1. Purpose

The intent of this guidance is to

- Define Reference Safety Information (RSI);
- Explain how RSI is used by the clinical trial sponsor (i.e., the Office of Sponsor and Regulatory Oversight (OSRO)), and
- Provide guidance for National Cancer Institute Principal Investigators on how to develop an alternative section in the clinical study protocol that serves as RSI for those Investigational Medicinal Products (IMPs) that are not supported by an Investigator's Brochure (IB).

2. Table of Contents

3. Introduction

The primary purpose of Reference Safety Information (RSI) is to serve as the basis for expectedness assessments of 'suspected' serious adverse reactions ('suspected' SARs) by the sponsor for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) and annual safety reporting to the Food and Drug Administration (FDA). Generally, RSI is presented in the Investigator's Brochure (IB) and only contains expected Serious Adverse Reactions ('expected SARs') to the IMP(s). A broader description of the safety profile of the IMP in addition to the RSI (e.g., tabular presentations of all observed adverse reactions including non-serious adverse reactions, suspected SARs that have occurred only once, and fatal and life-

threatening SARs that are considered unexpected and not included in the RSI), is described elsewhere in the IB.

For clinical studies using an IMP without an IB or other manufacturer-provided product information, the protocol must contain the RSI. When developing the RSI section for the protocol in these cases, refer to the following questions and answers that describe the specifications and expectations for the RSI to be provided in the protocol. These questions and answers are a subset extracted from a larger Q&A document recommending best practices for documenting RSI in IBs (Reference 15.1).

The RSI used by the sponsor to determine expedited reportability **must** be in either the product information provided by the manufacturer (IB, or package insert), or in the protocol. **No other document will be considered a source for the RSI**, for example Informed Consent forms (ICFs), publications, consensus guidances, etc. The RSI section should be specifically identified as such. It is not acceptable to consider the summary of previous information (Summary of Data and Guidance for the Investigator section of the IB, or equivalent in the protocol) to be the RSI. If there is no source for expectedness information for a product (commercial or not), the sponsor's assessment is that the event is unexpected and reportable to the FDA in an expedited manner.

4. What is the purpose of RSI for clinical trials and what should it contain?

The RSI is used for the assessment of the expectedness of all 'suspected' serious adverse reactions (SARs) that occur in clinical trials. The RSI is a list of expected serious adverse reactions, which are classified using Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA, see Reference 15.5). An expectedness assessment is required to be conducted by the sponsor on each 'suspected' SAR to determine expedited reporting of 'suspected unexpected serious adverse reactions (SUSARs). The information is used for the identification of SUSARs in the cumulative summary tabulation of 'suspected' SARs in the Development Safety Update Report (DSUR) or the FDA Annual Report.

The content of the RSI includes a clear list of 'expected SARs' to the IMP(s). These 'expected SARs' are restricted to 'suspected' SARs that were observed previously where, after a thorough assessment by the sponsor, reasonable evidence of a causal relationship between the event and the IMP exists. This confirmation is based, for example, on the comparative incidence of 'suspected' SARs in all previous and ongoing clinical trials and/or on a thorough evaluation of causality from individual case reports.

In general, each 'expected SAR' should also have been reported as a 'suspected' SAR more than once. 'Suspected' SARs that have occurred once cannot usually be considered expected, unless there is a very strong plausibility of a causal relationship with the IMP and a robust justification based on medical judgement is provided. Importantly, the occurrence of a 'suspected' SAR on more than one occasion is not per se adequate justification for the addition of the term to the RSI as an expected SAR.

The list of 'expected SARs' is based on 'suspected' SARs that were previously observed and not on the basis of what might be anticipated from the pharmacological properties of a medicinal product or the compound class (see section 2.C. of ICH E2A (Reference 15.2)).

The RSI should include the nature, frequency, and severity of the expected SARs. Usually, nature and severity are sufficiently described by the preferred term, however, in exceptional circumstances, life-threatening

and/or fatal expected SARs can be included in the RSI. Risk minimization measures including frequent clinical tests (as appropriate) to allow prompt detection of expected SARs listed in the RSI must be included in study protocols.

As a general rule, sponsors do not expect an IMP to cause fatal SARs. Life-threatening SARs are not considered expected for IMPs, unless supported by a positive benefit/risk balance. Thus, fatal and life-threatening SARs are usually considered unexpected even if previous fatal or life-threatening SARs have occurred.

When a fatal and/or a life-threatening SAR is added to the RSI section of a protocol, an update of the benefit/risk statement for clinical trial subjects must be provided and adequate risk minimization measures must be proposed in the updated clinical trial protocol(s).

When the RSI section of a protocol includes life-threatening and/or fatal expected SARs, the number of life-threatening (as assessed by the investigator) and fatal 'suspected' SARs that have previously occurred must be given in the RSI. While the number of all other life-threatening (as assessed by the investigator) or fatal 'suspected' SARs that have occurred and that are considered unexpected and need to be reported should be listed elsewhere in the protocol.

