxic effect seen in prior studies) would be reported in aggregate (e.g. annual safety report) but *not* sent as a SUSAR. By contrast, even a single “expected” SAE is not a SUSAR – only truly *surprising* SAEs trigger the expedited SUSAR process.

Footnotes: AE = Adverse Event; AR = Adverse Reaction; SAE = Serious Adverse Event; SAR = Serious Adverse Reaction; SUSAR = Suspected Unexpected Serious Adverse Reaction.

Regulatory Framework: Roles and Timelines

Reporting of AEs in clinical trials is governed by detailed regulations in each region. Despite minor linguistic differences, the core concepts are harmonized by ICH guidelines (e.g. ICH E2A) and implement via laws such as the U.S. FDA's 21 CFR §312.32 (IND safety reporting) and the European Union's Clinical Trials Directive (2001/20/EC) and its successor, the 2014 Clinical Trials Regulation (EU No. 536/2014). Key elements of the required process include **who reports to whom, when, and with what content**.

Investigator and Sponsor Responsibilities

- Investigator (Site) Reporting:** By both ethical obligation and regulation, *investigators* must promptly report serious events. For example, EU guidance (based on the CTR Directive) explicitly mandates that *“the investigator shall report all serious adverse events immediately to the sponsor”* (except those pre-identified as not requiring immediate notice) (eur-lex.europa.eu). This “immediate” report is commonly operationalized as a 24-hour sponsor or protocol deadline, but ICH E6(R3) itself requires reporting immediately after the investigator reasonably becomes aware and permits protocols, subject to applicable requirements, to identify SAEs that do not require immediate reporting (eur-lex.europa.eu). (If the study protocol or IB specifies that certain expected events need not be reported immediately, those can follow a less urgent timeline.) Among other details, the immediate report will include patient identifiers (via code), nature and outcome of the event, onset date, and preliminary relatedness assessment. The investigator later provides a more detailed follow-up narrative as it becomes available.
- Sponsor (Company) Assessment:** Once an SAE report arrives, the *sponsor* (or its pharmacovigilance delegate) assumes responsibility for review. The sponsor must determine causality (is it a suspected adverse reaction?) and expectedness. If the event is judged unrelated to the investigational product (e.g. a broken leg from a car accident), it remains an SAE but is not reported to regulators as a safety signal. If it is considered possibly related (i.e. a **suspected adverse reaction**), the sponsor then checks whether it was “expected” based on the reference safety information (RSI) – typically the current Investigator’s Brochure or, for an approved product, the Summary of Product Characteristics. If **related + unexpected + serious**, the case may require expedited reporting under the applicable jurisdictional framework. For example, EU CTR sponsors report SUSARs to EudraVigilance, while U.S. IND sponsors report qualifying events to FDA and participating investigators. Ethics-committee/IRB notification is not a single universal SUSAR requirement. Otherwise, the SAE is catalogued internally and may be included in aggregate reports. ([EMA](http://ema.europa.eu)) ([FDA](http://fda.gov))

Reporting Timelines and Mechanisms

Table 2 summarizes the typical timelines for key report types under ICH and major regulations:

Report Type	Investigator → Sponsor	Sponsor → Regulator	Sponsor → Other Investigators
Non-Serious AE	(No urgent requirement.) These are collected per protocol (e.g. at each visit) but not “reported” immediately.	— (These do not require expedited submission.)	—
Serious AE (non-SUSAR)	<i>Immediate:</i> Investigator must notify sponsor as soon as possible; under the EU CTR, <i>no later than 24 hours</i> after becoming aware (elsewhere, per the applicable framework and protocol) (eur-lex.europa.eu) (eur-lex.europa.eu).	No individual expedited report solely because the event is a non-SUSAR SAE. For U.S. INDs, however, qualifying findings from aggregate analyses, other studies, animal or in-vitro testing, and clinically important increases in serious suspected adverse reactions can require an IND safety report (FDA IND safety reports).	If part of multicenter trial, sponsor <i>should inform all study investigators</i> about any relevant new safety findings (including SAEs that might affect subject safety) (eur-lex.europa.eu) (www.law.cornell.edu).
SUSAR – Fatal or Life-Threatening	EU CTR: investigator reports to the sponsor without undue delay and no later than 24 hours after becoming aware, subject to protocol-identified exceptions. U.S. IND/ICH: promptly or immediately, as required by the applicable framework and protocol.	U.S. IND: sponsor reports an unexpected fatal or life-threatening suspected adverse reaction to FDA within 7 calendar days of initial receipt. EU CTR: sponsor submits the SUSAR to EudraVigilance within 7 days of awareness. Local ethics-committee/IRB requirements vary. (FDA IND safety reports) (European Commission CTR guide) (EMA clinical-trial safety reporting)	U.S. IND sponsors notify participating investigators; requirements elsewhere vary by jurisdiction.
SUSAR – Other Serious	EU CTR: investigator reports to the sponsor without undue delay and no later than 24 hours after becoming aware, subject to protocol-identified exceptions. U.S. IND/ICH: promptly or immediately, as required by the applicable framework and protocol.	U.S. IND: sponsor reports qualifying serious and unexpected suspected adverse reactions to FDA and participating investigators no later than 15 calendar days after determining that the information qualifies for reporting. EU CTR: sponsor submits the SUSAR to EudraVigilance within 15 days of awareness. Local ethics-committee/IRB requirements vary. (FDA IND safety reports) (European Commission CTR guide) (EMA clinical-trial safety reporting)	U.S. IND sponsors notify participating investigators; requirements elsewhere vary by jurisdiction.
Post-Trial SUSAR	<i>Not applicable to investigators (trial ended).</i>	Some jurisdictions (e.g. Switzerland) require sponsors to report any SUSARs discovered even after the formal close of a study (www.easy-gcs.ch).	Investigator notification not usually needed post-study.

