

Question and Answers to the Safety in Clinical Trials Frequently asked questions regarding the Reference Safety Information (RSI)

The Reference Safety Information serves different purposes like information to the investigators about the safety profile of an investigational medicinal product (IMP), basis for expectedness assessment of an adverse reaction by the (investigator) sponsor for expedite reporting and annual safety reporting, as well as surveillance of participant's safety in a clinical trial by regulatory (and ethic) bodies.

However, the RSI is specified slightly different in various regulatory documents like the Clinical Trial Directive 2001/20/EC, the CT-1 (2010/C 82/01) and CT-3 (2011/C 172/01) guidance of the EU Commission as well as ICH E2F (Development Safety Update Report) of the International Conference of Harmonization, with regard to type and format as well as update of the document.

Intent of this question and answers document is to inform sponsors of clinical trials about the common interpretation of these guidelines by the National Competent Authorities of the European Member States as represented by the Clinical Trial Facilitation Group (CTFG) of the Heads of Medicinal Agencies (HMA).

1 Which information is required to be contained in the Reference Safety Information?

The content of the Reference Safety Information should include a list of all observed cumulative adverse reactions (i.e. related adverse events, AR): The serious and non-serious adverse reactions including a description of nature of event and severity or grade as well as its frequency (see CT3 section 7.2.3.2. (51, 53)). The latter are preferred to be in categories similar to the Summary of Product Characteristics (SmPC, section 4.8, for details see Volume 2C; http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf). The list contains adverse reactions that could be observed once or multiple times, please see question 4. If different indications are being investigated for the investigational medicinal product, separate tables of expected adverse reactions by indication might be applicable to avoid misinterpretation, e.g. oncologic indications and immune mediated diseases.

Additional (relevant) information of the IMP's profile like potential safety risks as well as e.g. potential drug drug interactions, class effects and so on, this could be documented within other parts of the document which contains the RSI, please see Question 2.

2 Which document should contain the Reference Safety Information?

The RSI of an IMP without marketing authorization (MA) in the EU should be a clearly separated specific section within the Investigators Brochure (IB) (see CT3 (53)). This RSI section may either be integrated into section 7 of the IB 'Summary of Data and Guidance for the investigator' (please see ICH E6; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf) or be a new section e.g. section 8.

The RSI of an IMP with a marketing authorization in the EU should be the section 4.8. 'Undesirable Effects' of the appropriate Summary of Product Characteristics (SmPC). If the IMP has a marketing authorization (MA) in several Member States concerned with different SmPCs, the sponsor should justify its selection of the most appropriate SmPC, with reference to subject safety, as the RSI (see CT3 section 7.2.3.2. (54)).

The document chosen as RSI of an IMP used outside its marketing authorization conditions in the EU (i.e. *off-label* use) should be justified by sponsor. In case the SmPC covers appropriately the use of the medicinal product in the off-label use (e.g. in case off-label use is close to MA conditions), the RSI could be the section 4.8 of the SmPC. Otherwise the RSI should be a clearly separated specific section within the IB, which supports with additional relevant non-clinical and if applicable clinical data the off-label use. In cases where the IB is used as the RSI (rather than the SmPC) for IMPs with MA any differences between the list of expected adverse reactions in the IB and the SmPC should be highlighted and justified. In this latter case submission of SmPC for information is recommended.

In the case where a sponsor has applied for a marketing authorization for an IMP and the IMP has been granted a positive opinion by the CHMP but yet not the Commission's decision on its marketing authorization or is not yet marketed the choice of document should be justified. In general consistency is expected to be between the two RSI documents (SmPC and IB) and differences need to be justified.

Additional relevant safety information beside the list of expected ARs which stakeholders should be aware of (see Question 1), could be addressed within other respective sections of the SmPC (for details see Volume 2C, http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf) or e.g. within section 7 of the IB 'Summary of data and guidance for investigator' (ICH E 6; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step_4/E6_R1__Guideline.pdf)

Please always indicate in your cover letter where the RSI is located.

3 Which format should be chosen for the Reference Safety Information?

The RSI should include a list of observed expected adverse reactions, e.g. best in the form of a table, where all related adverse events (i.e. adverse reactions) are listed by body system organ class, followed by short description (*nature*) of event, which is followed by the *seriousness, severity* or grade of the event, then followed by *frequency* which might be given in categories similar to the SmPC (for details see Volume 2C, http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf) since frequencies will change with exposure and number of adverse reactions (also see Question 1). In case different indications, population, or combinations are being investigated for the IMP, separate tables of expected ARs by the different groups might be applicable to avoid misinterpretation.

In case further information is needed for clarification of specific risks, the table might be accompanied by a brief supplemental text below.

4 When is an update of the Reference Safety Information considered approvable (appropriate)?

It is recommended only to update the RSI, if necessary, once a year in alignment with the annual period for a development safety update report (DSUR). Therefore the DSUR information is the supportive data for justification of RSI update. E.g. if an adverse reaction is observed (considering nature, severity and frequency) during the last reporting period of

DSUR and should now be expected for the next reporting period, an RSI update could be supported by the DSUR.

In case the RSI is needed to be updated prior to the end of the reporting period of the DSUR a detailed / sound justification by data is expected. E.g. if a single occurrence of any event by itself solely might be sufficient to be expected, has to be assessed in the context of the IMP profile on a case by case basis.

Please be aware that an RSI update always is a substantial amendment.

In case of new expected adverse reactions added to the RSI it should be considered if they should be reflected in the subject information leaflet (informed consent).

Update of the IB is possible anytime with additional safety information like in section 7 (ICH E6), but the RSI should only be changed as stated above.

Any new events of concern could be made to an 'Events of Special Interest' at any time and thus become subject to reporting as for SAEs, with a review of whether they are to be expected at the time of the annual RSI review.

5 What about RSI in already approved ongoing clinical trials?

If the RSI is within the IB for an investigational medicinal product and there is not yet a clearly identified separate section to this effect, where all expected adverse reactions (i.e. related adverse events, AR):) are included e.g. in the form of a table (see above), we expect this to be implemented within your next (regular) IB update.

6 What needs to be considered while submitting (substantial) amendments?

While submitting a substantial amendment to an ongoing clinical trial, that involve an IB update, please indicate in your cover letter if the RSI is been updated. Where changes are proposed these should be clearly indicated using a Track Changes table, so differences can be easily viewed.

Any change to an RSI is considered a substantial amendment and it requires to be justified with supportive data. It is recommended to update the RSI, if necessary, in alignment with the annual period for a DSUR. If the date of RSI update is aligned this way the DSUR can act in part as justification for the RSI changes. In case your RSI is updated prior to the end of the reporting period of the DSUR a detailed justification by data is expected. Also see Question4.

It is recommended that all clinical trials which refer to the same RSI should be updated at the same time. This could be submitted to NCAs as one substantial amendment covering multiple CTs.