5. What format should be used for displaying the RSI?

The RSI is most effectively presented in tabular form. The nature of the 'expected SARs' must be listed by body system organ class and using Preferred Terms (PTs) as per the latest MedDRA version and followed by the frequency of occurrence which must be calculated on an aggregated level and based on previously observed 'suspected' SARs to the IMP.

If the IMP is under development for different medical conditions, then using separate tables of expected SARs grouped by indication may be appropriate, especially if the expected SARs are different for the different medical conditions, e.g., oncology conditions versus non-oncology diseases.

6. How should the frequency of expected SARs be presented in the RSI?

The frequencies of the expected SARs listed in the RSI are preferred to be in categories (i.e., Very Common, Common, Uncommon etc.; for details see ICH E2C(R2) (Reference 15.3)). If there is an insufficient number of participants exposed to the IMP to use these categories (e.g., during the early stages of product development), then the number of observed 'suspected SARs' for each 'expected SAR' should be provided, together with the number of participants exposed.

7. How should fatal and life-threatening 'suspected' SARs be presented in the RSI?

If there are expected life-threatening or fatal SARs listed in the RSI section, the RSI should include the number of suspected life-threatening and fatal suspected SARs that have occurred. These data should be provided in separate columns.

The numbers of all other life-threatening or fatal 'suspected' SARs that have previously occurred but that are considered unexpected should not be listed in the RSI; these should be listed elsewhere in the protocol. See Table 1 for an example of an RSI table.

Table 1. Example of an RSI table:

Serious Adverse Reactions for the IMP considered expected for safety reporting purposes.

System Organ Class	SARs	Number of subjects exposed (N) = 328		
		All SARs	Occurrence of Fatal SARs	Occurrence of Life-Threatening SARs
		n* (%)	n (%)	n (%)
Gastro-intestinal disorders	Diarrhea	25 (7.6)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	ALT increase	12 (3.6)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	AST increase	9 (2.7)	0 (0.0)	0 (0.0)
Cardiovascular disorders	Myocarditis	33 (10.0)	0 (0.0)	2 (0.6)

*n = number of subjects who have experienced the SAR

8. When are 'suspected' SARs considered unexpected because of specificity and/or severity?

A provision of severity grades using the CTCAE grading system in the RSI is not required. However, in accordance with ICH E2A guidance (Reference 15.2), reports which add significant information on specificity or severity of a known, already documented SAR represent unexpected events. Table 2 lists some SAR examples and the reasons for them being considered as suspected and unexpected.

Table 2. Example of SUSARs and reasons for their reporting.

SAR Listed in RSI	'Suspected' SAR in Individual Case Reports	Unexpected Due to Specificity or Severity
Acute renal failure	Interstitial nephritis	Specificity
Hepatitis	Fulminant hepatitis	Severity
Cerebral vascular accident	Cerebral thromboembolism	Specificity
Exfoliative dermatitis	Stevens-Johnson Syndrome	Severity and Specificity
Transient increase in liver function tests	Increased liver function tests persisting for several months	Severity
Hypertension	Hypertensive crisis	Severity
Herpes Zoster	Multi-dermal herpes zoster	Severity
Sepsis	Septic shock	Severity
Supraventricular Cardiac Arrhythmia	Atrial fibrillation	Specificity

9. How should expected SARs be listed in the RSI?

The use of medical concepts or unspecific terms in the RSI, e.g., "Rash", "Infections" or "Arrhythmia", is not acceptable. Only MedDRA preferred terms (PTs), e.g., exfoliative dermatitis, urticarial rash or hives, herpes zoster, pneumonia, sepsis, atrial fibrillation, are allowed. If there are multiple lower-level terms (LLTs) within a

single PT they are all expected (for example, if the PT hypophosphatemia is included in the RSI table, then the LLT hypophosphatemia is also considered expected). A product that is known to cause immunosuppression may also lead to infections, however only the PTs of the type of infections that have been observed should be considered expected, i.e., all infections cannot be considered expected. A 'suspected' SAR should be considered unexpected unless the PT is listed as an expected SAR in the RSI. For example, if 'urticaria' is not included in the RSI, the occurrence of an individual case of urticarial rash SAR should be classified as a SUSAR.

10. What is understood by synonymous medical terms and are they allowed in the RSI?

Synonymous medical terms (e.g., sedation, somnolence, drowsiness) representing truly the same medical phenomenon are allowed in the RSI (Table 3). This is not to be confused with different forms of the same medical phenomenon e.g., different forms of rash such as rash generalized, rash maculo-papular, rash papular, rash pustular, etc., which are not considered to be the same medical phenomenon and for which specific PTs in the RSI must be listed.

Table 3. Examples of preferred terms and synonymous medical terms.