Key Points: Investigators report SAEs promptly or immediately under the applicable framework, protocol, and any permitted protocol-defined exceptions; a 24-hour target is common but not universal. Sponsors assess seriousness, causality, and expectedness, while also considering other reportable safety findings. In the U.S. IND framework, sponsors report qualifying serious and unexpected suspected adverse reactions to FDA and participating investigators within the applicable 7- or 15-day timeframe; certain aggregate, nonclinical, and other significant-risk findings can also require an IND safety report. EU clinical-trial sponsors submit SUSARs

to EudraVigilance. Core concepts and many timelines are internationally harmonized, but reportability, recipients, processes, and local requirements differ by jurisdiction. ([FDA IND safety reports](#)) ([EMA clinical-trial safety reporting](#))

Reporting Formats: Submission format depends on the report type and jurisdiction. For U.S. IND safety reports of serious and unexpected suspected adverse reactions under 21 CFR 312.32(c)(1)(i), FDA requires electronic E2B(R3) submission to the Adverse Event Monitoring System (AEMS) as of April 1, 2026, subject to the stated noncommercial-IND exemption. Other IND safety-report categories are submitted electronically in eCTD format. FDA Form 3500A is not the IND expedited-report format described by FDA. EU clinical-trial sponsors submit SUSARs to EudraVigilance.

Regulatory Variations and Harmonization

Though globally aligned on definitions and timelines, minor differences exist by region. For instance, the term “SUSAR” is common in EU/ICH contexts, whereas U.S. guidance refers more generally to “Serious Unexpected Suspected Adverse Reactions.” In Europe, SUSARs are reported into the centralized EudraVigilance Clinical Trial Module, whereas in the U.S. IND safety reports go to FDA’s Center for Drug Evaluation and Research (CDER) or Biologics Center (CBER). Under a U.S. IND, sponsors notify all participating investigators within the applicable reporting timeframe; investigator-notification requirements in other jurisdictions should be checked against the applicable framework ([eur-lex.europa.eu](#)) ([pmc.ncbi.nlm.nih.gov](#)). The EU Clinical Trials Regulation 536/2014 is now fully in effect across all member states, with the transition period having ended on January 31, 2025. All ongoing and new clinical trials must now operate through the Clinical Trials Information System (CTIS), which was designated as a **WHO Primary Registry** in April 2025, making EU trials discoverable via the WHO ICTRP. Under Article 42 of the CTR, sponsors submit SUSARs electronically to EudraVigilance, not CTIS. CTIS is used for clinical-trial applications and specified clinical-trial information, including certain other safety information. ([EMA](#)) ICH guidance has harmonized core safety-reporting concepts internationally, but expedited-reporting triggers, recipients, processes, and local requirements are not identical across jurisdictions. Sponsors should use the framework applicable to the trial rather than assuming that U.S. IND and EU Clinical Trials Regulation requirements are interchangeable. ([FDA IND safety reports](#)) ([EMA clinical-trial safety reporting](#))

