

Clinical Trial Facilitation Group

CTFG

Q&A document – Reference Safety Information

Introduction

The CTFG has updated the Q&A document on Reference Safety Information (RSI) following detailed discussions between national competent authorities and sponsors, which arose from Clinical Trial application and substantial amendment procedures as well as GCP inspections. While the sponsor may use an approved Summary of Product Characteristics (SmPC) as RSI, it is more common that this information is provided in an Investigator's Brochure (IB) for Investigational Medicinal Products (IMPs). The RSI in the IB cannot be regarded the same way as the undesirable effects listed in the SmPC, as pharmacovigilance rules for post-marketing and safety monitoring and reporting rules for clinical trials are significantly different as are the purpose and means of approval of the IB and SmPC (see answer to question 2 below).

The CTFG advises sponsors that the primary purpose of the 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. Thus, the RSI section of an IB should only contain expected Serious Adverse Reactions ('expected SARs') to the Investigational Medicinal Product(s), as detailed in the following answers. It should be emphasized that a broader description of the safety profile of the IMP in addition to the RSI, e.g. tabular presentations of all observed adverse reactions (i.e. 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), should be included elsewhere in the IB. It is recommended to include this information either in a subsection on Safety under 'Effects in Humans' or in the section 'Summary of Data and Guidance for the Investigator', in accordance with ICH E6 (R2) guidance, to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial.

Clinical Trial Facilitation Group

CTFG

Abbreviations

AE: adverse event

AR: adverse reaction

CTCAE: Common Terminology Criteria for Adverse Events

DSUR: Development Safety Update Report – Required format of annual safety report (see ICH guideline E2F¹)

‘expected SAR’: SAR terms listed in the reference safety information section (see question 1 for more detail)

EV: Eudravigilance database, a centralised European database of ‘suspected’ adverse reactions to medicines that are authorised or being studied in clinical trials in the European Economic Area (EEA).

IB: Investigator’s Brochure, a structured compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to a trial (see ICH Guideline for Good Clinical Practice, ICH E6 (R2))

IMP: Investigational Medicinal Product

LLT: Lower Level Term

MA: Marketing Authorization

MedDRA: Medical Dictionary for Regulatory Activities

PT: Preferred Term

RSI: Reference Safety Information

SA: Substantial Amendment

SAE: serious adverse event - Any untoward medical occurrence or effect in a patient or clinical investigation subject administered a pharmaceutical product and may or may not have a causal relationship with this treatment and which is serious (i.e. results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect or is otherwise medically important). In contrast to the term SAR, SAEs include all serious events independent of whether they have a suspected causal relationship to the IMP or not.

¹ ICH Topic E2F — Development Safety Update Report (see http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm).

Clinical Trial Facilitation Group

CTFG

SAR: serious adverse reaction - all noxious and unintended responses to an investigational medicinal product related to any dose administered that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such important medical events should also be considered as serious. This implies a reasonable possibility of a causal relationship between the event and the IMP, i.e. evidence to suggest a causal relationship.

SOC - System Organ Class

EU-SmPC: European Union Summary of Product Characteristics

'suspected' SAR: refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator. All individually reported SARs are considered suspected.

SUSAR: Suspected Unexpected Serious Adverse Reaction.

