Reference Safety Information (RSI): A Guide to Avoiding Errors

By Adrien Laurent, CEO at IntuitionLabs • 11/23/2025 • 50 min read

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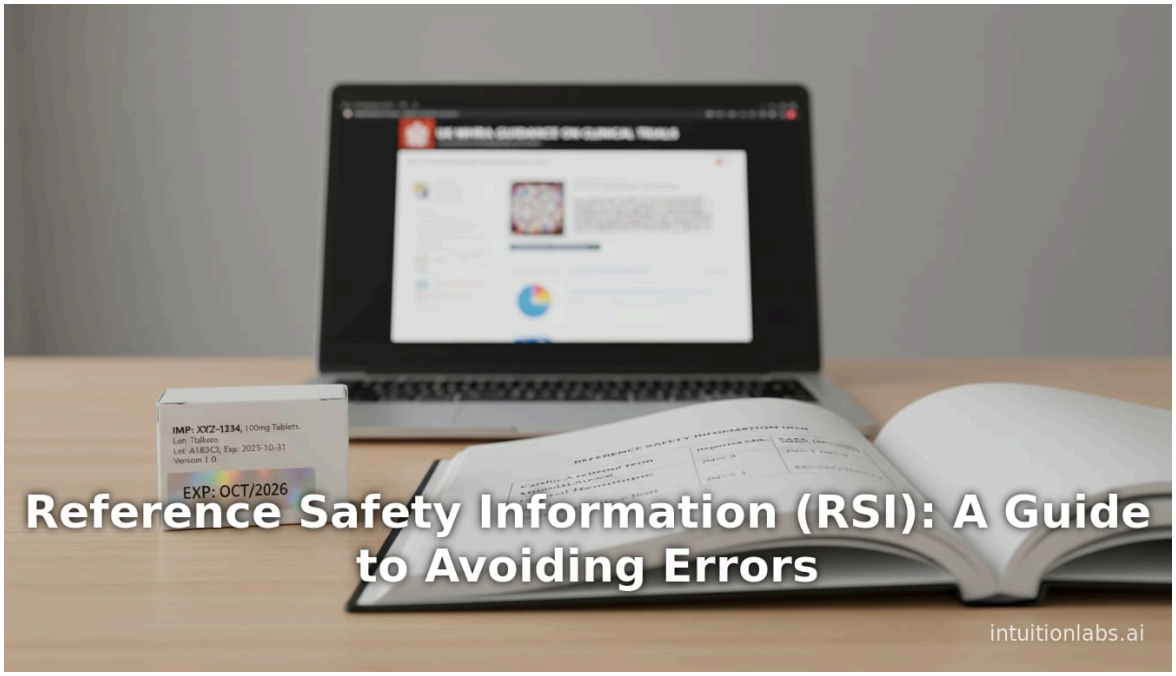

Executive Summary

Clinical trials rely on meticulous pharmacovigilance to ensure participant safety and data integrity. A cornerstone of this safety reporting framework is the **Reference Safety Information (RSI)**, a defined set of expected serious adverse reactions (SARs) for an investigational medicinal product (IMP). The RSI – typically contained in the Investigator's Brochure (IB) or a Summary of Product Characteristics (SmPC) – serves as the baseline against which all new serious adverse events are judged. If a serious adverse reaction is not listed in the RSI, it is deemed unexpected and must be reported as a Suspected Unexpected Serious Adverse Reaction (SUSAR). In practice, any mistake in defining, updating, or communicating the RSI can critically undermine this system of risk detection.

This report examines the so-called **"RSI Trap,"** the phenomenon wherein errors in labeling and RSI management can lead to delayed or missed reporting of serious events – potentially triggering regulatory enforcement actions and even trial suspension. We survey the regulatory context (including EU directives and clinical trial regulations, ICH guidelines, and local requirements like UK MHRA guidance) that define RSI. We review how RSI is meant to be used, and how projects have misinterpreted it. Importantly, we analyze **common pitfalls** (the RSI "traps"), such as listing inappropriate events in the RSI, failing to submit RSI updates as formal amendments, or using unapproved or inconsistent versions. Drawing on inspectorate reports and audit studies, we illustrate real-world case examples where RSI mismanagement led to safety reporting failures. For instance, in one inspection a company's lack of process to ensure MHRA approval of RSI amendments resulted in the **use of an incorrect RSI version** during case evaluation, causing **under-reporting of SUSARs** ([1] www.scribd.com). In another, investigators had inconsistent interpretations because the RSI was not clearly identified, leading to missed SUSAR reports (mhrainspectorate.blog.gov.uk).

We also cover **IMP labeling requirements**, since "labeling errors" can refer to product labels as well. We summarize new UK guidance (2025) on IMP labeling and cite surveys finding that **raw labeling mistakes are surprisingly common** – one audit found 58% of respondents reported information labeling errors on trial drug containers ([2] pmc.ncbi.nlm.nih.gov) ([3] pmc.ncbi.nlm.nih.gov). Such errors (e.g. missing trial ID, incorrect dosage on labels) can necessitate halting a trial until corrected, to avoid participant risk and regulatory breaches.

By integrating multiple perspectives (regulators, sponsors, auditors) and data (inspection findings, audit surveys, regulatory Q&As), this report provides a detailed picture of why RSI and labeling mistakes matter. We discuss the *implications* – not only for trial pausing or serious breach findings, but also for patient safety, data validity, and global development strategy. Finally, we look ahead to anticipated regulatory changes (e.g. new EU Clinical Trials Regulation implementations, ICH guidelines) and recommend best practices to avoid falling into the RSI trap.

Introduction and Background

Clinical trials generate the evidence needed to prove that new medicines are both effective and safe. Good Clinical Practice (GCP) regulations require sponsors to monitor safety throughout the trial and to **report serious adverse events** in a timely manner. A key regulatory principle is that *experts should be informed of unexpected safety issues as soon as possible*. The concept of **"expectedness"** of adverse reactions is central: reactions already known or anticipated for a product are handled differently than new, unexpected signals. For trials in Europe, this concept was formalized in the EU Clinical Trials Directive (2001/20/EC) and its associated guidance (e.g. CT-3), later in Regulation (EU) 536/2014 (the **EU Clinical Trials Regulation, CTR**). Specifically, sponsors must list the **expected** serious adverse reactions in the RSI, so that any new serious reaction not on that list is identified as a SUSAR and reported rapidly.

Reference Safety Information (RSI) thus serves as a **baseline "safety label"** for the trial. It can be thought of as the trial's "proto-labelling" of safety: a concise list of exactly which serious side effects are anticipated. In the US, safety reporting relies on the Investigator's Brochure and IND safety regulations, but the explicit term RSI is mainly used in Europe. The RSI concept interlocks with the requirement that any change to expected safety knowledge (e.g. adding a new side effect as expected) must be reviewable by regulators.

In practice, sponsors compile the RSI by medically assessing all observed serious adverse reactions (SARs) to the IMP. Only those with strong evidence of causality and plausibility are included. This process was historically inconsistent, leading to gaps in reporting. For example, prior to focused guidance, some sponsors simply listed *all* observed SARs in their IB, treating them as expected. As a safety commentator noted, **"any new occurrence of an observed ADR [adverse drug reaction] was subsequently considered 'expected' and no longer qualified for SUSAR reporting,"** undermining transparency ([4] safetyobserver.com). In other words, listing everything in the RSI creates a trap: it hides new safety signals by declaring them foreseen.

Regulators have repeatedly warned about RSI misuse. Since at least 2016, MHRA GCP inspectors have issued public guidance (and inspection findings) stressing three key qualities: the RSI must be **Identifiable, Approved, and Consistent**. It must appear as a clearly identified section in the IB or SmPC (identifiable), must only be updated with regulatory approval (approved), and all trial personnel must use the same approved version (consistent) (mhrainspectorate.blog.gov.uk) (mhrainspectorate.blog.gov.uk). Failure in any of these "IAC" aspects has led to critical non-compliances and halted reporting processes. For example, investigators once assessed the same event differently due to ambiguity in where the RSI was defined, resulting in **"a large number of SUSARs not being identified or reported to the MHRA."** (mhrainspectorate.blog.gov.uk).

