研究者手册中安全性参考信息撰写技术指导原则

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I. Overview

Reference Safety Information (RSI) is usually an expectation in the Investigator's Brochure (IB)

List of serious adverse reactions. Sponsors should evaluate clinical trial periods based on RSI

All suspected serious adverse reactions occurring during the period are expected.

This guiding principle is intended to guide the development of approved drugs (including traditional Chinese medicine, chemical drugs and biologics) clinical trials of RSI in IB. Apply these guidelines

If so, please also refer to the International Conference on Technical Coordination for the Registration of Pharmaceuticals for Human Use.

ÿ International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, ICHÿÿE2Aÿ

Management of Clinical Safety Data: Expedited Reporting Definitions and Standards", "E2F: Research and Development "Period Security Update Report" guidelines, etc.

This guideline only represents the current views and understanding of the drug regulatory authorities and does not It is legally binding. With the progress of scientific research, this guideline

The relevant content in the rules will be continuously improved and updated. These guidelines provide guidance for writing safe General considerations for sexual reference information do not cover all situations. If there is any failure to explain

If you have any clear and personalized questions, you can communicate with the Drug Evaluation Center.

2. Contents of safety reference information

(1) Expected serious adverse reactions

Expected serious adverse reactions for completed and ongoing drug clinical trials

Serious adverse events that occurred at least once during the trial and were fully approved by the sponsor

and after comprehensive evaluation, there is reasonable evidence to confirm a causal relationship with the experimental drug,

For example, by comparing the frequency of serious adverse events in clinical trials, or comparing individual cases

An adequate assessment of reported causal relationships is carried out. It is expected based solely on pharmacological properties that

Adverse reactions that may occur but have not been observed with the investigational drug are not expected

Adverse reactions can be found in other sections of the IB (e.g. "Effects in Humans" or "Data").

Summary and Researcher's Guide").

In general, a single suspected serious adverse reaction is not sufficient

List RSI unless there is compelling evidence based on the sponsor's medical judgment that

In fact, there is a clear causal relationship with the experimental drug, and relevant supporting evidence must be provided.

according to. Furthermore, not all suspected serious adverse reactions that occur more than once can be

The inclusion of RSI as an expected serious adverse reaction requires full and complete conduct by the sponsor.

Comprehensive assessment, while increasing expected serious adverse reactions and providing relevant supporting evidence

according to.

Considering that there are currently multiple causal relationship evaluation methods, it is allowed to use one or

Various methods are used to evaluate the adverse events occurring in clinical trials and whether the experimental drugs

There is a causal relationship. According to ICH E2A, adverse drug reactions are

There is at least a reasonable possibility of an adverse event, i.e. a causal relationship cannot be ruled out. because

Therefore, "possibly unrelated" causal relationships should be evaluated with caution. If the researcher cannot determine

To determine whether the adverse event is related to the investigational drug (i.e., “unevaluable”), the sponsor should

Communicate with and encourage researchers to assess relevance. If the judgment result is still

However, as “unevaluable”, the serious adverse event should be considered to be related to the investigational drug.

and reported as suspected and unexpected serious adverse reactions (Suspected Unexpected

Serious Adverse Reaction, SUSAR). However, if it does not support the "Unable to comment"

Serious adverse events that are “priced” are included in the RSI as expected serious adverse events.

(2) Fatal and/or life-threatening serious adverse reactions

In general, sponsors should not expect that an investigational drug will cause death and/or

Serious life-threatening adverse reactions. Therefore, even if there has been a previous fatality and/or

Serious life-threatening adverse reactions that are generally considered unexpected. But already

Serious adverse reactions that may lead to death are stated in the package inserts of marketed drugs as expected.

Serious adverse reactions. Therefore, for investigational drugs that are not yet on the market, the RSI does not

Serious adverse reactions leading to death should be included.

If the RSI contains expected serious adverse reactions that are fatal and/or life-threatening

Yes, the number and frequency of such serious adverse reactions should be listed separately in the list.

Rate. Other suspected serious adverse events that are considered unexpected and fatal and/or life-threatening

Responses can be found in the IB section "Effects in Humans" or "Data Summary and Guidance for Investigators"

chapter.