Clinical Trial Facilitation Group

CTFG

Table of contents

Introduction.....	1
Abbreviations.....	2
1. Question: What is the purpose of the Reference Safety Information section of an Investigator’s Brochure for clinical trials and what should it contain?	5
2. Question: Which document should contain the Reference Safety Information?	6
3. Question: Which format should be used for the Reference Safety Information in the Investigator’s Brochure?	7
4. Question: How should the frequency of expected SARs be presented in the RSI?.....	8
5. Question: How should fatal and life-threatening ‘suspected’ SARs be presented in the RSI?.....	8
6. Question: When are ‘suspected’ SARs considered unexpected because of specificity and/or severity?.....	10
7. Question: How should expected SARs be listed in the RSI?.....	10
8. Question: What is understood by synonymous medical terms and are they allowed in the RSI?.....	11
9. Question: What safety information should not be included in the Reference Safety Information of the Investigator’s Brochure?.....	11
10. Question: What should be included in the section Reference Safety Information in trials if there are no ‘expected’ SARs for the IMP?.....	13
11. Question: What is the procedure for update of the RSI during clinical trials?	13
12. Question: When is an update of the Reference Safety Information considered appropriate?.....	14
13. Question: Can the IB be updated with new safety information at any time without changes to the reference safety information?.....	17
14. Question: The RSI is not a clearly identified section in the currently approved IB used in ongoing clinical trials. Does the IB have to be amended?.....	17
15. Question: The RSI is not a clearly identified section in the IB accompanying a new clinical trial application. Does the IB have to be amended?.....	17
16. Question: What should be used as RSI for trials with combinations of IMPs?	18
17. Question: Should SAEs which are considered to be ‘unlikely’ related or ‘possibly’ related to an IMP be treated as ‘suspected’ SARs?	18
18. Which version of RSI should be used for determining expectedness of ‘suspected’ SARs for follow up reports?.....	19

Clinical Trial Facilitation Group

CTFG

1. Question: What is the purpose of the Reference Safety Information section of an Investigator's Brochure for clinical trials and what should it contain?

Answer:

1.1 The Reference Safety Information (RSI) is used for the assessment of the expectedness of all 'suspected' serious adverse reactions (SARs) that occur in clinical trials. Therefore 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). 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), and for the identification of SUSARs in the cumulative summary tabulation of 'suspected' SARs in the Development Safety Update Report (DSUR).

1.2 The content of the RSI should include a clear list of 'expected SARs' to the IMP(s). These 'expected SARs' should be restricted to 'suspected' SARs that were previously observed where, after a thorough assessment by the sponsor, reasonable evidence of a causal relationship between the event and the IMP exists. This confirmation should be 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.

1.3 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. Any additional documents used for the justification should also be submitted when adding an 'expected' SAR, providing full transparency on the process of selecting 'suspected' SARs fulfilling the criteria for 'expected SARs'. 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. As stated in point 1.2, a thorough assessment by the sponsor is also required for 'suspected' SARs that have occurred more than once, and justification for the addition to the RSI should be submitted alongside the proposed addition.

1.4 The list of 'expected SARs' should be 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 the note for guidance ICH E2A).

The RSI should include the nature, frequency, and severity of the expected SARs (see question 3, 4, and 5 for more detail). Usually, nature and severity is 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

Clinical Trial Facilitation Group

CTFG

prompt detection of expected SARs listed in the RSI must be included in the study protocols.

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

As the RSI should only include expected SARs, the listing of life-threatening or fatal SARs in the RSI of an IB indicates that the sponsor expects the IMP to cause these SARs at this level of severity. In some cases, the listing of life-threatening SARs in the RSI could be acceptable, if a robust justification is provided.

Fatal SARs can only be considered expected for IMPs with a MA in the EU, when it is clearly stated in the table or list of ARs in section 4.8 of SmPC that the IMP can cause these fatal SARs. Thus, the RSI of a product that has not received a MA in the EU should never include fatal SARs.

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

If the RSI section of an IB 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 IB**. It is recommended to provide this information either in a subsection on Safety under ‘Effects in Humans’ or in the section ‘Summary of Data and Guidance for the Investigator’. See questions 5 and 9 for more detail.

2. Question: Which document should contain the Reference Safety Information?

Answer:

2.1 If the sponsor prepares an IB for the IMP(s) in a trial, the RSI should be contained in the IB in a clearly-identified separate section titled “*Reference safety information for assessment of expectedness of serious adverse reactions*”. This section could e.g. be located within or close to section ‘Summary of Data and Guidance for the Investigator’. The SmPC or section of the IB used as RSI should be identified in the cover letter of the clinical trial application. When the RSI is contained within an IB, the sponsor should clearly indicate that the RSI section outlines expected SARs for regulatory reporting purposes and that the information

Clinical Trial Facilitation Group

CTFG

within the RSI section does not present a comprehensive overview of the safety profile of the IMP(s).