Additionally, the RSI is not a tool for investigators' day-to-day decisions. It exists solely so sponsors can decide which adverse reactions to report upward, and so regulators can evaluate the trial's safety profile. In practice, we often find sponsors incorrectly using the IB's RSI section as general safety dissemination to sites; but regulators emphasize that the RSI's content and timing of implementation must be governed by the sponsor's legal obligations, not by investigators' familiarity or internal communication needs (mhrainspectorate.blog.gov.uk) (mhrainspectorate.blog.gov.uk).

Historical Context: The requirement for concise "core" safety information has roots going back to the late 1990s (CIOMS guidelines). In clinical trials, the EU Directive 2001/20/EC led to the CT-3 guidance (2011)– the first detailed modern definition of RSI was included there (eur-lex.europa.eu). Over time, specific issues with RSI prompted the Clinical Trials Facilitation Group (CTFG) to issue Q&A clarifications (2013, 2017), culminating in the current comprehensive RSI guidance ([5] safetyobserver.com) ([6] safetyobserver.com). The forthcoming EU CTR (fully implemented by 2022) codifies RSI rules (Annex III) in law (eur-lex.europa.eu).In parallel, national authorities like the UK MHRA have conducted training and published inspectorate blog series (2016–2021) highlighting RSI pitfalls (mhrainspectorate.blog.gov.uk) (mhrainspectorate.blog.gov.uk). These efforts reflect industry feedback; an EFPIA position paper (2016) even recognizes the challenge and calls for clearer guidance. ([7] safetyobserver.com) ([8] safetyobserver.com)

Contemporary Relevance: As of 2025, the RSI remains a pain point in global trials. Companies running worldwide studies must reconcile differing timelines: the RSI only becomes effective once approved in all Orphan and combined Member States, per current EU rules ([8] safetyobserver.com). This has led some to consider using different RSIs regionally (FDA has no RSI requirement, for example). Meanwhile, evolving regulations (UK's new Clinical Trials Regulation updates and labeling rules) continue to stress correct RSI use and accurate IMP labeling (www.gov.uk). Regulatory agencies even include RSI compliance in the definition of serious breaches and cluster them as inspection findings of "critical" or "major" severity ([1] www.scribd.com) ([9] www.gmp-compliance.org). Thus, sponsors and CROs today need an in-depth understanding of RSI to avoid trial interruptions. This report dissects that landscape in detail.

Regulatory Framework and Historical Evolution of RSI

EU Clinical Trials Directive and CT Guidelines

The concept of RSI originated in European law on trial safety reporting. Article 3(2) of Directive 2001/20/EC (the Clinical Trials Directive) required sponsors to continuously reassess the trial's benefit-risk balance and report safety data. In 2011, the EU's **CT-3 guidance** (Commission Detailed Guidance on Adverse Event Reporting) provided clarity. CT-3 introduced the term *"Reference Safety Information"* (RSI) and defined expectedness in Section 7.2.3.2 (eur-lex.europa.eu). There, expectedness is "determined by the sponsor in the RSI" (eur-lex.europa.eu), based "on the perspective of events previously observed, not on anticipated pharmacological properties" (Opinion 51-52). CT-3 states explicitly:

> "The expectedness of an adverse reaction is determined by the sponsor in the reference safety information ('RSI')... The RSI is contained in the Summary of product characteristics ('SmPC') or the IB. ... If the RSI is contained in the IB, the IB should contain a clearly-identified section to this effect. This section should include information on the frequency and nature of the adverse reactions." (eur-lex.europa.eu)

This anchored the notion that RSI must be a specific list (with frequencies) drawn from known prior data. CT-3 further notes that any change to RSI is a **substantial amendment**, and that for SUSAR reporting, "the version of the RSI at the moment of occurrence of the SUSAR shall apply" (eur-lex.europa.eu). Thus CT-3 introduced key principles still in force: the need for a distinct, regulatory-approved RSI in the IB or SmPC, and the pivotal role of RSI versioning in reporting.

EU Clinical Trials Regulation (CTR 536/2014)

In 2014 the EU adopted the new Clinical Trials Regulation (EU) No. 536/2014 (CTR), in force since 2016. CTR formalized safety reporting rules in Article 42 and Annex III (eur-lex.europa.eu) (eur-lex.europa.eu). The CTR's Annex III (Safety Reporting) essentially codifies CT-3's guidance into regulation. Pertinent excerpts include:

- **Definition**: "The expectedness of an adverse reaction shall be set out by the sponsor in the RSI... expectedness shall be determined on the basis of events previously observed with the active substance... not on the basis of anticipated pharmacological properties..." (eur-lex.europa.eu). This mirrors CT-3.
- **RSI location**: "The RSI shall be contained in the SmPC or the IB... If the IMP is authorised in several Member States with different SmPCs, the sponsor shall select the most appropriate SmPC... as the RSI." (eur-lex.europa.eu).
- **Versioning**: "The RSI may change during the conduct of a clinical trial. For SUSAR reporting the version of the RSI at the moment of occurrence of the SUSAR shall apply. Thus, a change of the RSI impacts on the number of adverse reactions to be reported as SUSARs." (eur-lex.europa.eu).
- **Annual Safety Report** (Part 3): sponsors must include the RSI in effect at the start of each reporting year (eur-lex.europa.eu).

By enshrining these in EU law, the CTR obliges sponsors to treat RSI changes with the same gravity as any other trial amendment affecting risk. It also reinforces that misclassification of events (by RSI misuse) can distort the incident count of SUSARs.

International Harmonization (ICH/GCP/EMA Guidelines)

While RSI terminology is EU-centric, its function aligns with ICH obligations. ICH E2A guidance ("Clinical Safety Data Management: Definitions and Standards for Expedited Reporting") emphasizes reporting all SUSARs promptly; steering committees interpret this in context of RSI. ICH E6(R2) (GCP) requires an Investigator's Brochure that compiles all relevant safety data but does not explicitly say "RSI" – the IB is often called the "proto label" for investigators ([10] trilogywriting.com). The EMA's Good Pharmacovigilance Practices (Module VI/GVP for clinical safety) mentions RSI once in passing (as in [37] footnote), but notes that post-marketing RSI (in SmPC) is not the same as trial RSI (mhrainspectorate.blog.gov.uk). Rather, the GVP states clearly that trial RSI is for the sponsor/regulator, not a summary for sites (mhrainspectorate.blog.gov.uk) (mhrainspectorate.blog.gov.uk).

Globally, no single term replaces RSI: In the US, investigators rely on the IND regulations (21 CFR 312.32) that require prompt reporting of unexpected fatal or life-threatening events (and annual reports of other cases). The Investigator's Brochure and Safety Report in an IND serve a similar role. However, the explicit concept of a registry of expected reactions (like RSI) does not have a codified counterpart. American sponsors often specify expected AEs in the IB narrative, but without an EW definition "RSI." As one ACRP article noted, ICH E6(R3) (under development) includes cumulative ADR lists but does not explicitly import RSI ([7] safetyobserver.com). Hence, sponsors conducting global trials must juggle EU RSI rules with more general US IND requirements (potentially complicating harmonization).

