

## Reference Safety Information Guidance for Clinical Trials (of an Investigational Medicinal Product)

### 1.) What is Reference Safety Information?

Reference Safety Information (RSI) defines which reactions are expected for the Investigational Medicinal Product (IMP) being administered to subjects participating in a clinical trial.

The RSI will be one single definitive list or document that determines which Serious Adverse Reactions (SARs) require expedited reporting to the MHRA as Suspected Unexpected Serious Adverse Reactions (SUSARs).

The term 'expectedness' from a regulatory perspective (in relation to safety reports and SUSARs) means **whether or not the reaction is an expected side effect of the IMP**, thus establishing whether it does or does not need reporting in an expedited fashion.

***"RSI should be Identifiable, Approved and Consistent"***

### 2.) Why is it relevant to me and my study?

As a Chief Investigator working on behalf of Leeds Teaching Hospitals NHS Trust / University of Leeds as Sponsor, you must ensure your clinical trial protocol includes a clear safety reporting section, with definitions, procedures and responsibilities for recording, reviewing and reporting adverse events.

Your clinical trial application to the MHRA must also include supporting documentation to provide further information regarding the IMPs used within your trial, their safety profile and their side effects. The RSI to be used for the trial must be **clearly defined** within this submission.

For an event to be categorised as 'expected', and therefore excluded from expedited regulatory reporting, the reaction must be specifically listed in the RSI or may also be clearly defined in the current approved version of the protocol.

As an investigator you have 24 hours from first being aware of an SAE or SUSAR to inform the study Sponsor, who has the responsibility to report any fatal or life-threatening SUSARs to the MHRA no later than 7 days of first awareness or within 15 days for those which are non-fatal or non-life-threatening. It is therefore essential to be able to immediately identify and refer to the correct and current **approved** RSI for your study.

### 3.) Where is my RSI?

*“Your RSI needs to be **Identifiable**”*

Reference Safety Information should be clearly identifiable in the initial Clinical Trial Authorisation (CTA) application to the MHRA; it is usually contained within either an Investigators Brochure (IB) or Summary of Product Characteristics (SPC or *alternatively SmPC*).

It is crucial to remember that the entire IB or SPC is **not** the RSI, but instead a **specific section** of the relevant document that is clearly defined.

### 4.) Which is the current version of my RSI?

*“Your RSI needs to be **Approved**”*

The RSI must be included as part of the initial CTA application to the MHRA; once approved **this is the RSI that must be used unless the MHRA agrees otherwise** (i.e. a change to RSI is submitted via a substantial amendment and cannot be implemented until approval is issued).

**Note:** Although a newer version of an RSI document (IB or SPC) may already have been approved by the MHRA, it has been done as a post marketing tool for healthcare professionals and **not** as an RSI document in the context of an IMP and corresponding trial population.

Certain protocols may refer to the ‘latest version’ of an IB or SPC however the MHRA interprets this as being the document that is ‘current’ and approved at the time of CTA application; any subsequent RSI changes must still be submitted via a substantial amendment.

**“Any change in RSI is a change to the risk benefit ratio for participants”.**

### 5.) Is everyone working on my trial using the same RSI?

*“Your RSI needs to be **Consistent**”*

You must ensure that every member of the research team is using the same version of the RSI at the same time; this is essential when investigators are conducting the expectedness assessment.

For SPCs, you must control the version to ensure investigators are using the version that has been specifically **approved by the MHRA for use in your trial as the RSI**, rather than directing them to a website containing several versions (i.e. <https://www.medicines.org.uk/emc/> or similar generic resource).

For IBs, you must control the distribution and ensure that members of the research team are aware of which version is to be used for assessing expectedness (i.e. the version approved by the MHRA). If a new IB becomes available, this must be assessed for any changes to the RSI and an amendment may need to be submitted to the MHRA (please see section 6)

**Note:** all adverse events (and by extension all SAEs and SUSARs) should be assessed against the RSI that was in place at the time of the event, irrespective of the version that may be in place at the time of any potential follow-up information being received.

