UNIVERSITY OF LEEDS / NHS The Leeds Teaching Hospitals NHS Trust Standard Operating Procedure	Title	A Researcher's Guide to Reference Safety Information				
	Scope	*Information for researchers on the management and implementation of Reference Safety Information for CTIMPs.*				
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Distribution & Storage:

Distribution to:

Investigators and all members of research teams conducting or assisting with a CTIMP sponsored by the University of Leeds or Leeds Teaching Hospital NHS Trust.

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Electronic: http://www.leedsth.nhs.uk/research/information-for-researchers/key-documents

http://lthweb.leedsth.nhs.uk/sites/research-and-development/resources/Sponsored%20CTIMPs%20%28Quality%20Assurance%29

Contents

Please note: *This SOP should be used and followed in conjunction with other UoL / LTHT SOPs developed for researchers to support study set up and management. These can be found on the LTHT website or by contacting R&I / QA directly. For clinical trials where Leeds (i.e. UoL/LTHT) is not the trial Sponsor, please always refer to any sponsor-specific SOPs for further information.*

Section A: Introduction

1.1 This Standard Operating Procedure (SOP) outlines the procedure for the implementation and management of Reference Safety Information (RSI) for all Clinical Trials of an Investigational Medicinal Product (CTIMPs) sponsored by either the University of Leeds (UoL) or The Leeds Teaching Hospitals NHS Trust (LTHT).

1.2 The Reference Safety Information (RSI) is a list of medical events that defines which reactions are considered expected for the Investigational Medicinal Product(s) (IMP) being administered to subjects participating in clinical trials. Any events deemed to be expected do not require expedited reporting to the Competent Authority (i.e. the MHRA).

1.3 It is a responsibility delegated by the Sponsor to the Chief Investigator (CI) to ensure that RSI is appropriately managed throughout the trial.

1.4 The RSI should be reviewed on an ongoing basis to determine whether any changes have an effect on the risk-benefit ratio for trial participants.

Section B: Applicability

1.1 This SOP is applicable to all members of staff working on single-site, non-Clinical Trials Unit (CTU) managed CTIMPs sponsored by LTHT or UoL.

1.2 Deviations from this SOP must be discussed and agreed with the Sponsor Quality Assurance (QA) Office during protocol development and a written agreement must be in place (*i.e. delegation of duties to an external CTU managing the trial*).

1.3 For CTU managed trials, this SOP may not be applicable. Alternatively, please contact the CTU Head of Trial Management for RSI queries and support.

Section C: A Researcher's Guide to Reference Safety Information

1. Establishing the Trial's Reference Safety Information

1.1. Depending on the phase of a trial and whether or not the IMP is licensed (or in fact being used within its licensed indication), either an Investigators Brochure (IB) or Summary of Product Characteristics (SPC) is used.

1.2. An *entire* IB or SPC is not the RSI for a trial; instead it should be a **clearly defined section within each document**.

For example, if a SPC is being used, it should be clear that the RSI is defined within the '*Undesirable Effects*' section (*usually Section 4.8*).

1.3. Novel therapies where the IMP is being provided or sought from a third party (*e.g. a commercial pharmaceutical company*) are usually accompanied by an IB provided and managed by the IMP manufacturer. A section within the document should be clearly defined by the CI/Principle Investigator (PI) as the trial-specific RSI for that IMP.

Medications that are licensed, and subsequently used within their licensed indications, would ordinarily utilise a SPC as the document containing the RSI for that IMP.

1.4. Occasionally, investigators may wish to establish their own standalone RSI document informed by either the IB or SPC for that IMP. In this event, investigators must ensure the document is appropriately version controlled and clearly references the source of the information. As with an IB or SPC, the bespoke RSI document must also be submitted alongside the initial Clinical Trial Authorisation (CTA) application.

The content must also be reviewed periodically to ensure any relevant updates to the source are captured (*see Section 3.1 for further guidance*).

1.5. The trial's RSI should be clearly identifiable in the initial CTA application to the MHRA. The document containing RSI should always accompany this submission and be **explicitly referenced in the covering letter**, stating the document's version number and date, and also the section in which the RSI is contained.