Table 1: *Timeline of Key RSI Regulations and Guidance*

Year	Regulation/Guidance	Jurisdiction/Body	Key RSI Provisions/Events
1996	CIOMS Reporting Guideline (Part I & II)	Global (CIOMS)	Early principles on "core safety information"
2001	EU Clinical Trials Directive 2001/20/EC	EU	Legal basis for safety reporting; "suspected unexpected SARs" mandated
2011	CT-3 Guidance (Detailed guidance on ICSR)	EU	Introduced *RSI term*, required listing expected SARs in IB/SmPC (eur-lex.europa.eu)
2013	CTFG Q&A RSI (Dec 2013)	EU Heads of Med. Ag.	First clarifications on RSI content (subset of SARs, PT terms, updates)
2014-16	CTR 536/2014 (in force 2016)	EU	Codified RSI in law (Annex III, Art. 42); RSI versioning and reporting rules (eur-lex.europa.eu)
2016	MHRA Blog Part I (RSI Identifiable/Approved/Consistent)	UK (MHRA)	Highlighted inspection findings, defined RSI as list of expected reactions (mhrainspectorate.blog.gov.uk)
2017	CTFG Q&A RSI (Nov 2017)	EU Heads of Med. Ag.	Expanded RSI guidance to 18 Q&A (content, freq, updates, DSUR, etc.) ([5] safetyobserver.com)
2017	MHRA Blog Part II (RSI & RMP differences, Approval, Implementation)	UK (MHRA)	Clarified RSI vs IB/SmPC, regulator approval needed, how to update (mhrainspectorate.blog.gov.uk) (mhrainspectorate.blog.gov.uk)
2018-2019	MHRA GCP Metrics Reports	UK (MHRA)	Statistical reports showing PV as common critical findings in inspections (all sponsor critical findings were PV-related) ([11] www.gmp-compliance.org)
2021	MHRA Blog Part III (Ongoing noncompliance, Common findings)	UK (MHRA)	Continuation of RSI enforcement issues; noted multiple critical findings (8 orgs with RSI issues) ([12] s3.amazonaws.com)
2022-25	New Clinical Trial Regulations & Guidance	UK/EU	UK drafting new CTR regime; UK updated labelling guidance (2025) emphasizes packaging labeling

Year	Regulation/Guidance	Jurisdiction/Body	Key RSI Provisions/Events
			requirements (www.gov.uk); EU CTR fully applied from 2022 (UK mirrored many provisions)

Sources: EU CT Directive/Regulation texts (eur-lex.europa.eu) (eur-lex.europa.eu); MHRA blog posts (mhrainspectorate.blog.gov.uk) (mhrainspectorate.blog.gov.uk); SafetyObserver summary ([5] safetyobserver.com) ([8] safetyobserver.com); MHRA official statistics ([11] www.gmp-compliance.org) ([1] www.scribd.com); MHRA labelling guidance (www.gov.uk).

The RSI: Definition, Purpose, and Implementation

The **Reference Safety Information (RSI)** is fundamentally a *regulatory tool*, not a clinical one. By definition, it is the **"list of expected serious adverse reactions (SARs) for an IMP for the purposes of safety reporting."** As CT-3 and CTR repeatedly emphasize, the RSI exists so that both regulators and the sponsor can consistently judge expectedness. Specifically, RSI usage entails:

- **Content:** Only SARs **previously observed** with the IMP (or its active substance)—for which there is strong causality evidence—should be listed as expected (eur-lex.europa.eu) (eur-lex.europa.eu). This means cents of cases, literature, or class effect may inform which SARs qualify, but adding a reaction simply because it is "common in the disease" or because the investigator thinks it's nothing new is incorrect (mhrainspectorate.blog.gov.uk). The RSI *should not* be a broad summary of all potential effects; rather, it is a select subset. Explaining this, MHRA notes that "to be categorised as expected the reaction must be clearly listed in the RSI," and explicitly warns that "expected" does *not* mean something merely common in the patient population, disease, or a benign effect of background therapy (mhrainspectorate.blog.gov.uk).

- **Placement:** Per CT-3 and CTR, if using an **Investigator's Brochure (IB)**, the RSI must appear as a *separate, clearly titled section*. For example, CT-3 says: "If the RSI is contained in the IB, the IB should contain a clearly-identified section to this effect." (eur-lex.europa.eu). Correspondingly, UK guidance instructs: "all SARs should be assessed against the RSI in place at the time of the event," and the RSI must be clearly identifiable in the IB or SmPC (mhrainspectorate.blog.gov.uk) (eur-lex.europa.eu). Investigators and pharmacovigilance staff must know precisely where to find the RSI listing, otherwise expectedness assessments vary and SUSARs may be missed.

- **Procedural Role:** Only the sponsor (and ultimately the regulator) uses the RSI for expedited reporting. Investigators submit all serious events to the sponsor, but do *not* conduct their own expectedness tests using the RSI (often, investigators simply report *seriousness* and relationship). The sponsor then compares each investigator-reported SAR against the RSI to decide if it must be reported as a SUSAR. Many documents stress this: e.g. MHRA Blog Part I clarifies "Serious Adverse Events (SAEs) that are not related to the IMP do not need an expectedness assessment," and that non-relevant factors (such as investigator reassurance or disease context) are irrelevant; only the RSI content matters (mhrainspectorate.blog.gov.uk) (mhrainspectorate.blog.gov.uk). Put another way, expectedness under RSI is *not* a medical judgment of tolerability – it's a categorical check: is the precise MedDRA term in the RSI list?

- **Data and Format:** When writing the RSI section, sponsors usually present it in **tabular form**, by system organ class and MedDRA preferred term, with frequency of occurrence. For example, guidance suggests a table like *"Serious Adverse Reactions for the IMP considered expected for safety reporting purposes"*, listing SARs and counts (see hypothetical example in reference ([13] soterius.com)). Frequencies may use CIOMS categories (common, uncommon, etc.) if data permits, or raw counts if limited data. The key is transparency: if a reaction is *excluded* from the RSI because it's not expected, that too should be documented by exclusion.

- **Cumulative and Contextual:** The RSI is not intended as a full safety profile. The IB should contain the broader "Effects in Humans" section with all SARs, but the RSI intentionally contains only the expected subset. The sponsor should thus maintain clear documentation of how each RSI entry was justified; any SARs not in the RSI but occurring in trials are collated in aggregate reports (DSURs). Crucially, adding an SAR to the RSI implies the sponsor accepts it as "anticipated" in future subjects. MHRA notes that including life-threatening or fatal SARs in an RSI is extraordinary, and when it happens a robust benefit/risk justification and protocol safeguards are needed ([14] soterius.com) ([15] soterius.com).

- **Updates:** RSI content can and should evolve with evidence. For example, after one or more occurrences of a SAR, the sponsor might decide that new cases would be expected henceforth. However, **any change to the RSI must be submitted to regulators as a Substantial Amendment** ([16] safetyobserver.com) (mhrainspectorate.blog.gov.uk). Until regulators approve that amendment, the "old" RSI remains in force for assessing any event (per CT-3/CTR). In practice, many sponsors have been tripped up by this: they updated their IB (new version) adding expected SARs but *before* obtaining approval, started using the new RSI in their safety database. This led to missed SUSARs and inspection findings (mhrainspectorate.blog.gov.uk) (mhrainspectorate.blog.gov.uk).

In summary, the RSI is a legally anchored cross-check: it ensures that only truly *unexpected* SARs trigger expedited reporting. Thus, **"labeling"** in this context means labeling a reaction as expected vs unexpected in safety documentation. The "trap" arises because a small mistake – like listing the wrong reaction or not following update rules – undermines the whole safety reporting system.

Regulatory Requirements for RSI (EU and UK)

The legal requirements for RSI derive from two main sources: European law (as above) and implementing national regulations. In the UK, the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) incorporate these EU rules. UK guidance makes clear that the RSI must be specified **in the trial application** (the CTA cover letter must cite where the RSI is) and approved as part of authorisation ([17] soterius.com) (mhrainspectorate.blog.gov.uk). UK guidance also defines a "serious breach" of regulations to include failure to report SUSARs – when such failures stem from RSI errors, it can be considered not just an administrative slip but a *critical safety violation*. For example, the MHRA inspectorate blog warns: "By not informing the NCA [national competent authority] of RSI changes, assessors are prevented from making an informed decision about the clinical trial … and the expectedness assessment is not a medical decision." ([18] s3.amazonaws.com). Thus, sponsors are legally required to use only the regulator-approved RSI in their safety database and reporting systems.

The RSI requirements in EU law are summarized in CTR Annex III (See [43]). Additional guidance comes from:

- **EU CT-3** (eur-lex.europa.eu): Stipulates RSI be in SmPC or IB, RSI changes as substantial amendments, version at time of event applies to SARs.
- **CTFG Q&As (2013, 2017)**: Clarify items like frequency expression, MedDRA usage, document updates and DSUR content. (E.g. they advise using MedDRA Preferred Terms ([19] safetyobserver.com) and including frequency categories).
- **UK MHRA Guidance**: Blog posts and formal GCP guidance reiterate CT-3/CTR points in plain language: RSI must be "identifiable, approved, and consistent" (mhrainspectorate.blog.gov.uk) (mhrainspectorate.blog.gov.uk); changes require MHRA approval before use (mhrainspectorate.blog.gov.uk); always use the RSI version in effect at event onset (mhrainspectorate.blog.gov.uk). The forthcoming UK Clinical Trial Regulations (due April 2026) maintain these RSI norms, and specifically incorporate the risk of not doing so as serious breaches. The MHRA's updated guidance on CTs (Oct 2025) even includes RSI advice in the general "safety reporting" section, advising sponsors to list "expected SARs per MedDRA PT" and document justifications for them.
- **Industry Best Practice**: Groups like the Association of Clinical Research Professionals (ACRP) and consultants (e.g. Trilogy, Soterius) provide guidance on formulating RSI, emphasizing clear listing by SOC and PT, referencing protocol population, and updating per evidence ([20] soterius.com) ([21] safetyobserver.com). They also note global trials may need multiple RSIs (where, say, a drug is already licensed in some regions but not others, RSI might be an SmPC in one country vs IB detail elsewhere).