2.2 The RSI of an IMP with a marketing authorisation in the EU can be the table or list of ARs in section 4.8 ‘Undesirable Effects’ of the appropriate Summary of Product Characteristics (SmPC). This approach is acceptable if the IMP is used within the terms of the marketing authorisation. If the IMP has a marketing authorisation in several Member States with different SmPCs, the sponsor should justify its selection of the most appropriate SmPC, with reference to subject safety, as the RSI. Differences to the most recent version of an existing EU SmPC should be justified. A clearly separated specific section within the IB may also be used as RSI for an IMP within the terms of its marketing authorisation in the EU (for example for global clinical trials that include sites outside the EU).

If it is proposed to use an IMP outside the (EU) terms of marketing authorisation within the trial and/or if the sponsor does not have access to an IB for the marketed IMP, section 4.8 of the SmPC for the IMP(s) could be used as the RSI, if justified by the sponsor in the clinical trial application cover letter. Otherwise the RSI should always be a clearly separated specific section within the IB as detailed in point 2.1 above.

For an IMP with no marketing authorisation within the EU, the RSI should always be a clearly separated specific section within the IB.

3. Question: Which format should be used for the Reference Safety Information in the Investigator’s Brochure?

Answer:

The RSI should be presented in the form of a table, where 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, followed by the *frequency* (see question 4), which must be calculated on an aggregated level and based on previously observed ‘suspected’ SARs to the IMP (refer to table 1.0 below for example). See questions 4, 5, 6, and 7 for more detail.

If the IMP is under development in different medical conditions, separate tables of expected SARs by indication may be appropriate, if the expected SARs are different e.g. for oncology conditions and non-oncology diseases. This approach should be justified by the sponsor in a cover letter of the clinical trial application.

Clinical Trial Facilitation Group

CTFG

4. Question: How should the frequency of expected SARs be presented in the RSI?

Answer:

The frequencies of the expected SARs listed in the RSI are preferred to be in categories in analogy to the recommendation for the SmPC (section 4.8.) where possible (i.e. Very Common, Common, Uncommon etc.; for details see also ICH E2C(R2)). If there is an insufficient number of subjects exposed to the IMP to use these categories (e.g., during the early stages of product development), the number of observed ‘suspected SARs’ for each ‘expected SAR’ should be provided, together with the number of patients exposed (refer to table 1.0 below for example).

5. Question: How should fatal and life-threatening ‘suspected’ SARs be presented in the RSI?

Answer:

In addition to the guidance detailed in answers 1.5, 3 and 4 above, if there are expected life-threatening or fatal SARs listed in the RSI section of an IB, 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 (refer to table 1.0 below).

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 and should be listed elsewhere in the IB. It is recommended to provide this information either in a subsection on Safety under ‘Effects in Humans’ or in the section ‘Summary of Data and Guidance for the Investigator’.

Clinical Trial Facilitation Group

CTFG

Example of an RSI table:

Table 1.0 Serious Adverse Reactions for the IMP considered expected for safety reporting purposes.

SOC	SARs	Number of subjects exposed (N) = 328		
		All SARs	Occurrence of fatal SARs	Occurrence of life-threatening SARs
		n* (%)	n (%)	n (%)
Gastro-intestinal disorders	Diarrhoea	25 (7.6)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	ALT increase	12 (3.6)	0 (0.0)	0 (0.0)
	AST increase	9 (2.7)	0 (0.0)	0 (0.0)
Cardio vascular disorders	Myocarditis	33 (10.0)	0 (0.0)	2 (0.6)

n = number of subjects who have experienced the SAR

Clinical Trial Facilitation Group

CTFG

6. Question: When are ‘suspected’ SARs considered unexpected because of specificity and/or severity?

Answer:

A provision of severity grades using CTCAE grading system in the RSI is not required. However, in accordance with ICH E2A guidance, reports which add significant information on specificity or severity of a known, already documented SAR represent unexpected events (refer to table 1.0 and 2.0 for examples).

