

Reference safety information (RSI) guidance

The MHRA Blog “Reference Safety Information for Clinical Trials- Part I, II and III”: available on the MHRA website - should be read in conjunction with this guidance.

The Coordinating Investigator (CI) must ensure that the protocol defines the location of the RSI for the study. The RSI is usually held within a specific section within a named version of either the Summary of Product Characteristics (SmPC) or Investigator Brochure (IB) for an IMP.

The RSI must be reviewed for updates annually as a minimum during preparation of the development safety update report (DSUR). If there are mid-year changes to the RSI during the study the CI must assess, with the sponsor, whether a substantial modification is required. RSI must be updated via substantial modification if there have been any changes to the RSI text, specifically if there have been addition or deletion of events or a change in their categorisation. Where fatal or life-threatening event is added to RSI mid-reporting period a revised risk benefit analysis of the trial must be documented. Even if the changes are not thought to affect the trial, in this case the updated RSI should still be submitted but implementation may be deferred to the next DSUR reporting period. Evidence of periodic review can be documented on a file note or a specific RSI tracking log.

Steps and guidance for updating the RSI:

- Prepare Substantial modification and associated documentation including a risk benefit assessment statement
- Submit modification to GCP team for review
- Submit modification to REC/HRA & MHRA
- Once approved notify relevant parties of update and ensure changes are implemented. It is particularly important that those undertaking expectedness review are clearly informed of implementation date of new RSI to ensure correct assessment of expectedness of SAEs.

As there may be updates to IB/SmPC that do not affect the RSI, it is good practice to track RSI/IMP reference documents separately and to create a study or unit specific Standard Operating Procedure (SOP) for tracking and evidencing the review of RSI.

All versions of the RSI should be filed in the TMF with superseded versions clearly identified.