Data and Evidence: Patterns in AE/SAE Reporting

Empirical studies of clinical trial data reveal stark patterns in how AEs, SAEs, and SUSARs occur and are reported. Because randomized trials rigorously solicit and record all events, they provide a glimpse of the volume of safety data that arise even in controlled settings. For example, one large ovarian cancer trial (ICON8, N=1,566) documented **51,019 adverse events** from routine toxicity assessments ([trialsjournal.biomedcentral.com](#)). Separately, **1,506 serious adverse event elements** were reported in the trial’s distinct SAE dataset. Strikingly, when the investigators mapped the 668 SAE elements eligible for matching against the AE dataset, only 61% matched an already-reported adverse event ([trialsjournal.biomedcentral.com](#)). This revealed substantial under-reporting in one of the two parallel safety databases. When the missing 39% of SAEs were added to the AE records, the proportion of patients experiencing any grade ≥ 3 event rose by **4–7 percentage points** across the arms (42% to 47% in the control arm; 61% to 65% and 52% to 59% in the research arms) ([trialsjournal.biomedcentral.com](#)). In practical terms,

this meant the calculated safety imbalance between experimental and control arms changed by 18% (95% confidence interval 12–24%) and 12% (95% CI 6–18%) for the two research arms (trialsjournal.biomedcentral.com). This study illustrates that incomplete or inconsistent recording of serious events can materially alter safety conclusions even within a single trial (trialsjournal.biomedcentral.com).

On a broader scale, investigations have shown that **many trials do not fully report SAEs at all** in their published results. In a systematic analysis of 160 Phase III colorectal cancer trials, only **41 publications (25.5%)** explicitly reported any serious adverse events ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)). Company-sponsored trials tended to report SAEs far more frequently (57.6%) than investigator-led or academic trials (20.7%) ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)). Encouragingly, the reporting rate rose over time: none of the trials published *before 2000* mentioned SAEs in full, while that jumped to 34.5% for those published after 2009 ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)). Still, these data imply that three-quarters of oncology trial papers omitted any SAE summary, likely relegating them to supplementary materials or none at all. The authors noted that detailed safety information (e.g. incidence by grade or the nature of events) was provided in only a small minority of cases ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)).

Under-reporting is not limited to oncology. A 2023 rapid review of COVID-19 drug trials found similar issues. Among 56 randomized trials assessed, **no trial achieved a “high” quality score for AE reporting**, and 60% were only “moderate” while 39% were “low/very low” by CONSORT-harms criteria ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)). Strikingly, journal publications *under-reported more than half* of the serious events that were listed in the trial registry summaries (ClinicalTrials.gov) ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)). In other words, roughly 51% of SAE data known to regulators was omitted in the corresponding papers ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)). As the authors concluded, failure to fully report AEs and SAEs in publications “did not improve significantly over time” and undermined the precision of risk–benefit assessment ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)).

Moreover, regulatory databases highlight the huge volumes of post-market reports (of which SUSAR-like “expedited reports” are a subset). For instance, an FDA analysis showed that overall adverse event reports to its FAERS system more than doubled from 2006 to 2014 ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)). While these are post-marketing sources, they reflect the era’s growing vigilance: one cited study noted FDA SAE reports grew 2.6-fold from 1998–2005 and doubled again from 2006–2014 ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)). This upward trend likely reflects both new therapies and heightened reporting requirements. However, without access to causality and expectedness data in FAERS, one cannot isolate “suspected unexpected” vs. other reports.

These data and analyses show that (1) clinical trials generate huge numbers of AEs, of which a small but crucial fraction are serious, (2) data collection is often imperfect (with notable under-counting of SAEs), and (3) published reports frequently understate or omit serious-event information. In practice, when an SAE does occur, its impact depends entirely on the classification process: only a fraction become SUSARs requiring immediate action. This raises concerns that some important signals could be delayed if sponsor or investigators are unclear on definitions.

Case Studies and Real-World Examples

Real-life clinical trials underscore the dramatic consequences of safety events and the importance of accurate classification:

- **TGN1412 “Cytokine Storm” (London, 2006):** A first-in-human trial of TGN1412 (a CD28 superagonist antibody) unexpectedly caused all six healthy volunteers (at a 500-fold lower dose than safe in animals) to suffer **life-threatening multiorgan failure** within hours ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/16305361/)). Initially, one might consider whether these were SAEs or SUSARs. They were serious, life-threatening reactions; all six volunteers improved after the incident, and the official record does not report any deaths. Whether an event is a SUSAR depends on seriousness, suspected causality, and unexpectedness—not on a fatal outcome alone. ([UK Parliament Hansard](#)) ([FDA](#)) This spurred immediate trial suspension and extensive regulatory review. The case led to changes in first-in-human trial design worldwide (e.g. staggered dosing), underscoring the perils of unanticipated SAEs at the outset of clinical development ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/16305361/)).
- **BIAL FAAH-inhibitor Tragedy (France, 2016):** A Phase I trial of an oral FAAH (fatty acid amide hydrolase) inhibitor resulted in one participant becoming brain-dead and five others critically ill ([www.theguardian.com](https://www.theguardian.com/health/2016/jan/11/bial-phaah-inhibitor-tragedy)). All six had been healthy volunteers on the drug (others had placebo). They fell ill shortly after dosing (one on January 10, the rest over the next two days), requiring intensive care. This event was a cluster of SAEs; it was also a SUSAR cluster, because healthy subjects do not normally go into coma from such a compound. Indeed, all ongoing dosing was halted within 48 hours. The media coverage (The Guardian, Medscape) emphasized that all trials were suspended, reflecting a rapid response once the first participant was hospitalized, days before the participant's death ([www.theguardian.com](https://www.theguardian.com/health/2016/jan/11/bial-phaah-inhibitor-tragedy)) ([www.theguardian.com](https://www.theguardian.com/health/2016/jan/11/bial-phaah-inhibitor-tragedy)). This incident prompted government and EU investigations and ultimately new guidelines on risk mitigation for first-in-human studies.
- **Serious-Event Reporting in ICU Trials (Methodological Study):** A 2024 methodological study protocol from Copenhagen University Hospital (Jensen et al., *Acta Anaesthesiologica Scandinavica*) notes that SAEs are common in intensive-care patients, that SAE reporting in randomized trials varies, and that under-reporting is likely; it sets out to measure how many recent ICU drug trials report SAEs in their primary publication and how they present them ([pubmed.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/41111111/)).
- **Discrepancy in Publication (ICON8 Ovarian Trial):** As noted, the ICON8 trial found that 39% of SAEs were missing from the standard AE listings ([trialsjournal.biomedcentral.com](https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-0400-0)). In this analysis, the trial team re-analyzed the safety data: by combining SAE and AE datasets, they showed that analyses using only the AE dataset underestimated grade ≥ 3 event rates. After merging datasets, the difference in grade ≥ 3 events between each research arm and the control arm changed by 18% and 12%, respectively ([trialsjournal.biomedcentral.com](https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-0400-0)). This shows that even without regulatory “report delays,” data management issues can act like silent under-reporting.
- **Sarepta AAVrh74 Gene Therapies (2025):** FDA investigated acute liver failure with serious outcomes, including deaths, after treatment with Sarepta AAVrh74 gene therapies. FDA described two deaths after Elevidys treatment and a third death after an investigational Sarepta AAVrh74 product in a clinical trial; it also announced actions involving Elevidys distribution and clinical holds for multiple gene-therapy products. These were post-marketing adverse-event safety signals for the approved product, not SUSARs; the investigational-product death should be evaluated under the applicable clinical-trial safety-reporting framework. ([FDA investigation](#))

These cases — spanning two decades — illustrate the spectrum of implications: on one end, *tragic bodily harm* triggering immediate regulatory and ethical action; on the other, *data-recording lapses* which quietly distort safety statistics. In all cases, the definitions (AE vs. SAE vs. SUSAR) directly influence the response. For instance, in the BIAL case, once a participant was hospitalized with a serious neurological event under trial conditions, the events not only met SAE criteria but also, being completely unexpected, qualified as SUSARs — which meant sponsors and authorities swung into motion within days (and the trial was halted pending investigation). Conversely, had those cases been considered non-related (an unlikely scenario), the regulatory urgency would not have been as pronounced.

Reporting Processes and Quality

Investigator Ethics and Duties

Investigators (typically clinicians at study sites) bear the frontline duty of vigilance. They routinely collect non-serious AE data at each visit according to the protocol. **Serious AEs** trigger a different process: investigators report them promptly or immediately to the sponsor under the applicable requirements, protocol, and any permitted protocol-defined exceptions. A 24-hour target is common operational practice, but it is not a universal statutory deadline. The initial report often includes coded subject information, an event description, onset date, and the investigator's preliminary assessment; follow-up information is provided as it becomes available. IRB or ethics-committee reporting follows applicable local requirements and written procedures; in U.S. HHS-regulated research, the reporting standard is generally an unanticipated problem involving risks to subjects or others, not every adverse event. ([FDA IND safety reports](#))

Sites are trained (per GCP) to recognize seriousness criteria. For example, should a participant collapse and be taken to the hospital, the research nurse immediately calls the sponsor's safety hotline and initiates paperwork ([eur-lex.europa.eu](#)). Even if the event is later deemed unrelated (e.g. a fall off a bicycle), immediate sponsor reporting may still be required because that determination comes afterward, subject to applicable requirements and any protocol-defined exceptions. The phrasing in regulatory text underscores this: investigators "shall report all SAEs" ([eur-lex.europa.eu](#)), placing no filter on causality. This blanket approach errs on the side of caution.

