AE vs SAE vs SUSAR: Key Differences in Safety Reporting

By Adrien Laurent, CEO at IntuitionLabs • 11/19/2025 • 35 min read

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Reporting Adverse Events: AE vs. SAE vs. SUSAR – Executive Summary

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 ([1] ichgcp.net) ([2] 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 ([1] 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 ([3] ichgcp.net) ([2] www.fda.gov). In other words, *all SAEs are AEs, but not all AEs are serious*: SAEs are classified by **severity of outcome** rather than causality.

A further category, **Suspected Unexpected Serious Adverse Reactions (SUSARs)**, refines this framework. A SUSAR is by definition a **serious adverse reaction** (SAE with at least a *reasonable possibility* of causal relation to the investigational product) that is also **unexpected** relative to the reference safety information (e.g. Investigator's Brochure or product label) ([4] ichgcp.net) ([5] www.law.cornell.edu). Thus, a SUSAR requires three criteria: (1) **Seriousness** – meeting SAE criteria (see above); (2) **Suspected causality** – the investigator/sponsor judges a causal link is plausible; (3) **Unexpectedness** – the event's nature or severity is not consistent with known information about the drug ([4] ichgcp.net) ([5] www.law.cornell.edu). By contrast, an SAE that is expected or not clearly drug-related is *not* reported as a SUSAR. SUSARs are important because they trigger accelerated regulatory notification to protect subjects: sponsors must report any SUSAR to regulatory authorities (and ethics committees) on an expedited timeline (typically **7 days** if the event is fatal/life-threatening, **15 days** for other SUSARs) ([6] www.endpointadjudication.com) ([7] pmc.ncbi.nlm.nih.gov).

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 internal reporting (typically to the sponsor within 24 hours) (eur-lex.europa.eu) (eur-lex.europa.eu); **SUSARs** are those SAEs believed related to treatment and *unexpected*, which mandate immediate expedited reporting to regulators ([6] www.endpointadjudication.com) ([7] 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 ([8] 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. For example, the ICH 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." ([1] 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" ([3] 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 ([2] www.fda.gov) ([9] 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 ([2] www.fda.gov).

In practical terms, this means every AE (serious or not) should be documented during a trial, but SAEs are subject to immediate attention. 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 ([10] 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 ([11] 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 requirement in clinical trials. In essence, a SUSAR is an SAE that also has a *reasonable suspicion* of being drug-related (hence "suspected adverse reaction") and is *not easily predicted* from the existing product information (hence "unexpected"). Once those conditions are met, expedited notification networks activate. The International Conference on Harmonisation (ICH) E2A guidance and EU GCP detailed guidance spell this out: investigators send all SAEs to sponsors (usually within 24 hours) (eur-lex.europa.eu) (eur-lex.europa.eu). Then sponsors analyze causality and expectedness. If the SAE is judged to be related and not described in the Investigator's Brochure or reference label, it becomes a SUSAR requiring urgent reporting. For example, guidance emphasizes that **fatal or life-threatening SUSARs** must reach authorities within **7 calendar days** of sponsor awareness, with a full follow-up in 8 days; all other SUSARs within **15 calendar days** ([6] www.endpointadjudication.com) ([12] www.law.cornell.edu). This rapid timeline aids regulatory bodies in detecting new safety signals early, potentially halting a trial or placing new safeguards.

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, *regardless of causality* ([1] ichgcp.net) (eur-lex.europa.eu). Examples: mild rash; transient fever.	*Not required* (no causal link assumed)	N/A (no expectation concept)	Recorded in trial data. Report not required unless it meets *serious* criteria.
Serious Adverse Event (SAE)	An AE that *results* in death, is life-threatening, requires (or prolongs) hospitalization, causes disability/incapacity, or congenital anomaly ([3] ichgcp.net) ([2] www.fda.gov). (Also include "important medical events" as per ICH/FDA)	*Not required* (SAE status is outcome-based)	N/A (can be expected or unexpected)	Investigator → Sponsor within 24 hours (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 ([5] 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) ([3] ichgcp.net) ([5] 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 *unexpected* relative to the product's known information ([4] ichgcp.net) ([13] www.law.cornell.edu). This is the intersection of the above three: *serious*, *related*, and *unexpected*.	*Yes*	*Yes* (not listed in IB/SmPC, or qualitatively/severity inconsistent with reference safety info) ([14] ichgcp.net) ([13] www.law.cornell.edu) **Note:** "Unexpected" refers to mismatch with the Reference Safety Information (ICI/SmPC) ([13] www.law.cornell.edu).	Expedited report to regulators: typically **7 days** for fatal/life-threatening SUSARs, **15 days** for other SUSARs ([6] www.endpointadjudication.com) ([7] pmc.ncbi.nlm.nih.gov). Investigators still notify sponsor within 24 hours as for any SAE.