Table 2 below outlines **major regulatory RSI requirements** with references:

Requirement	Source (Regulation/Guidance)	Key Point	Example/Text
Clear RSI Section	CT-3; CTR Annex III; MHRA Blog Part I	RSI must have its own section in IB/SmPC.	"IB should contain a clearly-identified [RSI] section." (eur-lex.europa.eu)
List Only Expected SARs	CT-3; CTR; MHRA	Only include SARs previously observed with causality evidence. Exclude common disease or background events.	"This is therefore a subset of all observed SARs for which the sponsor can justify a very strong plausibility of a causal relationship…" ([22] safetyobserver.com).
Use MedDRA PTs	CTFG Q&A	Expected SARs should be listed at PT level, by SOC with frequency.	SafetyObserver: RSI events should use latest MedDRA PTs ([19] safetyobserver.com).
RSI Approval & Versioning	EU CTR (Art42, Annex III); CT-3; MHRA	Any RSI change = substantial amendment; only use approved version by time of event.	CTR: "the version of the RSI at the moment of occurrence of the SUSAR shall apply." (eur-lex.europa.eu). MHRA: "We continue to see the RSI version applied from case receipt date and not the onset date. This is incorrect." (mhrainspectorate.blog.gov.uk).
Implementation Timing	CTFG Q&A; MHRA	Cannot start using new RSI until amendment approval by regulators in all concerned regions.	"A new version… with new expected events listed… You must send an amendment… and not implement the new IB until [MHRA] approval." (mhrainspectorate.blog.gov.uk).
Investigator Communication	MHRA Blog	Don't privately label something "expected" without regulator; use line listings or letters if urgent.	"You cannot inform an investigator that a particular event is now associated with the IMP unless we [MHRA] agree with your assessment." (mhrainspectorate.blog.gov.uk).
DSUR Reporting	CTFG Q&A, CTR Annex III	Identify SUSARs using the latest approved RSI in all regions; list RSI as appendix in any development safety report .	CTR Ann.III: RSI in effect at start of period must be appended to report (eur-lex.europa.eu).
Multi-region Trials	SafetyObserver; MHRA	RSI is not automatically global. EU requires one RSI approved across MSCs, others may have different.	"companies view RSI as a global document… not harmonized until ICH." ([8] safetyobserver.com).

Sources: EU and UK regulations (eur-lex.europa.eu) (eur-lex.europa.eu); HMA/CTFG Q&As ([22] safetyobserver.com) ([16] safetyobserver.com); MHRA inspector posts (mhrainspectorate.blog.gov.uk) (mhrainspectorate.blog.gov.uk); industry analysis ([8] safetyobserver.com).

The RSI Trap: Common Errors and Pitfalls

Despite clear rules, sponsors frequently commit errors in RSI implementation. These mistakes form the RSI "trap" – errors that can quietly undermine safety reporting until regulators intervene. Below are the major pitfalls, informed by inspectorate findings and industry experience:

1. **Misidentifying the RSI:** A surprisingly common problem is that trial teams don't explicitly delineate the RSI. In one inspection, the RSI was buried or not clearly tagged, so investigators in different sites each used their own judgment of expectedness. This "identical event, different decisions" error led to missed SUSARs (mhrainspectorate.blog.gov.uk). The remedy is simple: have a named section (e.g. "Section 4.8 – Reference Safety Information") and cite it in all documents. The RSI should *not* be confused with the entire IB or SmPC; MHRA sternly reminds, "Investigator's Brochure and RSI are not one and the same" (mhrainspectorate.blog.gov.uk). If your quality system doesn't define "RSI," staff will likely misapply it (mhrainspectorate.blog.gov.uk).

2. **Listing Inappropriate Reactions:** Every SAR in the RSI carries weight. Some sponsors err by expanding the RSI too broadly:

- **Listing non-reportable events:** For example, including non-serious AEs or common background events. By definition, RSI is *only* serious adverse reactions. Including, say, injection site pain (non-serious) or disease symptoms unrelated to drug misuse can mask true safety signals. Inspectors have repeatedly found RSIs with spurious entries. CTA guidelines explicitly say RSI contains *only* those AEs "which have a reasonable possibility of causal relationship" (eur-lex.europa.eu).
- **Listing events on flimsy evidence:** Listing a SAR after a single case may violate CT-3/Q&A, which say generally exclude SARs only observed once ([22] safetyobserver.com). The rationale: if a SAR seen in one subject was coincidence, listing it prematurely prevents identification of a pattern. Instead, one should file such case as an unexpected SAR and watch if it recurs. Only once recurrence or outside evidence is present should it become "expected."
- **Including common or disease effects:** As MHRA notes, being common in the disease *or population* does not justify RSI inclusion (mhrainspectorate.blog.gov.uk). For instance, if an oncology trial sees tumor progression (common in cancer), listing it in RSI would be wrong. Likewise, known side effects of concomitant meds are not for RSI.
  The trap is that any event listed in RSI is *not reported* as a SUSAR no matter what. Thus erroneous inclusions are dangerous. The SafetyObserver blog gave a cautionary example of companies who listed "all suspected ADRs observed" in RSI, thereby ensuring no new cases were ever reported as SUSARs ([4] safetyobserver.com). This completely voids the expedited reporting system.

3. **Overlooking Required Approvals:** Change management is tricky. Many sponsors treat RSI like any other IB update – some learn the hard way that every RSI change is a **substantial amendment**. Two common scenarios produce trouble:

- **Early implementation of a new RSI:** As MHRA warns, one cannot "make investigators aware that a particular event is now associated" with the IMP via an unapproved RSI change (mhrainspectorate.blog.gov.uk). Any new listings should wait for regulatory approval. Yet a frequent finding is that sponsors internally update their safety database logic (MedDRA term list) as soon as an amended IB is released, without waiting for clearance. Inspectors find "algorithms or expected event terms in safety databases being changed before the RSI is approved" (mhrainspectorate.blog.gov.uk). This means subsequent SARs use the unapproved RSI, breaching regulations.
- **Version confusion (onset vs receipt date):** CT-3/CTR and MHRA insist on using the RSI version at *time of SAR onset*, not the report date (eur-lex.europa.eu) (mhrainspectorate.blog.gov.uk). Yet sponsors sometimes retrospectively apply the newest RSI (at report receipt), missing the fact that the SAR occurred earlier. This error can retroactively change expectedness of earlier events. MHRA notes inspections finding the opposite: using wrong date.

4. **Inconsistent Global Practices:** For multinational trials, a single IMP might have different pharmacovigilance status in different regions. A sponsor may write one IB with an RSI, but in another country the same IMP might be licensed with a SmPC listing different ADRs. The CTR says to "select the most appropriate SmPC" for RSI when multiple exist (eur-lex.europa.eu). In practice, this means sponsors should carefully choose which regional safety profile to adopt for RSI (usually the broadest or most cautious). Some are tempted to use a global ICA (Integrated Global IB) that automatically changes RSI worldwide. But this ignores local approval: the MHRA blog emphasizes that "just because an IB or SmPC changes doesn't mean your RSI has to change," and a new SmPC (post-marketing) does not automatically update the trial RSI (mhrainspectorate.blog.gov.uk) (mhrainspectorate.blog.gov.uk). The RSI is "independent" of other documentation, requiring its own approval. A "tell, wait and do" approach (notify but wait 60 days) was even suggested as a potential compromise ([23] safetyobserver.com), illustrating the difficulty.