Table 2.0 Example of SUSARs and reasons for their reporting

Listed SAR 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

7. Question: How should expected SARs be listed in the RSI?

Answer:

The use of medical concepts or unspecific terms in the RSI of an IB, 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 hypophosphataemia 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

Clinical Trial Facilitation Group

CTFG

occurrence of an individual case of urticarial rash SAR should be classified as a SUSAR.

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

Answer:

Synonymous medical terms (e.g. sedation, somnolence, drowsiness) representing truly the same medical phenomenon are allowed in the RSI. 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 have to be listed.

Table 3. Examples of synonymous medical terms:

Listed PTs for expected SARs in RSI	'Suspected' SARS in Synonymous medical terms
Pneumonia	Right upper lobe pneumonia
Gastrointestinal bleeding	Melena
Hypophosphatemia	Blood phosphorus decreased

Nevertheless, in accordance with ICH E2A guidance, 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, a lower respiratory tract infection SAR should be considered unexpected.

9. Question: What safety information should not be included in the Reference Safety Information of the Investigator's Brochure?

Answer:

9.1 The following safety information should not to be included in the RSI section of an IB, but should be presented elsewhere in the IB (e.g. in a table, preferably, located in the subsection on Safety under 'Effects in Humans' or in the section 'Summary of Data and Guidance for the Investigator', near the RSI section) if available:

Clinical Trial Facilitation Group

CTFG

- 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, unless they are included in section 4.8 of the correspondent EU SmPC,
- 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.
- SAR 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 authorized protocol by the competent authority to be treated as disease related 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. In accordance with CT-3 guidance, a causality assessment is required for each SAE, and if the investigator considers 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.

The subsection on Safety under ‘Effects in Humans’ or the section ‘Summary of Data and Guidance for the Investigator’ in the IB should provide the investigator with a detailed overview of the safety profile of the IMP (see answer 9.3 below), however, this cannot be considered to be the RSI, as the RSI should only include ‘expected’ SARs. The sponsor should assess changes of ARs that are not included in the RSI and adequate risk mitigation measures should be included in protocol(s). When updating this section, the sponsor should consider that any revision that has an impact on the risk/benefit assessment should be considered to be a substantial amendment.

9.3 In accordance with ICH E6 (R2) guidance, the Summary of Data and Guidance for the Investigator section should provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests,

Clinical Trial Facilitation Group

CTFG

observations, and precautions that may be needed for a clinical trial. Thus, additional information of the IMP's safety profile such as identified or potential risks, as well as e.g. potential drug-drug interactions, class effects and so on, should also be included in other parts of the Investigator's Brochure (IB), preferably in the Safety and Efficacy section under the chapter Effects in Humans and/or the Guidance for Investigators section. Measures to be taken to avoid and to monitor for specific adverse reactions or actions to be taken if specific reactions occur are recommended to be included in the same section of the IB. Such measures should also be included in the study protocol(s). If a SmPC is used as RSI, these risk minimisation measures should also be included in the protocol. **It is not acceptable to consider the entire Summary of Data and Guidance for the Investigator section of the IB to be the RSI.**

10. Question: What should be included in the section Reference Safety Information in trials if there are no 'expected' SARs for the IMP?

Answer:

There may be situations where there 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 of the IB 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 in the DSUR for the IMP, as per the following example:

Example of the RSI with no expected SARs:

Reference Safety Information

No SARs are considered expected by the sponsor for the purpose of expedited reporting of SUSARs and identification of SUSARs in the "Cumulative summary tabulation of serious adverse reactions" in the DSUR for the IMP.

Clinical Trial Facilitation Group

CTFG

11. Question: What is the procedure for update of the RSI during clinical trials?

Answer:

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 the update of the frequency of expected fatal and/or life-threatening SARs should always be considered to be substantial.