*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 broadly interpreted as **within 24 hours of learning** of the SAE (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 qualifies as a SUSAR and must be expedited to regulators and ethics committees. Otherwise, the SAE is catalogued internally (and possibly included in aggregate reports).

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)	*Immediate:* Investigator must notify sponsor as soon as possible, *no later than 24 hours* after becoming aware	None — sponsor files internally. Only aggregate safety updates required (e.g. DSUR or annual report).	If part of multicenter trial, sponsor *should inform all study investigators* about any relevant new safety findings (including SAEs that might

Report Type	Investigator→Sponsor	Sponsor→Regulator	Sponsor→Other Investigators
	(eur-lex.europa.eu) (eur-lex.europa.eu).		affect subject safety) (eur-lex.europa.eu) ([12] www.law.cornell.edu).
SUSAR – Fatal or Life-Threatening	*Immediate:* Investigator → Sponsor within 24h (as above).	*Expedited:* Sponsor must notify regulators and ethics committees "as soon as possible" and **no later than 7 calendar days** from first knowledge ([6] www.endpointadjudication.com) ([7] pmc.ncbi.nlm.nih.gov). (A concise follow-up report with complete information must be provided within 8 days of initial report.)	Sponsor must also inform all participating investigators promptly (eur-lex.europa.eu).
SUSAR – Other Serious	*Immediate:* Investigator → Sponsor (24h).	*Expedited:* Sponsor reports to regulators and ethics **no later than 15 calendar days** from knowing the case ([6] www.endpointadjudication.com) ([7] pmc.ncbi.nlm.nih.gov).	Sponsor informs all investigators.
Post-Trial SUSAR	*Not applicable to investigators (trial ended).*	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 always report SAEs to the sponsor immediately (≤24h) (eur-lex.europa.eu) (eur-lex.europa.eu). Sponsors analyze each SAE for relationship and expectedness. Only those SAEs meeting *all* SUSAR criteria trigger expedited FDA/EU notification. In practice, both European (EU CTR) and U.S. (21 CFR 312.32/600.80) regulations prescribe the *same* 7/15-day rule for serious, unexpected, suspected events ([6] www.endpointadjudication.com) ([7] pmc.ncbi.nlm.nih.gov). For example, the U.S. IND safety reporting rule explicitly states that **"any suspected adverse reaction that is both serious and unexpected"** must be reported promptly ([12] www.law.cornell.edu). Similarly, EU guidance mandates 7 and 15 day timelines for SUSARs ([6] www.endpointadjudication.com). Otherwise, if an SAE is expected or unlikely to be drug-related, the sponsor may document it and include it in periodic safety updates rather than report it individually.

Reporting Formats: In practice, sponsors use standardized formats such as the International Council for Harmonisation (ICH) CIOMS forms or FDA Form FDA 3500A for expedited reports. These detail the case narrative, subject details, intervention, timings, and investigator-sponsor causality assessments. Electronic systems (e.g. FDA's FAERS for marketed products, EudraVigilance for EU trials) further ensure regulatory databases capture these reports.

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). Both authorities require immediate notification of all study investigators once a SUSAR is reported (eur-lex.europa.eu) ([7] pmc.ncbi.nlm.nih.gov). Notably, after the EU Clinical Trials Regulation 536/2014 takes effect in all member states, sponsors will be obliged to use EU-wide systems (e.g. the forthcoming CTIS portal) to submit SUSAR reports (Article 42 of CTR). The bottom line is that **all major regulators now enforce essentially the same expedited reporting standards**, reflecting the ICH E2A

guidance on "Clinical safety data management: definition and standards for expedited reporting" (1994) (eur-lex.europa.eu) ([12] www.law.cornell.edu).