(3) Situations considered unexpected due to specificity and/or severity

The use of Common Terminology Standards for Adverse Events in RSI is not mandatory

ÿCommon Terminology Criteria for Adverse Events, CTCAEÿ

Perform severity rating. However, if there are suspected serious adverse reactions in individual case reports,

The specificity and/or severity of the reaction is different from the serious adverse reactions expected in the RSI,

That is, suspected serious adverse reactions are more specific than expected serious adverse reactions in the RSI and/or are of higher severity, the suspected serious adverse reaction is considered unexpected (see Table 1).

Table **1** Examples of SUSAR and reasons for reporting

Strict values listed in **RSI** Serious adverse reactions	in case reports Suspected serious adverse reactions	due to specificity and/or severity Unexpected
acute renal failure	interstitial nephritis	specificity
hepatitis	Fulminant hepatitis	severity
cerebrovascular accident	cerebral thromboembolism	specificity
Exfoliative dermatitis	Stevens-Johnson syndrome	Severity and specificity
Liver function test values transient increase	Liver function test values Increases last for several months	severity
hypertension	hypertensive crisis	severity
Herpes Zoster	Multiple Skin Bands herpes	severity
sepsis	septic shock	severity
supraventricular arrhythmia	atrial fibrillation	specificity

NOTE: The examples above only illustrate more specific and/or severe situations.

Preferred Term, Preferred Term for expected serious adverse reactions other than RSI PTÿÿ

If a suspected serious adverse reaction occurs more frequently than expected in the RSI

The frequency of adverse reactions, suspected serious adverse reactions are considered unexpected.

It is recommended that trained professionals from the sponsor respond to suspected serious adverse reactions.

A medical and scientific evaluation should be conducted based on the specificity and/or severity.

(4) Safety information that should not be included in safety reference information

The following safety information should not be included in the RSI, but can be found in the IB "Personal

In Vivo Actions" or "Data Summary and Guidance for Investigators" section.

For example:

(1) Adverse events that both the investigator and the sponsor believe are not related to the trial drug,

Includes serious adverse events and non-serious adverse events;

(2) Non-serious adverse reactions;

(3) Unexpected serious adverse reactions;

(4) Serious adverse reactions occurred only once, and medical-based treatment cannot be provided.

Strong evidence based on scientific judgment confirms a clear causal relationship with the experimental drug;

(5) In trial plans, death events and serious adverse events are often used as indicators of efficacy.

Endpoints, considered disease-related, are not reported as SUSAR. However, if

If the investigational drug enhances the severity of the adverse event or increases the risk of the adverse event

The frequency of occurrence should be carefully evaluated;

(6) Other drugs of the same type that are expected to occur based on pharmacological properties and have been developed

There are no serious adverse reactions that have been observed with this experimental drug.

3. Presentation form of safety reference information

(1) Location

The RSI is titled "Safety Reference Information" and is located under "Data Summary and Research "Researcher's Guide" chapter, or as a separate chapter in the "Data Summary and Researcher's Guide" chapter after.

The sponsor should clearly indicate that the RSI is for regulatory reporting purposes and summarize currently anticipated serious adverse effects of the investigational drug and the RSI does not provide a comprehensive overview Safety profile of the investigational drug.

(2) Presentation form

RSI should be presented in tabular form using the Medical Dictionary of Regulatory Activities ÿMedical Dictionary for RegulatoryActivities, MedDRAÿÿÿ version of System Organ Class (SOC) and PT to describe Describe the nature of “expected serious adverse reactions”. Summarize previously observed suspicious severity Adverse reactions, calculate their frequency. Please refer to the instruction manual for frequency of occurrence categories. Classification of frequency of adverse reactions (e.g. very common, common, rare, etc.). when The number of subjects exposed to the investigational drug is too small to classify or observe When the number of expected serious adverse reactions is small, each “expected serious adverse reaction” should be provided. number of adverse reactions” and the number of exposed subjects (see Table 2).