Any update to section 4.8 of a SmPC such as the addition of a new term is considered an update to the RSI and therefore also requires submission as a substantial amendment for approval before that RSI can be used for determining expectedness of ‘suspected’ SARs. When submitting a substantial amendment that involves an IB or SmPC update, the cover letter must indicate if the RSI is being updated or not. Upon submission of an IB in a substantial amendment application containing an update to the RSI, which is not accompanied by a protocol amendment, the sponsor should specify in the submission cover letter what risk mitigation measures are already in place in the protocol to manage any new safety issues and if these new safety issues are adequately covered in the subject information leaflet (informed consent form) or if it needs to be updated. References to any parallel DSUR submission should also be given in the cover letter. A tracked changes version of the IB should be provided so differences can be easily viewed. In cases where justifications for amendments to the RSI are provided in additional documents, these documents should be submitted simultaneously. It is strongly recommended to submit a substantial amendment application that includes an updated RSI to all Member States concerned at the same time.

12. Question: When is an update of the Reference Safety Information considered appropriate?

Answer:

The RSI is used for assessing expectedness of ‘suspected’ SARs for the purposes of expedited reporting of SUSARs and for the identification of SUSARs in the ‘Cumulative summary tabulation of serious adverse reactions’ in the DSUR (in accordance with CT-3² and ICH E2F guidance ³). The date of approval of a new

² 2011/C 172/01 Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’) (see Eudralex volume 10).

³EMA/CHMP/ICH/309348/2008: ICH guideline E2F on development safety update report Step 5

Clinical Trial Facilitation Group

CTFG

version of RSI for expedited reporting will be different from the date of implementation of a new version of RSI for the DSUR, as detailed below.

Depending on whether the RSI is contained in the IB or the SmPC, one of the following recommendations should be followed:

- If the RSI is within the IB prepared by the sponsor, it is highly recommended to update the RSI section of the IB (if necessary) only once per year, after the DSUR data lock point, along with the new DSUR. It is expected that cumulative safety data from across the preclinical and clinical development program is reviewed during the annual IB update, and that the IB update can take place while preparing the DSUR (i.e. within the 60 days after the DSUR annual reporting period).

Substantial amendments for all trials that use the IB should be submitted to the authorities in all EU Member States where trials are ongoing in parallel to the DSUR submission. The DSUR may include the supportive data for justification of the RSI update (e.g. reference may be made to the tables, line listings or other data within the DSUR to support a proposal to add an expected SAR).

The newly updated RSI can only be used for assessment of expectedness of 'suspected' SARs for the purposes of expedited reporting after the approval of the substantial amendments in all of the Member States where trials are ongoing. Thus, if additional SUSARs occur before the new RSI is approved, these should be reported as SUSARs in the usual expedited manner.

For the purposes of the identification of SUSARs in the 'Cumulative summary tabulation of serious adverse reactions' in a DSUR, the version of the RSI most recently approved in all Member States should be used i.e., this should be considered to be the "RSI in effect at the start of the annual reporting period", (as per paragraph 129 of CT-3 guidance - see IB v. 6 in example in Fig 1). Thus, only 'suspected' SARs that are unexpected as per the RSI that was most recently approved should be highlighted as SUSARs in the DSUR, and not any 'suspected' SARs that would have been considered to be SUSARs in previous versions of the RSI. In accordance with ICH E2F guidance, the RSI used to identify SUSARs in the DSUR should be submitted with the DSUR, as well as the proposed new RSI, and any changes to the RSI should be detailed in the 'Changes to the Reference Safety Information' section of the DSUR (Note that if the IB has been updated and there are no proposed changes to the RSI, the new IB should still be submitted).