Preferred Term for Expected SAR in RSI	'Suspected' SAR in Synonymous Medical Term
Pneumonia	Right upper lobe pneumonia
Gastrointestinal bleeding	Melena
Hypophosphatemia	Blood phosphorus decreased

Nevertheless, in accordance with ICH E2A guidance (Reference 15.2), reports which add to the specificity of an expected SAR should be considered unexpected. For example, if respiratory tract infection is listed as an expected SAR, then a lower respiratory tract infection SAR should be considered unexpected.

11. What safety information should not be included in the RSI?

The following safety information should not be included in the RSI section of a protocol, but should be presented elsewhere in the protocol:

- Adverse events (AEs) that were considered unrelated to the IMP by both the investigator and the sponsor.
- Serious adverse events (SAEs) that were considered unrelated to the IMP by both the investigator and the sponsor.
- Non-serious ARs.
- Fatal 'suspected' SARs that are considered unexpected and need to be reported as SUSARs.
- Life-threatening (as assessed by the investigator) suspected SARs that are not considered to be 'expected' SARs for the IMP and need to be reported as SUSARs.
- SARs that have occurred only once, unless there is a very strong plausibility of a causal relationship with the IMP and a robust justification based on medical judgment is provided.
- Deaths or SAEs also considered efficacy endpoints in trials with high mortality or morbidity accepted in the approved protocol by the FDA to be treated as disease related outcome events and not subject to systematic unblinding. However, careful assessment should be performed in cases where disease related

events appear to be enhanced by the IMP. A causality assessment is required for each SAE, and if the investigator considers the disease related event to be IMP-related and the event is serious then it must be reported as a SUSAR.

- SARs that are expected for similar products within the therapeutic class, which did not occur in subjects taking the IMP.

12. What should be included in the RSI in trials if there are no 'expected' SARs for the IMP?

There may be situations where the IMP is not expected to cause any SARs. For example:

- Early in the clinical development of an IMP when subject exposure is low, there may be no 'suspected' SARs reported for the IMP.
- Later in clinical development, some 'suspected' SAR cases may have occurred, but upon evaluation of the available cumulative evidence are not considered to be 'expected' SARs by the sponsor.
- Treatment with certain IMPs does not result in the occurrence of SARs at any point during the clinical development or in post-marketing.

In these cases, a clearly defined section called RSI should still be present, followed by a brief text stating that no SARs are considered expected by the sponsor for the purpose of expedited reporting and identification of SUSARs. Representative text is the following:

> No SARs will be considered expected by the sponsor for the purpose of expedited reporting of SUSARs.

13. What is the procedure for updating the RSI during a clinical trial?

A substantial amendment is always required to be submitted if there are changes to the RSI. However, changes to the format of the table that do not affect the expected SARs or slight modification of exposure rates that do not result in a change in the category of frequency without the addition of new expected SARs and/or new PTs classification are not considered substantial. The addition of new expected SAR PTs as well as an update of the frequency of expected fatal and/or life-threatening SARs is always substantial.

14. What should be used as the RSI for a trial using a combination of IMPs?

For a trial using multiple IMPs, RSI that includes expected SARs for that IMP combination is the best case. When that is not available, then RSI that includes expected SARs based on an evaluation of 'suspected' SARs to a similar combination in previous trials may be used. If there is no data from previous trials which have used the proposed IMP combination, then RSI for each individual IMP may be used. When deciding between these two options, the consequences of using multiple RSI sources on SUSAR reporting when the causality assessment concerns the combination rather than the individual IMPs should be considered (i.e., if a 'suspected' SAR is not expected for any of the IMPs or occurs with increased severity for any of the IMPs, it will be required to be reported as a SUSAR).

15. References

15.1. Clinical Trial Facilitation Group (CTFG), Q&A document – Reference Safety Information.

15.2. ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, October 1994

15.3. ICH E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER), December 2012

15.4. ICH E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry (FDA), March 2018

15.5. Medical Dictionary for Regulatory Activities (MedDRA)

15.6. 21 CFR Part 312.32 Investigational New drug Application – IND safety reporting

15.7. FDA website IND Application Reporting: Safety Reports | FDA (accessed 12Jul2023)

15.8. 21 CFR Part 201.57 Labeling – Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1)

16. Change Summary

Revision Number	Effective Date	Description of Change
1	26JUL2023	New Document

17. Appendix – Definitions

17.1. **Adverse event (AE)**: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (Reference 15.6).

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (Reference 15.4).

17.2. **Suspected adverse reaction (SAR)**: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (Reference 15.6).

17.3. **Adverse reaction**: any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event (Reference 15.7).

For the purposes of prescription drug labeling, the term adverse reaction is defined to mean "an undesirable effect, reasonably associated with use of a drug, that may occur as part of the

pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event" (Reference 15.8).

17.4. **Unexpected**: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (Reference 15.4).

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure (IB) or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. Additionally, adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation are defined as unexpected (Reference 15.6).

17.5. **Serious**: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (Reference 15.6).

17.6. **Life-threatening**: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death (Reference 15.6).

17.7. **Serious and unexpected suspected adverse reaction (SUSAR)**: Any suspected adverse reaction that is both serious and unexpected (Reference 15.6).