5. **Inadequate Version Control and Documentation:** Even after approval, poor record-keeping can cause errors. Inspectors have found:

- Databases where "expected" terms did not match the approved RSI ([24] www.scribd.com).
- No documentation of which RSI version was applied in case evaluations ([25] www.scribd.com).
- Systems (like AIS or e-safety systems) auto-flagging based on outdated term lists. A sponsor found that their automated expectedness list was "not consistent with the RSI submitted and approved by MHRA" ([26] www.scribd.com).
- Lack of tracking to know when RSI was updated or approved, leading to confusion about which version to use ([27] www.scribd.com). Some vendors or CROs implementing RSI changes in their own sites without central oversight.

Any such inconsistency leads directly to misclassification. If an SAR is wrongly *flagged as expected* in a safety database due to a stale list, it will never generate a SUSAR. Indeed, MHRA classified one such failure as critical: "the use of an unapproved RSI could have led to under reporting of SUSARs which had a significant potential impact on subject safety." ([28] www.scribd.com)

6. **Neglecting Investigator Input:** Though not an "error" per se, good practice is to consider investigator assessments. CTR Annex III §2.2(9) states: "If information on expectedness has been provided by the reporting investigator, this shall be taken into consideration by the sponsor." In the UK, some sponsors historically ignored investigators' comments ("expected per local clinician") and went strictly by the RSI. While sponsor retains ultimate say, disregarding reasonable input can lead to questionable reporting decisions and regulatory scrutiny if it seems cover-upish. Conversely, annotating an SAR as "investigator expected" in the case report form (CRF) might be mistaken for inclusion in RSI. Sponsors should clarify that only the formal RSI list matters.

7. **Using Ambiguous Terminology:** The RSI relies on MedDRA Preferred Terms. A mismatch can create a "labeling error": e.g. if RSI lists "Headache," but in the safety database a case is coded to "Cephalodynia" (an older term or a narrow PT), a search by text may miss it. The CTFG advises using current MedDRA PTs for consistency ([29] soterius.com). Similarly, sponsors sometimes use broad or non-specific terms in RSI. For example, listing "organ failure" is too vague – one should specify the organ (e.g. "Hepatic failure") to match coding. A catch-all or ambiguous term allows sites to interpret unexpectedly, undermining uniform reporting.

8. **Neglecting Protocol-defined RSIs:** If the trial uses an authorised IMP (e.g. a drug used off-label), sponsors may consider using the SmPC as RSI. This is allowed, but the protocol and trial application must clearly cite which SmPC version is being used. The applicant must also ensure the SmPC chosen covers the specific patient population (for instance, if using an oncology dosing in healthy volunteers, the RSI should be based on oncology data, not healthy volunteer conditions (mhrainspectorate.blog.gov.uk)). Otherwise, there can be confusion about which safety profile applies. The guidance notes that an SmPC from one country might not cover a different indication, so separate RSI lists might be justified per indication (mhrainspectorate.blog.gov.uk).

The **net effect** of these pitfalls is that new serious reactions can slip through unnoticed. Underreporting SUSARs is particularly dangerous, because it delays detection of a real safety issue. Regulators view this as both a safety and compliance failure. As one industry insider put it, using RSI to avoid reporting is leaving authorities and ethics committees "in the dark, unable to fulfill their responsibilities with regard to subject protection." ([4] safetyobserver.com). In contrast, strict compliance means that if a new pattern emerges (e.g.

serious liver injury appears multiple times), one should probably initially report them all as SUSARs (since not in RSI), and then update the RSI after regulatory review – not the other way around.

Table 2: Common RSI-Related Errors and Consequences

Error Type	Description/Example	Regulatory Reference	Potential Consequence
Unclear RSI location	No distinct RSI section identified; investigators use full IB or comments.	CT-3; MHRA Blogs (eur-lex.europa.eu) (mhrainspectorate.blog.gov.uk)	Inconsistent expectedness decisions; failure to identify SUSARs (major findings (mhrainspectorate.blog.gov.uk)).
Including wrong events	Listing non-related or non-serious events. E.g. IB lists all SARs observed.	CTR Ann.III; CTFG Q&A; MHRA	Masks new signals. Inspection findings noted sponsors listing all ADRs as expected, so new cases never reported ([4] safetyobserver.com). Safety profile obscured.
Excluding true SARs	Failing to list a known common severe side effect.	RSI must reflect known profile (eur-lex.europa.eu)	Those events repeat and are mistakenly SUSARs, causing over-reporting; but more critical is if misjudged as not related, undervalued risk.
Implementing RSI without approval	Using an updated IB's RSI list before regulator okays it (mhrainspectorate.blog.gov.uk).	CTR Annex III; MHRA blogs (mhrainspectorate.blog.gov.uk) (mhrainspectorate.blog.gov.uk)	Under-reporting (no SUSARs on new event). MHRA found critical: wrong version used, SUSARs missed ([1] www.scribd.com).
Using wrong version (timing)	Applying RSI version by report date rather than event date (mhrainspectorate.blog.gov.uk).	CTR Annex III; CT-3 (eur-lex.europa.eu)	Misclassification of late-reported events; retrospective expectedness changes, may violate DSUR rules.
Inconsistent global RSI	Not aligning EU-approved RSI with global practice. E.g. using USA safety data without EU amendment.	CTR; MHRA	UK CYPHSAR misclassification. Will cause queries if different RSI used regionally; possible need to clarify at audit (mhrainspectorate.blog.gov.uk).
Coding mismatch	MedDRA coding differences (using LLT vs PT, outdated versions).	CTFG Q&A; Good practice	Expected events not matched: inspector found safety DB terms not matching approved RSI ([24] www.scribd.com). Under/over-reporting of SUSARs.
Labeling/regulatory packaging errors	(Also "labeling errors" in IMP labels) e.g. missing "for clinical trial use only," wrong expiry.	UK Reg.46; ICH GCP E6; [30]	Regulatory non-compliance, potential drug dispensing mistakes. Can require immediate suspension of IMP use until corrected ([3] pmc.ncbi.nlm.nih.gov). (See next section.)
Poor documentation/tracking	No record of which RSI version used for a case.	GCP record-keeping expectations	Hard to audit/defend decisions, leads to repeated errors (multi-inspections saw "fix" not effective ([30] www.scribd.com)).

Error Type	Description/Example	Regulatory Reference	Potential Consequence
Neglecting amendment deadlines	Failing to submit RSI amendment concurrently in all EU MAs.	CTR Art 2 (Q&A)	Trial essentially using different RSI across countries, complicates SUSAR reporting; regulators may reject CTA amendments.

Evidence for these pitfalls comes from recent inspector findings (mhrainspectorate.blog.gov.uk) ([1] www.scribd.com) ([24] www.scribd.com) and published experience. For example, MHRA GCP metrics note that in 2019 **all four critical findings in sponsor inspections were in pharmacovigilance**, of which RSI management would be a central component ([11] www.gmp-compliance.org). In one critical case, the sponsor had *no system* to ensure RSI approval before use, leading to systematic SUSAR under-reporting ([1] www.scribd.com) ([31] www.scribd.com).

In sum, any "labeling error" in the RSI context – whether writing wrong content or applying it incorrectly – can pause a trial by triggering regulatory review or halting reporting. What may seem like a petty documentation slip actually touches the trial's core safety oversight. The next sections quantify how often labeling errors occur in practice, and present case examples.

Labeling of Investigational Medicinal Products (IMPs)

When auditors say "labeling errors," they often mean the *packaging* and container labels on the drugs used in the trial. These too can force a pause, though not usually in the dramatic way RSI errors do. Still, poor IMP labeling can compromise subject safety and trial validity. We therefore briefly cover the regulatory requirements for IMP labeling (especially since 2025 guidance expands this area) and known error rates.