Clinical Trial Facilitation Group CTFG

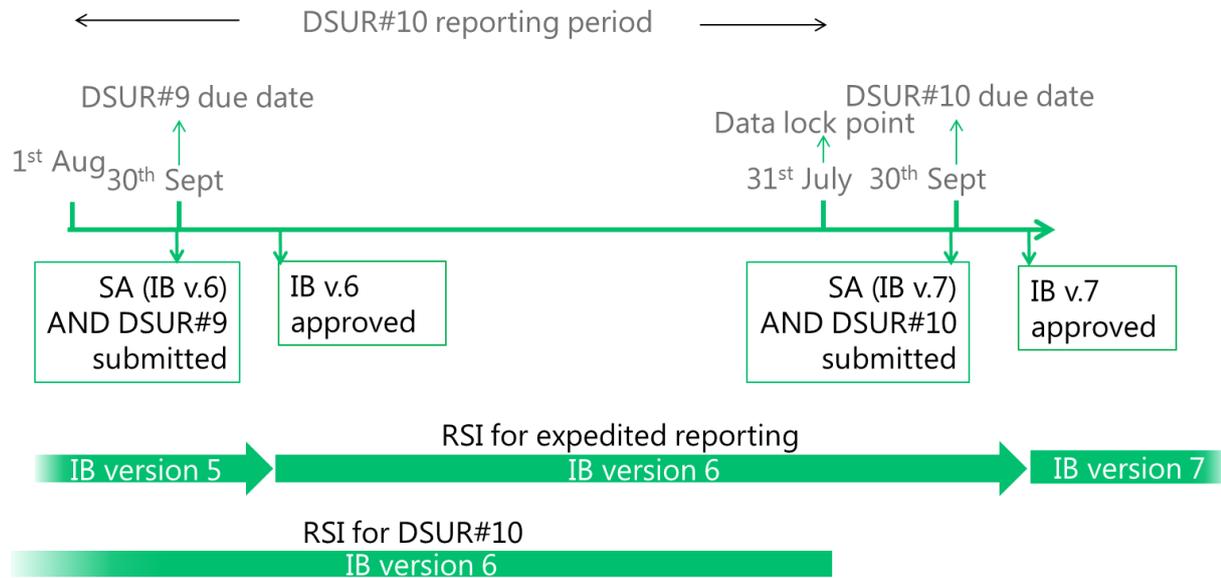


Fig. 1: Example of IB RSI update following DSUR reporting period.

For a DSUR with reporting period 1st August – 31st July, the annual review of the IB should occur following the DSUR data lock point (31st July), in parallel with the preparation of the DSUR (DSUR due date is 60 days after the Data Lock Point). Where an update to the RSI section is considered necessary by the sponsor, the IB should be updated (to version 6 in this example) and submitted as a substantial amendment (SA) preferably in parallel with (i.e. on the same day or shortly thereafter) the DSUR (DSUR#9 in this example). **The most recently approved IB (i.e. IB version 5) should be used as the RSI (for DSUR#9) and both IB version 5 and the new IB (version 6) should be submitted with the DSUR.** For the purposes of expedited SUSAR reporting, the RSI in the new IB should be used as the basis for expectedness assessments for ‘suspected’ SARs following approval of the new IB in all Member States where the trial is ongoing. In the example above, when the DSUR#10 is prepared, **IB version 6 should be used as RSI for expectedness assessment (in the reporting period starting with DLP) of all ‘suspected’ SARs tabulated** in the Cumulative Summary Tabulation of Serious Adverse Reactions.

- **If the RSI is within an IB which is not prepared and updated by the sponsor** itself (e.g. for non-commercial sponsors using a company’s IB), the non-commercial sponsor should have a written agreement in place with the company in which the updated *approved* IB is sent to the sponsor immediately. If the company has submitted a substantial amendment to authorities in EU Member States in relation to the updated IB (for any trial for which it is sponsor), the (non-commercial) sponsor should await the completion of the assessment of the substantial amendment and submit the approved IB, together with any of the

Clinical Trial Facilitation Group

CTFG

necessary amendments to the protocol as a substantial amendment for their own clinical trial.

- **If the RSI is in section 4.8 of the SmPC and this section is updated during the trial**, it is recommended to submit a substantial amendment requesting approval of the update to the RSI immediately following completion of the variation procedure. Following approval of the SmPC for use as RSI in all Member States where the trial is ongoing, the updated SmPC should be used for the purposes of expedited reporting.