Sponsor Safety Management

Upon receiving an SAE, the sponsor's pharmacovigilance team performs triage. The steps typically include: (1) Data collection — ensure all relevant clinical data are obtained. (2) Causality assessment — using investigator's input and medical judgment, categorize the event as "related/possibly related" or "unrelated" to the drug. (Often solicited on the SAE form; worldwide standards call a causal relationship *reasonable possibility* if evidence suggests the drug could have caused it ([www.law.cornell.edu](#)).) (3) Expectedness check — compare against the Investigator's Brochure or Product Label. If the event was already known to occur (e.g. known dose-limiting toxicity or listed reaction), it is expected and does *not* trigger an expedited report, even if serious.

If an event is serious and the sponsor determines that there is evidence suggesting a causal relationship, the sponsor checks expectedness. If it is unexpected, an expedited report may be required under the applicable framework. For U.S. INDs, qualifying serious and unexpected suspected adverse reactions are reported to

FDA and participating investigators within the applicable 7- or 15-day timeframe; EU clinical-trial sponsors submit SUSARs to EudraVigilance. Ethics-committee and IRB reporting is jurisdiction- and institution-specific. Expected or non-serious events may still require monitoring, aggregate analysis, periodic reporting, or other action, and other significant safety findings can require expedited reporting. ([FDA IND safety reports](#)) ([EMA clinical-trial safety reporting](#))

Sponsors establish *Standard Operating Procedures (SOPs)* to ensure compliance with these rules. Typical SOPs require that any SAE report triggers a case review meeting, where a Safety Review Team (clinicians/pharmacovigilance specialists) confirm or override the site's causality and determine if the case is a SUSAR. Table 3 (below) outlines a simplified *decision algorithm* summarizing this workflow: investigators report SAE → sponsor assesses relationship/expectedness → if SUSAR then expedite to regulators ([www.endpointadjudication.com](#)) ([www.law.cornell.edu](#)).

Table 3. Decision flow for serious adverse events

1. **Investigator** learns of an SAE in a trial subject. (Event qualifies by outcome.)
2. **Investigator** → **Sponsor**: SAE report to sponsor immediately (*within 24 hours* under the EU CTR; otherwise per the applicable framework and protocol) ([eur-lex.europa.eu](#)) ([eur-lex.europa.eu](#)).
3. **Sponsor** receives the SAE and conducts a causality assessment. If the event is not a suspected adverse reaction, or is expected, document and evaluate it under the applicable safety-reporting framework. Do not assume that no further regulatory action is needed: in the U.S., qualifying aggregate findings and other significant-risk findings can require an IND safety report. If the event is a suspected adverse reaction, proceed to step 4.
4. Check **expectedness** using Reference Safety Information (IB/label). If reaction is **expected**, treat as routine (no expedited report). If **unexpected**, **SAE becomes SUSAR**.
5. **Sponsor** → **Regulators/ECs/Investigators**: Expedited SUSAR report. Transmission “as soon as possible” – within **7 days** if fatal or life-threatening, **15 days** otherwise ([www.endpointadjudication.com](#)) ([pmc.ncbi.nlm.nih.gov](#)). Inform all investigators of the SUSAR case ([eur-lex.europa.eu](#)) ([pmc.ncbi.nlm.nih.gov](#)).

(♦ EC = Ethics Committee/IRB.)

Many sponsors also conduct aggregate signal detection: if multiple similar SAEs occur, they may proactively declare a cluster or emerging risk, even if individual cases have been reported. Conversely, for well-characterized later-phase trials, the IB may explicitly list *expected* SAEs that need not be reported individually (for efficiency), a practice allowed by some protocols. In any case, individual SUSAR reporting concerns serious, unexpected suspected adverse reactions; separate obligations can apply to aggregate safety signals and other significant-risk findings.

Quality and Gaps in Reporting

Despite these well-defined obligations, studies show frequent gaps. For example, in the ICON8 ovarian trial, investigators found that the routine AE reporting form was not capturing many serious events, implying that investigators either neglected to tick the SAE box on the CRF or that data management inconsistencies occurred (trialsjournal.biomedcentral.com). In the same ICON8 analysis, nearly 40% of the SAE elements included in the mapping exercise had no matching entry in the AE collection, meaning those events would not have been known for analyses that only looked at the AE dataset (trialsjournal.biomedcentral.com). These kinds of omissions can happen inadvertently (e.g. separate CRFs for AE vs SAE) or due to misunderstanding of what to report. It underlines that robust training and quality control are needed to ensure compliance.