1.6. Once the initial CTA application has been approved by the MHRA, it becomes the specific RSI version that must be used unless the regulatory authority (*i.e. the MHRA*) states otherwise.

1.7. Any changes to the RSI are deemed a change to the risk-benefit assessment and would require the submission of a substantial amendment to the MHRA in order to change it (*see Section 3 for further guidance*).

2. Identifying the Trial's Reference Safety Information

2.1. Every member of the research team must use the same version of the RSI at the same time; this is essential when investigators are conducting the expectedness assessment.

2.2. The **document** containing the trial's RSI (*i.e. the IB or SPC*) should be clearly stated within the trial protocol.

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 the CTA application. Any subsequent RSI changes must still be submitted via a substantial amendment (*see Section 3*).

2.3. The version number (and/or date) of the document containing RSI should **not** be stated within the protocol as any change to the RSI document would subsequently require an amendment to the protocol.

2.4. Links to third-party websites which publish SPCs (*i.e. the eMC or EMA*) should not be provided within the protocol, as they will invariably provide the *newest* published version, rather than the version specifically approved by the MHRA for use in the trial.

2.5. A copy of the approved RSI document(s) should be clearly labelled and filed within the Trial Master File (TMF) and disseminated to all investigators assessing the expectedness of events.

2.6. It is expected that a trial's RSI remains consistent throughout each annual Development Safety Update Report (DSUR) reporting period (*i.e. the approved RSI at the time of the beginning of reporting period should be used throughout the remainder of the period*).

Should a need to change RSI mid-reporting period be identified, then the CI/PI **must** notify the Sponsor QA Office immediately for advice on how to proceed.

Please note: such a change may also affect the content and format of the DSUR report.

2.7. All Serious Adverse Reaction's (SARs) should be assessed against the current RSI at the time of the event (*i.e. the time at which the initial event occurred*). If an updated RSI is implemented at a later date, the assessment of follow-up information should **not** be made against the updated RSI.

3. Managing Changes to the Trial's Reference Safety Information

3.1. **In line with the DSUR submission:**

3.1.1. A formal review of any potential changes to RSI should be routinely aligned with the preparation for the annual DSUR submission to the MHRA, Research Ethics Committee (REC) and Sponsor.

If relevant changes to the RSI are noted, then a substantial amendment must be submitted to the MHRA in parallel with the DSUR submission to ensure it is approved for use at the start of the trial's forthcoming reporting period (please see *QCRES 03 - Researcher's Guide to Notification of Amendments for UoL/LTHT Sponsored CTIMPs* for further information regarding the amendment process).

3.1.2. Any change to the RSI requires notification to the MHRA as a substantial amendment (*as per QCRES_03*) and **must not be implemented until the MHRA have provided their approval.**

3.1.3. It is important to note that not every change to the IB or SPC in its entirety is a change to the RSI. Although a new document may have been released, there is no requirement to instantly use it as the RSI. Instead the decision should be based on a **documented risk assessment.**

3.1.4. The risk assessment must be made by a medically qualified investigator, usually the trial's CI. This task can be formally delegated to another, appropriately qualified investigator. In **all** instances this clinical risk assessment **must** be formally documented and filed within the TMF.

3.2. **Mid-DSUR reporting period:**

3.2.1. If new information is published mid-DSUR reporting period, it is possible to risk assess the new version of the IB or SPC against the current approved version. If the RSI changes are minimal or not relevant to the trial or patient population, the research team may continue to use the **current RSI for the remainder of the reporting period.**

3.2.2. If there are new events listed in the most recent RSI, a substantial amendment (*as per QCRES_03*) must be submitted to the MHRA.

3.2.3. During the mid-DSUR reporting period, it is permitted to submit an amendment to the MHRA with the caveat that the changes will not be implemented until the immediate end of the current DSUR reporting period. **This must be clearly stated within the amendment submission.**

3.2.4. Should the above guidance not be followed, and a change to the RSI is implemented mid-reporting period, it will have an impact on the forthcoming DSUR.

3.3. Any changes to a trial's RSI, or other significant safety-related change to the IB or SPC, within the reporting period should also be detailed within the 'Changes to Reference Safety Information' section of the DSUR (usually Section 4).