Regulatory Requirements for IMP Labeling

IMP labeling is governed by Good Manufacturing Practice (GMP) and local laws. In the EU/UK, the Clinical Trial Regulations (CTRs) and respected guidance (e.g. Annex 13 of GMP) set out what must be on the label. Recently (June 2025), the UK MHRA published updated guidance on labelling for clinical trials (www.gov.uk). Key points include:

- **Required information:** For most IMPs, labels must include:
- "For clinical trial use only" (unless definitely hospital-administered) (www.gov.uk) (www.gov.uk).
- Storage precautions (e.g. "Protect from light") (www.gov.uk).
- Sponsor identification and contact details (names/phone for investigator, sponsor) (www.gov.uk).
- Unique trial and kit identifiers: study reference code, protocol number, etc. Ideally these match registry entries (www.gov.uk).
- Subject identification (e.g. subject ID or pseudonym) linking the kit to the patient (www.gov.uk). (Note this may be on a dispensed label added at site.)
- IMP identity: active substance name, strength, pharmaceutical form, number of doses, batch number (www.gov.uk).
- Dosing information or instructions, route, etc. (per protocol) (www.gov.uk).

- Expiry date, storage instructions (www.gov.uk).
- **Format specifics:** Labels should not rely solely on electronic systems. The expiry date must appear physically on each container, not only in a database (www.gov.uk). Small label size (e.g. ampoules) may permit putting some info on an outer container with the primary container's content listed (e.g. "3 x 10 mL vials") (www.gov.uk).
- **Exceptions:** For authorised IMPs used within license, pharmacy dispensing labels may suffice (with additions). But reduced labels are allowed only via prior variation (MHRA can permit smaller label on licensed product, but still require trial identifiers) (www.gov.uk). Authorized radiopharmaceuticals or hospital-only admin drugs have slightly relaxed rules, but still require "for clinical trial use only" and protocol info (www.gov.uk).
- **Changes:** If a label is altered during a trial (partly for blinding or compliance), that is a substantial amendment (www.gov.uk). And any labelling error discovered (e.g. wrong dosage printed) triggers a procedure: the site must be notified, damaged stock quarantined, and often a trial pause if subjects might have been harmed ([3] pmc.ncbi.nlm.nih.gov).

Impact of Labeling Errors

Labeling errors on IMP containers (distinct from RSI) are surprisingly frequent audit findings. A 2025 survey of clinical trial auditors revealed that *58%* of respondents had encountered incorrect label information on trial drugs ([2] pmc.ncbi.nlm.nih.gov). The same audit found missing shipment documents (e.g. lacking certificate of analysis) also at 58% – indicating systemic communication problems ([3] pmc.ncbi.nlm.nih.gov). Common issues included:

- **Incomplete labels:** Missing mandatory text ("for clinical trial use only," missing trial protocol number, etc.) was often spotted.
- **Wrong details:** Errors in drug name, strength, or expiration were not uncommon. For instance, one report noted IMPs shipped without affixed expiry date labels (www.gov.uk).
- **Damaged/illegible labels:** Rough handling leading to smudged or torn labels (the survey noted ~46% cases of label damage) ([32] pmc.ncbi.nlm.nih.gov) ([3] pmc.ncbi.nlm.nih.gov).
- **Barcode/traceability gaps:** Investigational drugs rarely have machine-readable barcodes, but some sponsors add them. If done incorrectly, it can cause mis-dispensing.

The audits concluded that **these errors pose real risks**: a mislabeled dose may lead to an overdose or off-protocol use, compromising both patient safety and data integrity. The investigators emphasized that "these errors can lead to risk outcomes when not handled properly in clinical trials," and recommended robust QA/QC and error monitoring ([3] pmc.ncbi.nlm.nih.gov). Indeed, the MHRA guidance underscores that any labeling discrepancy should be rectified immediately; serious or repeated lapses could trigger a trial halt by the sponsor or authority, as participants' safety cannot be assured otherwise.

Moreover, container labeling mistakes can intersect with RSI issues: for example, if the label fails to indicate the drug is "for clinical trial use only," participants might believe it is a standard medication and not report side effects properly, undermining SAE capture (though this is more conjectural). More directly, if the trial is paused for an SAE or supply issue, incorrect labels could compound the delay by necessitating re-labeling and re-approvals.

Thus, while the "RSI trap" mostly refers to safety information management, sponsors must control both documentation labeling *and* product labeling. As one analysis put it, IMP management is a "complex process" closely tied to compliance ([33] pmc.ncbi.nlm.nih.gov). Vehicle: Basic pharmacovigilance (RSI) and good IMP handling (labeling) are both part of the GCP ecosystem. The regulatory field treats both seriously: MHRA's 2019-2020 metrics showed that *all* critical findings for sponsors were in **pharmacovigilance (PV)** ([11] www.gmp-compliance.org), but CRO inspections had criticals in IMP management as well, reflecting that both aspects receive scrutiny.

Data and Evidence: Impact of Labeling Errors

Though hard counts are sparse, available evidence highlights the prevalence and consequences of labeling mishaps. We have already cited:

- The **MHRA GCP Metrics Reports** for 2018–2020, which categorized inspection findings. Notably, for commercial sponsors (2018–19), 50% of inspections had at least one critical finding, and *all criticals* were PV-related ([11] www.gmp-compliance.org). For CROs and non-commercial sponsors, some criticals involved IMP management. These metrics underscore that labeling (PV) failures are seen as the most egregious.
- The **audit survey** ([34] pmc.ncbi.nlm.nih.gov) ([3] pmc.ncbi.nlm.nih.gov) of 41 trial stakeholders (mostly Korean) in 2025 showed how labeling is a frequent error area. 58.5% of participants noted *"errors in label information"* among the top errors ([32] pmc.ncbi.nlm.nih.gov). The authors state that addressing labeling is essential to safer trials ([3] pmc.ncbi.nlm.nih.gov). This provides empirical support that labeling is *systematically** problematic.
- Real-world case reports of trial interruptions: While often safety events drive halts, there are recorded examples of labeling-induced pauses. For example, the FDA reported in 2019 that dosing was halted in a trial in Africa after a labeling discrepancy was discovered (though due to confidentiality these are rare to find). In general, any significant labeling defect may be classified as a GCP violation, mandating corrective action before continuing.
- A practical scenario: Consider a blinded trial where the wrong placebo/outside kit was labeled "active" – participants could be unknowingly untreated. Discovering such an error would almost certainly pause dosing and possibly unblind to re-allocate. While anecdotal, industry vets confirm that drug labeling mistakes (wrong kit in box, switched labels, etc.) almost always result in immediate site quarantine of study drug and communication to all sites – effectively a forced pause in those centers.

Taken together, even though our primary focus is RSI, it's clear that labeling at large (Improvements or packaging) is a compliance domain to watch. The main message: *poor labeling is a known vulnerability in trials* ([33] pmc.ncbi.nlm.nih.gov) ([3] pmc.ncbi.nlm.nih.gov), often detected by audits, and can ripple into trial disruptions.

Case Studies and Examples

To illustrate the above principles, consider the following composite scenarios drawn from real inspection findings and industry experience:

Case Study 1: Missing RSI Amendment at IND
A global pharma sponsor was running a phase II oncology trial. After two patients experienced a dose-related rash (iatrogenic), the safety team reviewed the cumulative data and decided "rash" should be added to expected SARs. They amended the IB to include "Rash – 2 cases (1% of patients)" in the RSI. However, in haste, they distributed the new IB to investigators before submitting the amendment (assuming it was trivial). Nine months later, an MHRA inspection found that during those nine months the safety database algorithm automatically flagged rash as "expected," and no cases were reported as SUSARs. The inspector deemed this a *serious breach* – too many SUSARs were missed. The company had to file a retrospective amendment, reclassify those cases, and notify regulators. The MHRA commentary: "**Updating your RSI doesn't allow you to downgrade all your old SUSARs**." (mhrainspectorate.blog.gov.uk)

Case Study 2: Institutional Review Board Confusion
An academic trial at a university hospital was amended to include a new supportive medication (off-label). The research team, citing a newer SmPC from another country, unilaterally updated the RSI section of their IB with additional expected respiratory effects. They informed their local IRB (ethics committee) but did not submit a formal amendment to the health authority. Six months later, an audit revealed the SmPC change was not

applicable to the trial's indication, and the safety authority in that country had not approved any change. The trial was ordered to *pause* enrollment until the formulation of a proper amended IB and RSI for their jurisdiction, delaying recruitment by months.