RSI can include serious adverse reactions observed after marketing, but they occur frequently. The rate should not be entered as "Unknown". Since it is impossible to know the true frequency of occurrence after listing category, therefore the number of reports for each serious adverse reaction should be provided, and may also be

Methods in the Guidelines for Spontaneously Reported Adverse Reactions provide frequency categories (see Table 1

2ÿÿ

Table **2** Expected serious adverse reactions of investigational drugs for safety reporting purposes

SOC	Number of subjects exposed to SARs (N) = 328		
	All SARs cause death	SARs1	life threatening SARs1
	n (%)	n (%)	n (%)
Gastrointestinal system disease sick	Intestinal perforation 9 (2.7) 3 (0.9) 6 (1.8)		
Various tests for alanine and ammonia	base transferase rise 12ÿ3.6ÿ	THAT	THAT
	aspartate acid transamination Elevated transferase 9ÿ2.7ÿ	THAT	THAT
heart disease	Myocarditis 33 (10.0) NA 2 (0.6)		
sick	Bradycardia (rare) 2 NA		THAT

Note: SOC system organ classification; SARs serious adverse reactions; n occurrence

Number of subjects for SAR; NA not applicable

Note 1: In special circumstances, if the investigational drug is considered to be lethal and/or

2 Summary of Product Characteristics (SmPC) Guide, September 2009, Second Edition

https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

Expected serious adverse reactions that are life-threatening should be clearly listed in the table. other
Unexpected fatal and/or life-threatening serious adverse reactions (line), you can fill in "No
applicable" and indicate in a footnote unexpected fatal and/or life-threatening serious
Adverse reactions can be found in other chapters of the IB. If the trial drug is not considered fatal
and/or expected life-threatening serious adverse reactions, then the text portion of the RSI
Indicated separately, the corresponding columns do not need to be listed in the table.

Note 2: Bradycardia is derived from post-marketing safety information and is based on self-reported
Frequency categories are provided using methods in the Guidelines for Reporting Adverse Effects.

If the sponsor is testing the investigational drug for a different indication (e.g., oncology,
non-oncology diseases) or clinical development in different populations (e.g., adults, children), if
The expected serious adverse reactions are different, and the RSI should be listed separately by indication or population.

(3) Terms for expected serious adverse reactions

Expected serious adverse reactions should not use broad medical terms or non-specific
terms such as "rash," "infection," or "arrhythmia." MedDRA should be used
PT, such as exfoliative dermatitis, urticaria, herpes zoster, infectious pneumonia, pus
Toxicity, atrial fibrillation. If the PT in the RSI contains multiple Lowest Level terms
Term, LLT), multiple LLTs are considered expected (such as RSI including PT Low Ph
acidemia, LLT hypophosphatemia is also expected). Known immunosuppression
drugs may cause infections, but all types of infections cannot be expected
of. Unless the RSI lists PT for a specific infection type, it should be considered non-preventive
Expect.

Synonymous medical terms refer to the same medical phenomenon if RSI contains a term

slang, other synonymous medical terms are considered expected. But for the same medical phenomenon

of different types, such as different types of rashes, namely common rash, maculopapular rash, pimple

For exanthematous rash, pustular rash, etc., specific PT must be used.

(4) Safety reference information for expected serious adverse reactions has not yet been found

In some cases, the investigational drug may not be expected to cause any serious adverse effects

adverse reactions (e.g., in the early stages of clinical development of an investigational drug, a relatively large number of subjects are exposed

(less time), but there should still be a separate RSI section in the IB, which can be a paragraph

A brief description explaining how to quickly report SUSAR to regulatory authorities and what is under development

Development Safety Update Report,

SUSAR is identified in the "Cumulative Summary Table of Serious Adverse Reactions" of DSUR, cut-off

So far, the sponsor believes that no expected serious adverse reactions have been found.

4. Applicable versions of security reference information

The current version of RSI when a suspected serious adverse reaction occurs should be used to judge its prognosis.

Periodicity. Follow-up reports use the same version of the RSI as the initial report, and the sponsor does not

SUSAR should be downgraded based on the updated RSI.

5. Changes to security reference information

If the RSI changes during drug clinical trials, the sponsor shall follow the regulations

determined, fully evaluated the impact on the safety of the subjects, and determined that the safety of the subjects would not be affected

, can be implemented directly and reported in the DSUR.

IB's RSI can be updated annually in accordance with the DSUR's annual reporting cycle.

To identify SUSAR in the "Cumulative Summary of Serious Adverse Reactions" in the DSUR,

Sponsors should use the current version of the RSI at the beginning of the annual reporting period.

In some circumstances, the sponsor or regulatory authority may deem urgent updates necessary

Safety information in the new IB can be found in other sections of the IB (such as

or "Data Summary and Guidance for Investigators") to provide urgent updates to safety information.

