Reference Safety Information (RSI) for a Clinical Trial

For <u>new</u> clinical trial applications:

When submitting a **clinical trial application** the reference safety information (RSI) should be, when applicable, within the Summary of Product Characteristics (SmPC) or within the Investigators Brochure (IB).

If the RSI is within **IB** it should be a clearly identified separate section. This section should include a list of expected adverse reactions, e.g. in the form of a table, where all ***related*** adverse events (i.e. adverse reactions) are listed by nature and severity including frequency (see CT1 section 2.3. (32.), CT3 section 7.2.3.2. (51 to 53)). If different indications are being investigated for the investigational medicinal product (IMP), separate tables of expected adverse reactions by indication might be applicable to avoid misinterpretation, e.g. oncologic indications and immune mediated diseases.

If RSI is within the **SmPC,** the list of expected adverse reactions is contained in section 4.8 Undesirable Effects. Please note that relevant safety information may also be contained in other sections, for further details please see Volume 2C,
http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm.

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).

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.

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

For <u>ongoing</u> 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 ***related*** adverse events (i.e. adverse reactions) are included e.g. in the form of a table (see above), we expect this to be implemented within your **next** (regular) **IB update.**

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

Changes during a clinical trial – (Substantial) Amendment to a clinical trial:

While submitting a (**substantial) amendment** to an ongoing clinical trial, e.g. an IB update, please indicate in your cover letter if the RSI is updated. Where changes are proposed these should be clearly indicated using a Track Changes table.

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 development safety update report (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.