**6.) What do I do if the document containing the RSI changes throughout the trial?**

Any change to the **RSI** requires notification to the MHRA as a substantial amendment (please see “QCRES 03 - Researchers guide to Notification of Amendments for UoL/LTHT Sponsored CTIMPs” SOP) and must not be implemented until the MHRA have provided their approval. However **not every change to the IB or SPC is a change to the RSI.**

Below are three scenarios outlining the Investigator's required action when the document containing the RSI is altered:

Scenario		Action
1.	<i>A new version of an IB is issued at the time of the DSUR for the new reporting period. <b>New events</b> have been listed within the RSI.</i>	You must <b>send an amendment to the MHRA and not implement the new IB until you have obtained approval.</b>  Any change in RSI is a change in risk benefit!
2.	<i>A new version of the IB is issued at the time of the DSUR for the new reporting period. <b>There are no changes to the RSI.</b> (No new events listed as expected and no events removed)</i>	There is no need to submit an amendment to the MHRA before implementing the new IB, however you <b>must document this assessment within the TMF</b> to demonstrate the RSI has not changed.
3.	<i>A new version of the IB is issued mid-DSUR reporting period and there are new events listed.</i>	You must send an amendment to the MHRA and <b>not implement the new IB until you have obtained approval.</b>  However you may <b>risk assess the changes</b> and choose not to implement the IB at this time.  If the RSI changes are minimal or not relevant to your study or patient population, then you can choose to continue with the current RSI in the current IB version for the remainder of the DSUR reporting period.  Please ensure that you <b>document the whole process</b> and remember that if you do change mid period, it will have an impact on your DSUR as you have to use the RSI in place at the start of the reporting period for all of your DSUR line listings.  You could also submit an amendment at the time of the release of the new IB stating that you will not implement the new RSI until the end of the current DSUR period.

**Note:**

- *The above scenarios apply equally to both IBs and SPCs depending on which contains the RSI for your particular study.*
- *There is no need to instantly use a new document just because it has been updated; such decisions should be dependent on a risk benefit assessment and be formally documented.*
- *These processes specifically apply when you are acting on the behalf of the Sponsor (in this case LTHT or UoL); for hosted trials (those Sponsored by an external party where you are only a participating site) the IB changes should be managed by the Sponsoring organisation/CI.*

**Key Resources & Further Reading:**

Reference Safety Information for Clinical Trials	<i>MHRA Inspectorate Blog</i>	<a href="https://mhrainspectorate.blog.gov.uk/2016/03/02/reference-safety-information-for-clinical-trials/">https://mhrainspectorate.blog.gov.uk/2016/03/02/reference-safety-information-for-clinical-trials/</a>
Reference Safety Information II	<i>MHRA Inspectorate Blog</i>	<a href="https://mhrainspectorate.blog.gov.uk/2017/01/18/reference-safety-information-ii/">https://mhrainspectorate.blog.gov.uk/2017/01/18/reference-safety-information-ii/</a>
QCRES01 - Pharmacovigilance for Researchers for UoL / LTHT Sponsored CTIMPs	<i>Sponsor QA (LTHT / UoL)</i>	<a href="http://lthweb.leedsth.nhs.uk/sites/research-and-development/research-and-development-homepage/ga-documents/standard-operating-procedures/">http://lthweb.leedsth.nhs.uk/sites/research-and-development/research-and-development-homepage/ga-documents/standard-operating-procedures/</a>
QCRES 03 - Researchers guide to Notification of Amendments for UoL/LTHT Sponsored CTIMPs	<i>Sponsor QA (LTHT / UoL)</i>	<a href="http://lthweb.leedsth.nhs.uk/sites/research-and-development/research-and-development-homepage/ga-documents/standard-operating-procedures/">http://lthweb.leedsth.nhs.uk/sites/research-and-development/research-and-development-homepage/ga-documents/standard-operating-procedures/</a>
Good Clinical Practice Guide	<i>MHRA</i>	<a href="https://www.tsoshop.co.uk/MHRA/Good-Clinical-Practice-Guide/">https://www.tsoshop.co.uk/MHRA/Good-Clinical-Practice-Guide/</a>

**\*Should you have any queries or concerns, or would like further information regarding the content of this bulletin, then please do not hesitate to contact the Sponsor Quality Assurance Office on Tel: 0113 392 0143\***