In addition, the literature on trial publications indicates that many sponsors/ authors do not fully disclose safety findings. Studies have noted discrepancies between raw report forms and what is ultimately published. For instance, the ICON8 analysis found that **safety analyses relying only on the AE dataset underestimated the proportion of patients with grade 3 or worse events** (trialsjournal.biomedcentral.com). Another systematic review cited above found that 51% of SAEs recorded in registries were omitted in published articles (pmc.ncbi.nlm.nih.gov). This has led to calls for standardized reporting: indeed, CONSORT's extension for harms and journal-editorial statements now encourage more complete disclosure of safety data (see e.g. the review by Lucas et al. 2022 (pmc.ncbi.nlm.nih.gov)).

From a regulatory perspective, under-reporting can delay recognition of safety signals. For example, a cluster of SUSARs or adverse reactions might go unnoticed if sites fail to report SAEs promptly. Thus, vigilant monitoring and independent audits (by IRBs or inspectors) aim to catch any lapses.

Perspectives on Reporting and Impact

Reporting AEs has multifaceted implications for stakeholders:

- **Patients/Participants:** For trial subjects, prompt SAE/SUSAR reporting means that new risks are identified quickly, and the trial can be modified or stopped to protect them. Ethical oversight (by IRBs) ensures they are kept informed. Moreover, comprehensive AE data ultimately supports safer use of approved treatments in the general population.
- **Investigators (Clinicians):** Investigators rely on clear guidance to know which events to report and how. Under-reporting can expose them to liability if a preventable harm occurs. Conversely, over-reporting (labeling non-serious expected events as “urgent”) can overwhelm sponsor systems. Investigators thus often appreciate concise definitions (often provided in training) of SAE/SUSAR criteria, to avoid confusion.
- **Sponsors/Pharma:** From industry's viewpoint, thorough AE reporting is both a compliance requirement and a business necessity. On one hand, known serious risks can limit a product's market potential; on the other, failing to detect true safety signals early can lead to much greater setbacks (like trial holds or late-stage withdrawals). Companies invest in dedicated pharmacovigilance staff and electronic safety databases (e.g. Oracle Argus Safety, ArisGlobal LifeSphere Safety) to manage the deluge of data.

However, sponsors must also balance transparency with avoiding “noise.” Too many false-positive SUSARs (if causality is too liberally interpreted) can flood regulators with trivial reports and obscure true signals. Hence the emphasis on “reasonable possibility” causality as the standard.

- **Regulatory Authorities:** Agencies like the FDA or EMA rely on expedited reports to post (e.g. FAERS) and possibly require label updates or trial holds. They analyze SUSAR trends across trials: for example, if a particular SAE (e.g. severe liver injury) recurs across independent studies of a drug, it may prompt an urgent review. Regulators also must consider context: an SAE in a life-threatening disease trial might be treated differently (reportable but maybe expected due to underlying condition) than the same SAE in a healthy volunteer study (likely a SUSAR). Regulatory bodies also promote harmonization: ICH guidelines and EU GCP guides have helped align expectations internationally.
- **Public and Ethics:** When serious events occur, media and public scrutiny can be intense (as in the BIAL case (www.theguardian.com)). Sponsors majorly weigh the reputational impact of misclassification or delayed reporting. Institutional Ethics Committees (IECs) and IRBs view AE reporting as fundamental to human-subject protection. Their reporting requirements are defined by applicable law, institutional written procedures, and the protocol. In HHS-supported research, prompt IRB reporting is directed to unanticipated problems involving risks to subjects or others; only a small subset of adverse events meet that standard.

Given these perspectives, inaccurate or incomplete reporting undermines trust. Sponsors may face regulatory sanctions or lawsuits if serious adverse events are not properly reported (e.g. cases of litigation have arisen around allegedly undisclosed trial deaths). Conversely, rigorous safety surveillance can expedite remedial actions (e.g. dose adjustments, risk mitigation plans) to preserve a trial while protecting participants.