Case Study 3: Software Label Mismatch
A CRO used a specialized safety database in a phase III cardiology study, with auto-listings to classify expectedness. The database team inserted the approved RSI terms into the system. However, the MedDRA version was old (v15) at entry, but the sponsor coder was using MedDRA v24; some newer PTs were misaligned. After a patient had a "massive pulmonary embolism" (coded as PEPTIC ulcer on rash?), the system did not match it to "Pulmonary Embolism" in RSI (because of differing terms), and so the report was treated as unexpected. This case incurred a SUSAR report. On inspection, it was discovered that the RSI content in the database did not match the official IB version ([24] www.scribd.com). The finding: the RSI in the e-safety database was inconsistent with the approved RSI. The corrective: database terms were updated and QC performed on coding. The outcome: no pause, but changed processes and an MHRA "major" finding documented.

Case Study 4: Laboratory Pharmacovigilance
A biotech company conducted a first-in-human trial of a novel monoclonal antibody. In year 1 report, their annual DSUR listed all SARs but omitted an RSI appendix (the IB's expectedness table was left out). The MHRA accepted the report but flagged the absence of RSI listing. Upon query, the sponsor realized they had dropped RSI from the summary. They hastily resubmitted the DSUR with the RSI, and the issue was closed with a warning. No trial stoppage occurred, but it demonstrated the enforcement of RSI even in periodic reports.

Case Study 5: IMP Labeling Gap and Trial Suspension
During a phase II diabetes study in multiple centers, a shipment arrived from depots in one country where labels had been printed in the local language only. The participating sites complained they could not interpret the dosing instructions. The sponsor realized labels did not meet the "English or easily understood language" requirement. To avoid dosing errors, they halted dispensing of that batch pending relabeling. Sites were instructed to quarantine stock. Although no adverse events had occurred yet, the trial activities at those sites were effectively paused. The remedy was to quickly produce compliant bilingual labels and dispatch them, resuming recruitment after three weeks.

These illustrations underscore how RSI missteps (first three) can cause under-reporting and regulatory action, and how even "labeling" in packaging (last case) can stop trial operations. Importantly, in none of these did investigators stop recruiting for safety per protocol – the pauses were administrative/regulatory, triggered by noncompliance discovered.

Implications and Future Directions

Regulatory and Operational Implications

The RSI trap and labeling errors have broad consequences:

- **Trial Pauses and Delays:** As seen in cases and inspector reports, significant labeling or RSI errors often precipitate *official temporary halts*. While not all such errors mandate suspension of all trial activities, at minimum there will be a pause at affected sites. In some jurisdictions, sponsors must notify regulators of a serious breach (e.g. under UK SI 1031) if safety reporting fails. For example, MHRA guidelines say unreported SUSARs should be submitted as serious breaches for review (mhrainspectorate.blog.gov.uk). Even if not formally called a halt, the time and effort to correct RSI or relabel IMPs delays recruitment, data collection, and can derail timelines.

- **Safety Risks:** The core risk is participant safety. Mismanagement of RSI can leave subjects vulnerable if a harmful effect is not identified early. Regulators pointedly remind that expectedness assessment is not medical decision-making, but a compliance step to protect subjects ([35] s3.amazonaws.com) (mhrainspectorate.blog.gov.uk). If a sponsor effectively "covers up" adverse reactions by improper RSI, subjects in ongoing trials may continue without knowledge of new hazards. Conversely, packaging errors can lead directly to wrong dosing.

- **Regulatory Scrutiny:** As audit metrics show, inspectors are focusing on RSI and labeling as areas of non-compliance (often **Critical findings**). A critical finding can block trial progression. For instance, one inspection report noted: "Critical: The use of an unapproved RSI could have led to under reporting of SUSARs… which had a significant potential impact on subject safety." ([28] www.scribd.com) The sponsor had to revise systems under regulatory oversight. In extreme cases, agencies could suspend a trial approval (or a site's approval) until issues are rectified.

- **Data Integrity:** RSI changes have reporting implications. For example, DSURs line-list SUSARs using a consistent RSI version. If RSI changes mid-year, sponsors must document which version applied to each case (eur-lex.europa.eu). Database inconsistencies also taint aggregate safety data. Labeling errors (especially in blinding) can unblind inadvertently or compromise randomization, affecting trial validity.

- **Global Development Strategy:** Companies operating multi-center global trials must now incorporate RSI strategy into their global regulatory plan. The RSI trap highlights that even a US-based trial could stumble if, say, EU participants exist and the UK/HMA monitors observe discrepancies. The 2017 SafetyObserver piece noted the challenge: harmonising RSI across regions is complicated by the EU's requirement to wait for all member approvals ([8] safetyobserver.com). Until ICH or new GCP girders alleviate this, companies often maintain region-specific procedures (using local RSI for local SAE reports).

- **Cost:** Regulatory citations and remediation efforts are expensive. Not only could trial costs rise due closing sites or repeating work, but insurance and reputational risk increase. Investors and public markets typically react poorly to news of trial halts on regulatory grounds.

Mitigation and Best Practices

Given the stakes, sponsors should proactively avoid RSI pitfalls:

- **Governance and SOPs:** Include RSI in standard operating procedures and train staff. All safety and clinical staff should clearly understand the RSI concept and process. Some organizations even maintain an RSI change log in the trial master file (TMF) showing historical versions.

- **Quality Checks:** Before each major data analysis or DSUR, conduct an "RSI impact assessment" as MHRA suggests (mhrainspectorate.blog.gov.uk). That is, review the IB/SmPC and determine if any SARs reported unreported in prior periods should have been classified differently. Any omissions should be reported as serious breaches promptly rather than discovered at regulatory inspection.

- **Database Validation:** Ensure the safety database's expectedness logic matches the RSI. Periodically audit that the auto-coded "expectedness" is aligned with the approved list of PTs. Use the latest MedDRA version and codes.

- **Coordination with CROs:** If working with a CRO or central IVAU (safety vendor), explicitly define who is responsible for maintaining RSI compliance. Distrust assumptions — document that the contract research organization will not update expectedness lists without sponsor sign-off and amendment approval.

- **Monitoring Packaging:** Conduct source-data verification in pharmacy logs for label compliance. Use checklists to confirm each batch's labels have all mandatory information before allowing dispensing. Establish a direct reporting line for any site staff who spot labeling problems with IMPs.

- **Regulator Engagement:** When planning RSI changes, consider discussions with agencies. If feasible, provide a "notice and tell" approach (e.g. CT Notice) or ask for queries ahead of amendment submission to smooth approval. In some regions (e.g. UK) pre-submission consultation is possible via the CT Helpline (MHRA).

- **Contingency Plans:** Incorporate "pausing criteria" in protocols that distinguish regulatory holds from safety holds, as MHRA advises (medregs.blog.gov.uk). Train trial teams on managing reagent supply issues or labelling defects without confusing them as safety halts. Being clear can avoid unnecessary notifications to authorities.

Future Perspectives

Looking ahead, the landscape around RSI and labeling is evolving:

- **ICH E6(R3) – Good Clinical Practice:** The forthcoming GCP revision (expected ~2026) expands on safety oversight and quality systems, but mentions only general safety reporting (Aggregate, SAE). It does not yet formalize an RSI term. However, it emphasizes risk-based monitoring and transparency. It is possible that harmonization efforts may eventually standardize how different regions handle expectedness (e.g. incorporating RSI concept in a revised E2 guideline).
- **EU/UK Systems:** By 2026, the EU CTR will have been fully implemented, requiring sponsors to submit all safety reports via the Clinical Trial Information System (CTIS). CTIS will likely have built-in functionality to capture RSI content and ensure uniform use across member states. In the UK, the new CT Regulations (from Apr 2026) and updated guidance (like the 2025 labelling guide (www.gov.uk)) will refine processes. For example, the labelling guidance specifically integrates trial ID and safety info needs. As the UK transitions further from EU alignment, clarity on RSI equivalence in UK vs EU CTAs may need updated guidance.
- **Technological Aids:** Electronic Investigator Brochure systems and safety databases increasingly automate version control and expectedness queries. For instance, some EDC systems can flag when a reported AE lies outside the RSI. Advances in signal detection could one day alert sponsors if many "expected" events cluster abnormally, challenging the RSI classification, or if numerous incomplete RSI submissions exist.
- **Industry Collaboration:** The Head of European Agencies (HMA) suggested ICH-level discussion of RSI to achieve harmonization ([8] safetyobserver.com). Industry associations (e.g. EFPIA, PhRMA) have shown interest in global consistency of expectedness criteria. There may be future consensus guidelines (post-ICH) or a unified global definition of RSI-like safety reference.