Changes in RSI may be considered when preparing and writing the DSUR (for SUSAR

analysis and evaluation) rather than multiple updates during the reporting cycle.

6. Quality management system for safety reference information

The sponsor should clarify the implementation and change management procedures of RSI (including but not limited to

in clear change management and traceability processes, implementation time of RSI, etc.) and retain

Relevant documentation. In addition, the impact of updates to MedDRA versions on RSI products should be evaluated.

impact on life.

7. For safety reference information, please refer to the adverse reactions in the drug inserts on the market.

corresponding situation

RSI of clinical trials of drugs marketed overseas and unmarketed domestically, if the indications

It is consistent with the indications approved overseas. Please refer to the strict instructions in the package inserts of the marketed drugs.

Serious adverse reactions. If the indications are different from those approved overseas or have been listed in China

If new indications are added to municipal drugs, if the sponsor still uses the approved indications

Serious adverse reactions in the book are regarded as RSI, and their rationality should be explained.

For generic drugs/biosimilar drugs, if there is evidence that they are similar to the reference drug,

For consistency/biosimilarity, please refer to the RSI of the reference drug.

8. Safety reference information for combined medication

In combination clinical trials, the sponsor can base the same

Develop a new RSI based on experience with active drug combinations, or refer to the RSI of each single drug.

9. References

[1] EU. Clinical Trials Regulation (EU) NO 536/2014 Draft Questions & Answers Version 4.1. https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/regulation5362014_en.pdf.

[2] CTFG. Q&A document Reference Safety Information. https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf.

[3] ICH. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A. https://database.ich.org/sites/default/files/E2A_Guideline.pdf.

[4] I. Development Safety Update Report E2F. https://database.ich.org/sites/default/files/E2F_Guideline.pdf.

[5] CDE. Regarding the release of "Standards and Procedures for Rapid Reporting of Safety Data During Drug Clinical Trials" Pass Know https://www.cde.org.cn/main/news/viewInfoCommon/f86be6d655db5c711fe660bef22c3bf1.

[6] CDE. Notice on the release of the "Management Specifications for Security Update Reports During Research and Development (Trial)". https://www.cde.org.cn/main/news/viewInfoCommon/afced30f3c45431f04b47a7f3faee971.

[7] EC. A Guideline on Summary of Product Characteristics (SmPC). https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf.

Example: This example is only a presentation form of RSI, and the sponsor may adjust the relevant content and format as appropriate based on the guidelines.

Security reference information

This chapter/section only outlines the requirements for expeditiously reporting SUSAR to regulatory authorities and

For the purpose of identifying SUSAR in the "Cumulative Summary Table of Serious Adverse Reactions" of the DSUR

expected serious adverse reactions and did not provide a comprehensive overview of the safety profile of Investigational Drug

Symptoms, see Chapter X for more safety information.

All fatal and life-threatening serious adverse reactions to Investigational Drug

If not expected, it will be submitted as SUSAR.

Table **1** Expected serious adverse reactions of investigational drug **X** for safety reporting purposes

answer

SOC	Frequency of SARs occurrence	Rate Category 1	Number of subjects exposed ÿNÿ2=328
			All SARs
			n (%)
Gastrointestinal system systemic diseases	Intestinal perforation	common	9ÿ2.7ÿ
Various inspections check	Alanine transamination Elevated enzymes	common	12ÿ3.6ÿ
	aspartate amino Elevated transferase	common	9ÿ2.7ÿ
Cardiac myocarditis is very common 33 (10.0)			

organ disease		See	
	Bradycardia is rare		(rare) 3

SOC system organ classification; SARs serious adverse reactions; n occurrence

Number of subjects with SAR

Note 1: Occurrence frequency category: very common (ÿ1/10); common (ÿ1/100

to <1/10); occasionally (ÿ1/1,000 to <1/100); rare (ÿ1/10,000 to

<1/1,000); very rare (<1/10,000).

2: Includes Study 1, Study 2….

3: Bradycardia is derived from post-marketing safety information and is not based on spontaneous reports.

Methods in the Adverse Reaction Guidelines provide frequency of occurrence categories.

MedDRA version 24.0, data lock date May 1, 2021,

Based on global security database.