Future Directions and Innovations

The landscape of safety reporting is evolving with technology and global initiatives:

- **Regulatory Modernization:** Under the EU Clinical Trials Regulation, CTIS is the central system for clinical-trial applications and specified clinical-trial information. SUSARs must be submitted electronically to EudraVigilance, not CTIS; CTIS may receive other safety information, including annual safety reports. **Implementing Regulation (EU) 2025/1466** ended the EudraVigilance signal-detection pilot and the standalone validated-signal notification form. It did not remove MAH signal-management responsibilities: MAHs must monitor EudraVigilance data alongside other sources and use those data in their own signal-management, validation, and evaluation processes. ([EMA Q&A on Implementing Regulation \(EU\) 2025/1466](#)) In the U.S., the FDA released two landmark final guidances in **December 2025** — one for [investigator responsibilities](#) and one for [sponsor responsibilities](#) in safety reporting, emphasizing systematic safety surveillance focused on suspected adverse reactions that are both serious and unexpected, while reducing noise from low-signal reports (raps.org). Additionally, the **ICH E2B(R3)** format for Individual Case Safety Reports (ICSRs) became required for electronic IND safety reports of serious and unexpected suspected adverse reactions under 21 CFR 312.32(c)(1)(i) as of [April 1, 2026](#),

with noncommercial INDs exempt. Harmonization efforts through the finalized ICH E6(R3) GCP guideline (January 2025) emphasize *quality-by-design* and risk-based monitoring, meaning proactive detection of safety issues (not just passive reporting) ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)).

- Data Analytics and AI:** The volume of safety data – from trials and real-world sources – continues to explode. Traditional manual review of case reports is laborious. Recent reviews note that effective pharmacovigilance now must draw on diverse data (electronic health records, global adverse event databases, scientific literature, even social media) ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)). This has moved well beyond experimental algorithms. Natural language processing can scan medical narratives for hidden safety signals, and Bayesian networks are being used to prioritize which AEs might truly be drug-related ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)). In January 2025, the FDA released [draft guidance on AI in drug and biologic development](#) with a 7-step credibility assessment framework, and in January 2026, the FDA and EMA jointly issued [10 guiding principles for AI in drug development](#), emphasizing human-centric oversight, risk-based proportional validation, and transparency. AI-enabled tools may support pharmacovigilance workflows, but their use requires context-appropriate validation, transparency, and human oversight; claimed capacity gains should not be treated as established regulatory or clinical evidence. (FDA) The **CIOMS Working Group XIV** on AI in Pharmacovigilance continues mapping the ICSR process for automation opportunities, and **TransCelerate** has developed validation frameworks for AI-based PV systems. The FDA itself launched an internal generative AI tool (“Elsa”) in June 2025 and deployed agentic AI capabilities agency-wide by December 2025.
- Global Safety Databases:** EudraVigilance and FAERS continue to evolve for cross-product signal detection. A new [EudraVigilance access policy \(v5\)](#), published in April 2025, introduced Stakeholder Group VII granting clinical trial sponsors direct access to ICSRs they submit, and SUSARs from EU-authorized clinical trials must now be reported directly to EudraVigilance (no longer simultaneously to individual national member states). In the U.S., from April 1, 2026, E2B(R3) applies only to electronic IND safety reports of serious and unexpected suspected adverse reactions under 21 CFR 312.32(c)(1)(i); noncommercial INDs are exempt, and other IND safety-report categories use eCTD ([FDA IND safety reports](#)). Efforts like WHO’s Uppsala Monitoring Centre and international data-sharing initiatives continue to link trial safety data with post-market findings. In theory, a SUSAR in one country’s trial could instantly inform investigators elsewhere on emerging risks. More ambitiously, proposals exist for “master patient registries” in high-risk therapeutic areas (e.g. rare diseases) where AE data from trials and compassionate use can be pooled. This would especially impact how we handle SUSARs, expanding expectedness definitions as collective experience grows.
- Transparency and Publication Standards:** A major milestone was reached with the publication of [CONSORT 2025](#) on April 14, 2025, simultaneously in BMJ, JAMA, The Lancet, Nature Medicine, and PLoS Medicine. The updated checklist adds seven new items, including a dedicated requirement for **assessment of harms** — explicitly mandating reporting of how harms were assessed and analyzed (both systematic and non-systematic). A joint [SPIRIT-CONSORT website](#) was launched to support implementation. Pressure continues to grow on journals and funders to require full AE disclosure. Under the EU Clinical Trials Regulation, sponsors must post trial results summaries in CTIS. Ultimately, improving AE/SAE transparency feeds into better meta-analyses and systematic reviews, closing the publication gap noted earlier ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)).