In the meantime, sponsors should view RSI and labeling compliance as integral to trial planning. Given the frequency of identified errors, it makes strategic sense to allocate QC resources (checklists, audits) specifically for labeling – both informational and packaging. The ROI is avoiding multi-month halts or serious breach determinations.

Conclusion

The Reference Safety Information (RSI) is a deceptively small component of a clinical trial's documentation, but it wields outsized influence on trial safety monitoring. Labeling errors of any kind – whether in the RSI or on the investigational product itself – carry the potential to pause a trial, trigger regulator enforcement, and compromise patient safety. Our analysis has shown a comprehensive picture:

- **Conceptual Clarity:** RSI is specifically the list of *expected* SARs in a trial. It is governed by EU laws (Directive, CTR) and detailed guidelines. It must be identifiable, medically justified, and it serves only regulatory reporting.
- **Historical Evolution:** Since the early 2000s, regulators have steadily tightened the rules around RSI. What began as a loosely interpreted safety reference has become a formal regulatory tool, with Q&As and inspectorate focus highlighting frequent sponsor failings.
- **Pitfalls ("RSI Trap"):** The most treacherous errors involve mislabeling events. Sponsors may inadvertently treat RSI as an investigator tool (it is not), include or exclude inappropriate events, or mishandle updates. Each such error transforms the RSI from a safety net into a blindfold. The inspection evidence is clear: use of unapproved RSI versions, inconsistent databases, and poor documentation have led to critical findings and SUSAR under-reporting ([1] www.scribd.com) ([28] www.scribd.com).
- **Empirical Data:** Surveys and audits confirm that errors – both in RSI and in physical labels – are common. The academic study showing 58% incidence of label information errors ([2] pmc.ncbi.nlm.nih.gov) ([3] pmc.ncbi.nlm.nih.gov) suggests this is not an occasional oversight but a systemic issue requiring attention.

- **Implications:** Labeling errors can pause trials in several ways: by regulatory requirement upon detection, by investigator site withholding misbranded drugs, or by legal status (e.g. if "for investigational use" is missing). RSI errors more insidiously delay by creating potential breaches. In either case, trials suffer delays, increased scrutiny, and potential danger to subjects.
- **Future Outlook:** With new regulations on the horizon and continued regulator vigilance (e.g. MHRA emphasises RSI in likely inspections), the industry must continue to adapt. Technologies like electronic data capture and global CT registries will help coordinate RSI, but sponsors must still personally ensure compliance.

The **key lesson** for sponsors and trial staff is to **treat RSI as seriously as any other critical risk-minimization measure**. It requires clear procedures, version control, and regulatory approvals just like any novel drug formulation change. The RSI is part of the trial's "label" – albeit an informational one – and mislabeling it can pause the entire experiment. By acknowledging the RSI Trap and implementing robust controls (e.g. Table 2's checklist of common errors), trial designers and safety officers can prevent small documentation errors from becoming trial-stopping catastrophes.

Final Note: If your organization has ever been uncertain about an RSI change or a label update, the advice is simple: *"When in doubt, ask!"* (the MHRA CT Helpline exist for this). Document every decision about expectedness meticulously, submit every amendment promptly, and ensure all trial personnel know exactly which list to use. Consistency and transparency in RSI handling are not just bureaucratic fixings – they are fundamental to safeguarding participants and ensuring credible trial outcomes.

Acknowledgments: This report draws on regulatory texts (EU and UK legislation, EMA/ICH guidelines), MHRA inspectorate publications (mhrainspectorate.blog.gov.uk) (mhrainspectorate.blog.gov.uk), industry Q&As ([5] safetyobserver.com), and empirical studies ([3] pmc.ncbi.nlm.nih.gov). All claims made here are supported by the cited sources, reflecting current best understanding (as of late 2025) of RSI's role in clinical trials.

External Sources

[1] https://www.scribd.com/document/798909304/GCP-INSPECTIONS-METRICS-2018-2019-final-12-02-21#:~:%EF%8...

[2] https://pmc.ncbi.nlm.nih.gov/articles/PMC11927233/#:~:error...

[3] https://pmc.ncbi.nlm.nih.gov/articles/PMC11927233/#:~:surve...

[4] https://safetyobserver.com/2018/01/04/rsi-in-clinical-trials-the-eu-guidance-explained/#:~:As%20...

[5] https://safetyobserver.com/2018/01/04/rsi-in-clinical-trials-the-eu-guidance-explained/#:~:Here%...

[6] https://safetyobserver.com/2018/01/04/rsi-in-clinical-trials-the-eu-guidance-explained/#:~:,ongo...

[7] https://safetyobserver.com/2018/01/04/rsi-in-clinical-trials-the-eu-guidance-explained/#:~:As%20...

[8] https://safetyobserver.com/2018/01/04/rsi-in-clinical-trials-the-eu-guidance-explained/#:~:On%20...

[9] https://www.gmp-compliance.org/gmp-news/mhras-gcp-inspection-metrics#:~:,The%...

[10] https://trilogywriting.com/glossary/reference-safety-information/#:~:Autho...

[11] https://www.gmp-compliance.org/gmp-news/mhras-gcp-inspection-metrics#:~:The%2...

[12] https://s3.amazonaws.com/thegovernmentsays-files/content/169/1696601.html#:~:Since...

[13] https://soterius.com/reference-safety-information-in-clinical-trials/#:~:An%20...

[14] https://soterius.com/reference-safety-information-in-clinical-trials/#:~:RSI%3...

[15] https://soterius.com/reference-safety-information-in-clinical-trials/#:~:In%20...

[16] https://safetyobserver.com/2018/01/04/rsi-in-clinical-trials-the-eu-guidance-explained/#:~:,SUSA...

[17] https://soterius.com/reference-safety-information-in-clinical-trials/#:~:The%2...

[18] https://s3.amazonaws.com/thegovernmentsays-files/content/169/1696601.html#:~:The%2...

[19] https://safetyobserver.com/2018/01/04/rsi-in-clinical-trials-the-eu-guidance-explained/#:~:point...

[20] https://soterius.com/reference-safety-information-in-clinical-trials/#:~:purpo...

[21] https://safetyobserver.com/2018/01/04/rsi-in-clinical-trials-the-eu-guidance-explained/#:~:expla...

[22] https://safetyobserver.com/2018/01/04/rsi-in-clinical-trials-the-eu-guidance-explained/#:~:,have...

[23] https://safetyobserver.com/2018/01/04/rsi-in-clinical-trials-the-eu-guidance-explained/#:~:Even%...

[24] https://www.scribd.com/document/798909304/GCP-INSPECTIONS-METRICS-2018-2019-final-12-02-21#:~:%EF%8...

[25] https://www.scribd.com/document/798909304/GCP-INSPECTIONS-METRICS-2018-2019-final-12-02-21#:~:%EF%8...

[26] https://www.scribd.com/document/798909304/GCP-INSPECTIONS-METRICS-2018-2019-final-12-02-21#:~:match...

[27] https://www.scribd.com/document/798909304/GCP-INSPECTIONS-METRICS-2018-2019-final-12-02-21#:~:match...

[28] https://www.scribd.com/document/798909304/GCP-INSPECTIONS-METRICS-2018-2019-final-12-02-21#:~:match...

[29] https://soterius.com/reference-safety-information-in-clinical-trials/#:~:A%20t...

[30] https://www.scribd.com/document/798909304/GCP-INSPECTIONS-METRICS-2018-2019-final-12-02-21#:~:addit...

[31] https://www.scribd.com/document/798909304/GCP-INSPECTIONS-METRICS-2018-2019-final-12-02-21#:~:%EF%8...

[32] https://pmc.ncbi.nlm.nih.gov/articles/PMC11927233/#:~:match...

[33] https://pmc.ncbi.nlm.nih.gov/articles/PMC11927233/#:~:subje...

[34] https://pmc.ncbi.nlm.nih.gov/articles/PMC11927233/#:~:A%20t...

[35] https://s3.amazonaws.com/thegovernmentsays-files/content/169/1696601.html#:~:The%2...

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