3.4. **Implementing a new RSI document:**

3.4.1. If changes to the RSI are approved by the MHRA, any previous documents containing RSI should be retained within the TMF but be clearly marked as superseded.

3.4.2. Updated documents that are pending Sponsor and regulatory approvals should be held separately until the necessary permissions are in place. The same also applies to any approved RSI documents that are being held for implementation until the start of the next DSUR reporting period.

3.4.3. Upon approval of the updated documentations, it is the responsibility of the CI/PI to ensure that the research team are notified of the new RSI in line with the DSUR periodicity.

3.4.4. The associated changes in criteria and the assessment of expectedness of reactions should also be clearly communicated.

3.4.5. Investigators must remember that updating RSI does not permit the downgrading of historical SUSARs assessed for expectedness against the previous RSI.

4. Implementing Updated Documentation Containing Unchanged RSI

4.1. If a new version of the document (*i.e. IB or SPC*) containing the RSI is issued and there **are no RSI changes identified**, there is no need to submit an amendment to the MHRA before implementing the new document at the start of the new DSUR reporting period.

4.2. No change to RSI is defined as no new events being listed as 'expected', as well as no events being removed.

Remember: This **must** still be documented in a clinical assessment to demonstrate that the RSI has not changed. This assessment must be filed within the TMF.

5. Further Reading

5.1. Please see **Appendix A** for a simplified flow chart illustrating the Process for '*RSI Review & Management*'.

5.2. Please see **Appendix B** for typical scenarios that may affect the trial's RSI and how to manage them appropriately.

Section D: References

MHRA Good Clinical Practice Guide 2012

Clinical Trial Facilitation Group Q&A Document – Reference Safety Information 2017

MHRA Inspectorate Blog:
https://mhrainspectorate.blog.gov.uk/2016/03/02/reference-safety-information-for-clinical-trials/
https://mhrainspectorate.blog.gov.uk/2017/01/18/reference-safety-information-ii/

QCRES_01 - Researcher's Guide to Pharmacovigilance

QCRES_03 - Researcher's Guide to Notification of Amendments for UoL/LTHT Sponsored CTIMPs