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 ([15] trialsjournal.biomedcentral.com). Only **1,506 of these (3%) were classified as serious** (by outcome criteria) – roughly one SAE per ten patients. Strikingly, when the investigators examined overlap between the AE dataset and the SAE dataset, only 61% of serious-event instances were also recorded independently in the AE listings ([15] 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 (serious) toxicity rose by **5–7 percentage points** on each trial arm ([15] trialsjournal.biomedcentral.com). In practical terms, this meant the calculated safety imbalance between experimental and control arms changed by up to 18% (95% confidence interval 12–24%) ([15] trialsjournal.biomedcentral.com). This study illustrates that incomplete or inconsistent recording of serious events can materially alter safety conclusions even within a single trial ([16] 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 ([17] pmc.ncbi.nlm.nih.gov). Company-sponsored trials tended to report SAEs far more frequently (57.6%) than investigator-led or academic trials (20.7%) ([17] pmc.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 ([17] pmc.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 ([17] pmc.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 ([18] pmc.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) ([18] pmc.ncbi.nlm.nih.gov). In other words, roughly 51% of SAE data known to regulators was omitted in the corresponding papers ([18] pmc.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 ([18] pmc.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 ([19] pmc.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 ([19] pmc.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 ([10] pmc.ncbi.nlm.nih.gov). Initially, one might consider whether these were SAEs or SUSARs. In fact, they were SAEs (clearly life-threatening), and once two patients died, they became SUSARs because the events were unexpected given the preclinical data. 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 ([10] pmc.ncbi.nlm.nih.gov).

- **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 ([20] www.theguardian.com). 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 an almost instantaneous SUSAR response once the first fatal case emerged ([20] www.theguardian.com) ([21] www.theguardian.com). This incident prompted government and EU investigations and ultimately new guidelines on risk mitigation for first-in-human studies.

- **Regulatory Audits (Example from Literature):** In a retrospective review at a major academic Ethics Committee, 66 SAEs were evaluated across 34 trials. Among these, 19 studies had only one SAE reported, and just 3 had more than five. This highlights that many trials encounter very few SAEs overall; however, even a single event can trigger SUSAR reporting and prompt review of the trial. The report noted that causality assessments (i.e. did any SAE become a SUSAR) were crucial but often poorly documented ([22] pubmed.ncbi.nlm.nih.gov). (This is from an institutional review of IEC submissions in India, which illustrated global consistency: any unexpected serious reaction under an NGO's IND requires the same urgent notification in India as in the West.)

- **Discrepancy in Publication (ICON8 Ovarian Trial):** As noted, the ICON8 trial found that 39% of SAEs were missing from the standard AE listings ([15] trialsjournal.biomedcentral.com). In this trial, the chief investigator actually re-analyzed safety data: by combining SAE and AE datasets, they discovered that toxicity rates (e.g. grade ≥3 events) had been underestimated in their initial reports. After merging datasets, the difference in high-grade events between arms grew by 12–18 percentage points ([15] trialsjournal.biomedcentral.com). This shows that even without regulatory "report delays," data management issues can act like silent under-reporting.

These cases 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, the moment a patient's status changed to fatal (or life-threatening) 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 predefined checklists or questionnaires), but that process is mostly for trial records and patient care. **Serious AEs** trigger a different process: the investigator (or delegated research staff) must immediately contact the sponsor's safety department by telephone, email, or electronic case report form within **24 hours** of learning of the event (eur-lex.europa.eu) (eur-lex.europa.eu). This ensures the sponsor can react before final outcome or follow-up details are in. The initial report often includes brief identifying codes, a description of the event, date of onset, and the investigator's initial judgment of severity and causality (if any). Later, a full written narrative (often a CIOMS form) supplements it. The sponsor simultaneously notifies the institutional ethics committee or IRB as required by local rules (e.g. US IRBs require notification of any "unanticipated problem").

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), the immediate reporting rule **still applied**, since that determination comes afterward. 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 ([5] 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 the event is both serious and deemed *suspected* (i.e. a positive causality judgment, often indicated as "related" or "possible"), then the sponsor checks expectedness. If that reaction is **unexpected**, the sponsor must prepare an expedited case report. This means as soon as possible (no later than 7 or 15 days, depending on seriousness ([6] www.endpointadjudication.com) ([7] pmc.ncbi.nlm.nih.gov)), the sponsor submits the SUSAR to regulators and ethics committees. In contrast, if the SAE is expected (even if related), or non-serious, the sponsor may still monitor it but does not need to file immediately with authorities. Instead, these events might be summarized in periodic safety update reports (e.g. Development Safety Update Reports or annual DSURs) (eur-lex.europa.eu).