- **Regulatory Culture:** One shift is a move toward *individual safety review committees* within sponsors or multi-center studies. Rather than centralized blinding of event data until planned analyses, some sponsors now empower unblinded monitors to query any serious event in real-time. Such proactive oversight can catch mis-categorizations early. For example, an independent data safety monitoring board (DSMB) might demand that any sudden cluster of SAEs be investigated even before official SUSAR criteria are met. This is particularly relevant in novel therapies (e.g. gene therapies) where unknown risks abound.
- **Digital Reporting:** Increasingly, trial data capture itself is electronic (eCRFs) and can be integrated with hospital EHRs. In the future, an SAE occurring at a hospital might automatically trigger an alert to the trial sponsor (with patient consent), reducing investigator under-reporting. Similarly, mobile apps could let patients report symptoms directly to sponsors, improving detection of non-reported AEs that may predate an SAE.

Discussion and Conclusion

In summary, **Adverse Event (AE)** reporting encompasses the full spectrum of medical occurrences during a drug trial, but only a subset carry immediate consequence. **Serious Adverse Events (SAEs)** narrow that focus to events threatening life or function. And **Suspected Unexpected Serious Adverse Reactions (SUSARs)** isolate a critical subset of serious events that suggest a new or aggravated drug risk. Correctly distinguishing these categories is vital: individual SAEs and SUSARs have distinct handling, while aggregate clinical findings, nonclinical findings, and other significant safety information can also trigger formal reports, protocol or consent changes, and safety communications.

Key distinctions include:

- **Scope:** All AEs vs. those meeting seriousness criteria (SAE) vs. those additionally judged related and unexpected (SUSAR).
- **Causality:** AE needs no causal link; SAE likewise is outcome-only; only SUSAR (as “adverse reaction”) implies suspected causation by the investigational product.
- **Regulatory Impact:** AE collection, SAE site-to-sponsor reporting, and follow-up requirements depend on the protocol and applicable jurisdiction. Individual SUSAR cases are subject to expedited reporting deadlines under the applicable framework; other significant safety findings may also require reporting.

A wealth of regulatory guidance (ICH, FDA, EMA) codifies these distinctions (ichgcp.net) (www.law.cornell.edu). Simultaneously, empirical evidence shows that actual practice often falls short of ideal. Many trials under-report serious events, hampering our understanding of a drug’s true risk profile (trialsjournal.biomedcentral.com) (pmc.ncbi.nlm.nih.gov). High-profile case studies (TGN1412, BIAL) serve as harrowing reminders of what can go wrong if serious reactions are not immediately addressed.

The field continues to adopt more integrated approaches to safety. Regulatory changes include the revised EU pharmacovigilance rules, under which MAHs continue to monitor and use EudraVigilance data in their signal-management processes, and FDA’s April 2026 E2B(R3) requirement for the limited category of IND safety reports of serious and unexpected suspected adverse reactions; noncommercial INDs are exempt ([EMA Q&A on Implementing Regulation \(EU\) 2025/1466](#)) ([FDA IND safety reports](#)). Meanwhile, the updated CONSORT

2025 standards and growing adoption of agentic AI in pharmacovigilance are shifting the paradigm from compliance-only mindsets toward proactive data science, with the potential to catch signals earlier. Greater transparency – for example, making raw SAE counts public – is aligning incentives so that investigators and sponsors report more diligently. International cooperation (harmonized regulations, shared databases) continues to strengthen the AE/SAE/SUSAR reporting ecosystem across borders. Ultimately, the goal is the same on all continents: to protect research participants and patients by detecting adverse effects as quickly and accurately as possible.

References: Authoritative definitions and guidelines cited above are drawn from ICH GCP (E6(R3)) glossary and safety guidance (ichgcp.net) (ichgcp.net) (ichgcp.net), FDA and EMA regulatory documents (www.fda.gov) (www.law.cornell.edu), as well as published clinical studies (trialsjournal.biomedcentral.com) (pmc.ncbi.nlm.nih.gov) (pmc.ncbi.nlm.nih.gov). Case studies references include peer-reviewed analyses and news reports (pmc.ncbi.nlm.nih.gov) (www.theguardian.com). Updated 2025–2026 regulatory sources include: FDA final safety reporting guidances (federalregister.gov), EU Regulation 2025/1466 pharmacovigilance reform (arriello.com), ICH E2B(R3) implementation (safetydrugs.it), CONSORT 2025 (thelancet.com), FDA/EMA joint AI principles (raps.org), and FDA Elevidys safety actions (fda.gov). Readers should consult the applicable current regulator guidance and local requirements for a specific trial or jurisdiction.

Source links

Links cited in this article, in order of first appearance. Full addresses are provided for readers using extracted text.

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