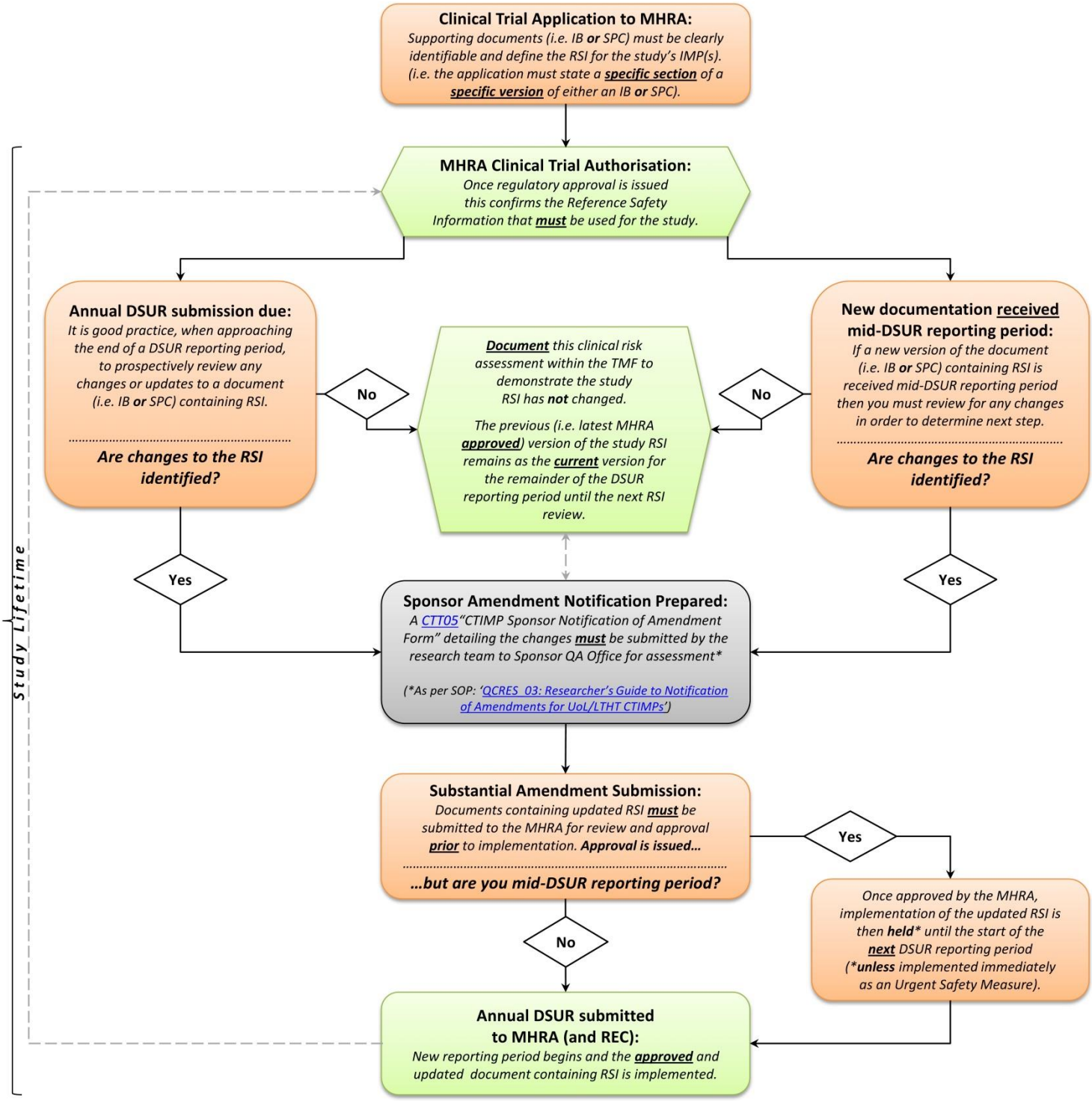
Section E: Acronyms

CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DSUR	Development Safety Update Report
EMA	European Medicines Agency
eMC	electronic Medicines Compendium
IB	Investigator Brochure
LTHT	The Leeds Teaching Hospitals NHS Trust
MHRA	Medicines and Healthcare Products Regulatory Agency
PI	Principal Investigator
QA	Quality Assurance
R&I	Research and Innovation
REC	Research Ethics Committee
RSI	Reference Safety Information
SAR	Serious Adverse Reaction
SOP	Standard Operation Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UoL	University of Leeds

Section F: Previous Versions of Document

Version no.	Valid from	Approved by	Date approved
1.0	19/03/2018	Clare Skinner, Louise Brook	12/04/2018

Appendix A: Process for RSI Review & Management



Appendix B: Example Scenarios

1.1. Below are three scenarios outlining the Investigator's required action when a document containing Reference Safety Information is altered:

	Scenario	Action
1.	A new version of an IB/SPC is issued at the time of the DSUR for the new reporting period. New events have been listed within the RSI.	An amendment must be sent to the MHRA (*as per 'QCRES_03' SOP*), and must not be implemented until the new IB/SPC has obtained approval. **Note:** Any change to the RSI is a change in risk-benefit.
2.	A new version of the IB/SPC is issued at the time of the DSUR for the new reporting period. There are **no changes** to the RSI. (No new events listed as expected and no events removed)	There is no need to submit an amendment to the MHRA before implementing the new IB/SPC. However a clinical assessment must be filed within the TMF to demonstrate the RSI has not changed.
3.	A new version of the IB/SPC is issued mid-DSUR reporting period and there are new events listed.	An amendment must be sent to the MHRA (*as per 'QCRES_03' SOP*), and must not be implemented until the new IB/SPC has obtained approval. However, after risk assessing the changes, it may be decided that the IB/SPC does not need to be implemented at this time. If the RSI changes are minimal or not relevant to the study / patient population, it is possible to continue with the current RSI in the current IB/SPC version for the remainder of the DSUR reporting period. If changes ***are*** implemented mid period, this will impact the DSUR as the RSI in place at the start of the reporting period must be used for all DSUR line listings. This process must be documented. An amendment may be submitted at the time of the release of the new IB/SPC stating that the new RSI will not implemented until the end of the current DSUR period.