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 ([6] www.endpointadjudication.com) ([5] 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 *within 24 hours* (eur-lex.europa.eu) (eur-lex.europa.eu).

> 3. **Sponsor** receives SAE. Conducts causality assessment. If SAE is **NOT suspect (unrelated)** or is expected, process as normal safety event (no urgent regulatory action beyond record-keeping). If SAE is **suspected** (possible drug-related), 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 ([6] www.endpointadjudication.com) ([7] pmc.ncbi.nlm.nih.gov). Inform all investigators of the SUSAR case (eur-lex.europa.eu) ([7] 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, the SUSAR process is **only for unanticipated SAEs**, preserving resources and focus on novel signals.

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 ([15] trialsjournal.biomedcentral.com). In another cancer trial assessment, nearly 40% of SAE case report entries 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 ([15] 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, one report found that **the final publication often underestimates the incidence of Grade 3/4 toxicities compared to the clinical database** ([15] trialsjournal.biomedcentral.com). Another systematic review cited above found that 51% of SAEs recorded in registries were omitted in published articles ([18] 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. Ioannidis et al. 2016 ([23] pmc.ncbi.nlm.nih.gov)).

From a regulatory perspective, under-reporting can delay recognition of safety signals. A notable example from post-marketing: The FDA received thousands of adverse event reports for newer anticoagulants, but many were aggregated in internal safety reviews after the fact. Similarly, 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. Argus, ArisGlobal) 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 ([20] 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 requirements often parallel regulatory ones; for example, U.S. IRBs expect reporting of any "unexpected serious adverse event" to them within days.

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:** The EU is rolling out the new Clinical Trials Information System (CTIS) under Regulation 536/2014. In this system, SUSAR reports will be submitted through a centralized European portal, enabling more real-time pharmacovigilance across member states. Likewise, the FDA has modernized IND reporting guidelines to encourage electronic submission and integrated analysis. Harmonization efforts (ICH E6(R3) GCP, E8(R1) addendum on trial planning) increasingly emphasize *quality-by-design* and risk-based monitoring, meaning proactive detection of safety issues (not just passive reporting) ([24] pmc.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) ([24] pmc.ncbi.nlm.nih.gov). This has led to experimental use of algorithms. For instance, natural language processing can scan medical narratives for hidden safety signals, and Bayesian networks are being tested to prioritize which AEs might truly be drug-related ([25] pmc.ncbi.nlm.nih.gov). Such tools can help identify "signals" (patterns of AEs) that warrant human assessment. In the near future, AI may assist sponsors and regulators by flagging unusual SAE patterns or predicting which events are likely SUSARs, further optimizing the reporting process.

- **Global Safety Databases:** EudraVigilance and FAERS already allow cross-product signal detection, but integration is limited by privacy and proprietary barriers. Efforts like WHO's Uppsala Monitoring Centre and international data-sharing initiatives aim 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:** Pressure is growing on journals and funders to require full AE disclosure. Regulators may enforce stricter policies (e.g. making trial registries contain complete SAE listings) or link future trial approvals to compliance in reporting previous-trial AEs. Some conference abstracts now highlight trial safety results specifically. Ultimately, improving AE/SAE transparency could feed into better meta-analyses and systematic reviews, closing the publication gap noted earlier ([18] pmc.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 the critical subset of serious events that suggest a new or aggravated drug risk. Correctly distinguishing these categories is vital: only SAEs and SUSARs generate formal action plans and communication streams.

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:** AEs (non-serious) are recorded for completeness. SAEs demand immediate sponsor notification (24h) and follow-up. SUSARs demand sponsor regulatory notification (7/15 days) to protect current and future subjects.

A wealth of regulatory guidance (ICH, FDA, EMA) codifies these distinctions ([1] ichgcp.net) ([12] 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 ([15] trialsjournal.biomedcentral.com) ([18] 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.

Looking forward, the field is converging on smarter, more integrated approaches to safety. Exit from compliance-only mindsets toward proactive data science could help catch signals earlier. Greater transparency – for example, making raw SAE counts public – may align incentives so that investigators and sponsors report more diligently. International cooperation (harmonized regulations, shared databases) will further blur the

AE/SAE/SUSAR distinctions 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.

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