- When expected SARs are newly added to the RSI contained in the IB or the SmPC, the sponsor should also update the subject information leaflet (informed consent form), if necessary.

13. Question: Can the IB be updated with new safety information at any time without changes to the reference safety information?

Answer:

Yes. An urgent update to the safety data in the IB may be deemed necessary by the sponsor or regulatory authorities at any time during the conduct of a clinical trial. This information can be added to other sections of the IB (preferably to the Safety and Efficacy section under Effects in Humans and/or Summary of Data and Guidance for Investigators section). However, the RSI section of the IB should only be updated following the DSUR reporting period, and ideally should be submitted in parallel with the DSUR, in accordance with the recommendations in the answer to question 12 and Fig. 1.

14. Question: The RSI is not a clearly identified section in the currently approved IB used in ongoing clinical trials. Does the IB have to be amended?

Answer:

Yes, if the RSI is within the IB for an IMP and there is not yet a clearly identified section to this effect, where all expected SARs are included in the form of a table (see question 3 for more detail), an RSI section should be included in the IB at the next routine update, and a substantial amendment should be submitted. Until the RSI section is clearly identified in an approved version of the IB, all ‘suspected’ SARs should be reported as SUSARs.

Clinical Trial Facilitation Group

CTFG

15. Question: The RSI is not a clearly identified section in the IB accompanying a new clinical trial application. Does the IB have to be amended?

Answer:

Yes, if the RSI is within the IB for an IMP and there is not yet a clearly identified section to this effect, where all expected SARs are included in the form of a table (see the answer to question 3 for more detail), the clinical trial application risks to be rejected. If there are no 'expected SARs' for the IMP at the point of submission please see question 10 for further instructions.

16. Question: What should be used as RSI for trials with combinations of IMPs?

Answer:

The sponsor may use the reference safety information (an IB or SmPC, section 4.8) that includes expected SARs for the combination of IMPs, based on an evaluation of 'suspected' SARs to a similar combination in previous trials. If the sponsor does not have data in an IB or section 4.8 of an SmPC from previous trials which have used the proposed IMP combination, multiple IBs or SmPCs, may be used as RSI (i.e. one for each IMP). When deciding between these two options, the sponsor should consider the consequences of using multiple IBs or SmPCs on SUSAR reporting when the causality assessment concerns the combination rather than the individual IMPs (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).

17. Question: Should SAEs which are considered to be 'unlikely' related or 'possibly' related to an IMP be treated as 'suspected' SARs?

Answer:

Causality categories are not recognised in Dir.2001/20/EC or in EMA (GVP module I and VI) or ICH E2F DSUR guidance. In accordance with ICH-E2A, the definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected. Thus in a clinical trial setting, a causal relationship to the IMP is either considered to be suspected or not for each individual adverse event which occurs. If an investigator uses the WHO classification categories of causality when assessing causality, 'highly probable', 'probable', 'possible' should be regarded as related by the

Clinical Trial Facilitation Group

CTFG

sponsor, while ‘unlikely’ and ‘not’ may be considered to be not related. In case of ARs assessed as ‘unknown’ or ‘not assessed’ for which the investigator cannot make a decision with regard to relatedness to the IMP, in accordance with CT-3 European Commission guidelines, the sponsor should consult the reporting investigator and encourage him/her to express an opinion. The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator’s causality assessment, the opinion of both the investigator and the sponsor should be provided with the report. If (despite all efforts) the causality assessment cannot be made, these SAEs should be considered to be related to the IMP and reported as SUSARs if they are not listed as an expected SAR in the RSI. In general, SAEs with “unknown causality” or “causality not assessed” will not be accepted to support the inclusion of expected SARs in RSI.

18. Which version of RSI should be used for determining expectedness of ‘suspected’ SARs for follow up reports?

Answer:

The RSI in place at the time of occurrence of the ‘suspected’ SAR should be used to assess expectedness for follow up reports to Eudravigilance (EV). SUSARs should not be downgraded in EV on the basis that the RSI was updated after the occurrence of the event.