Royal Papworth Hospital
NHS Foundation Trust

Document Title: Reference Safety Information (RSI)

Document Number: PTUC SOP079

Staff involved in development: Job titles only	Senior R&D Manager, R&D Administration Manager, Clinical Project Managers
Document author/owner:	R&D Administration Manager
Directorate:	Research and Development
Department:	Research and Development
For use by:	NHS Staff Trust-Wide
Review due:	March 2026

Summary of Amendments

Version Number	Modification:
Version 4.0	Minor Amendments Throughout
Version 5.0	Minor Amendments Throughout

Key Points of this Document

- This document sets out the procedures to be followed by all Royal Papworth Staff who are involved in Clinical Trials of Investigational Medicinal Products (CTIMP) for research studies to be managed by Royal Papworth Trials Unit Collaboration or sponsored by Royal Papworth Hospital NHS Foundation Trust.

- It provides guidance on the steps involved in definition, documentation, and oversight of Reference Safety Information (RSI) to ensure compliance with the Trust's policies and current regulations and guidance.

1. Purpose and Contents

a. In order to ensure compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments (2004/1031, 2006/1928, 2006/2984, 2008/941, 2009/1164), a sponsor of a clinical trial of an investigational medicinal product (CTIMP) is responsible for completion of reporting of suspected unexpected serious adverse reactions (SUSARs) in accordance with regulatory timelines.

b. In order to determine whether a serious adverse reaction (SAR) occurring within the CTIMP is expected or not, both the PI/CI and the sponsor must complete an expectedness assessment of each event by identifying which events are listed within the reference safety information (RSI) (expected events) or those which are not (unexpected events).

c. Please refer to SOP012: Safety event reporting – for detail of safety reporting

2 Roles & Responsibilities

a. This Policy applies to all personnel that are conducting research at the Trust.
b. Staff involved in CTIMPs must comply with the requirements set out in section 5.
c. It is the responsibility of the department's personnel to ensure that they are familiar with and adhere to all current SOPs and have signed the relevant log in their training record.

3 Policy

a. This SOP is mandatory and, as per the Trust's Information Governance and Records Management framework, non-compliance with may result in disciplinary procedures.

4 Definitions/Regulations/Guidance

a. The RSI is a list of medical events that defines which reactions are expected for the Investigational Medicinal Product (IMP) within a given trial.

b. For an IMP with a marketing authorisation, the RSI will be documented with the Summary of Product Characteristics (SmPC).

c. If the Investigational Medicinal Product (IMP) has a marketing authorisation in several Member States with different Summary of Product Characteristics (SmPCs), the Sponsor should select the most appropriate SmPC, with reference to the subject safety, as the RSI.

d. For an IMP without a marketing authorisation, the RSI will usually be documented within the Investigator's Brochure (IB). If the RSI is contained in the Investigators Brochure (IB), the IB should contain a clearly-identified section to this effect. This section should include information on the frequency and nature of the expected adverse reactions.

e. The RSI for an IMP provides listings of all adverse reactions to an IMP along with the frequency with which these are expected.

f. The RSI, therefore, determines which treatment-related events the Sponsor of a trial must report in an expedited manner as SUSARs. The RSI serves to define all reactions related to a given IMP that are expected. In the event that a serious adverse reaction (SAR) occurs within a clinical trial, the investigator must report this immediately to the Sponsor. The Sponsor must then use the RSI to determine the expectedness of the SAR. If the reaction is listed within the RSI as being expected then no further expedited reporting is required. In the event that the reaction is not listed, then the event becomes a SUSAR and is subject to expedited reporting as outlined above.

g. The RSI may change during the conduct of a clinical trial. This is always submitted as a substantial amendment to the MHRA.

h. For the purpose of SUSAR reporting the version of the RSI approved by the MHRA at the moment of occurrence of the SUSAR applies.

5 Procedure

a. The RSI must be identified for any IMP and referenced in the protocol. The RSI is usually, either, contained within the IB or, for IMPs already holding a marketing authorisation, will be within the SmPC. The RSI for any given CTIMP must be approved by the MHRA prior to beginning the trial (PTUC SOP014: Gaining regulatory approval from the MHRA).

b. The RSI must be clearly identified as a separate section (in whichever document details the RSI) including all expected adverse reactions listed by nature, severity and frequency as follows:

- Nature
  Listed adverse reactions should be based on reactions previously observed and not on the basis of what might be anticipated from the pharmacological properties of an IMP, as inclusion of previously unseen reactions will mean that there is no regulatory oversight of any new safety signals.

- Severity
  Only previous serious adverse reactions can be considered as expected. Non-serious reactions may be included in the RSI table but serious reactions must be clearly highlighted. In the event that non-serious adverse reactions are included in the RSI then sponsors must be clear that if such an event then becomes serious, expedited reporting must then take place as the definition of unexpected includes an increase in severity.

- Frequency
  The preference for presentation of this information is in categories. However, if insufficient numbers of subjects have been exposed to the IMP to define categories, then the frequencies can be expressed as a number together with the number of patients exposed. Reactions that have occurred only once cannot usually be considered as expected and a robust justification should be provided if these are included in the RSI.

c. Once a CTIMP is approved, it is the responsibility of the chief investigator (or person to whom responsibility for this has been delegated) to periodically review the RSI applicable to the trial for updates and highlight any potential implications for the trial. The frequency of RSI review for updates must be proportionate to the risk profile of the IMP and/or the trial. For example, a licensed IMP being used within its marketing authorisation may require review for updates to the RSI every 6-12 months. However, an IMP without a marketing authorisation or being used outside of indication in a particularly vulnerable patient group may require the RSI to be reviewed every 12 weeks. The planned frequency and dates for this must be agreed prior to

initiation of the trial and must be documented in the trial's pragmatic risk assessment (FRM024) and/or the trial master file.

6. Updates to the RSI may occur in the middle of the annual timeframe of the developmental safety update reporting (DSUR) period.

a. The annual reporting period is defined as the period of one year from the date of regulatory approval and occurring annually thereafter.

b. RSI that is updated during the DSUR reporting period do not have to be implemented immediately and it is the sponsor's responsibility to determine whether or not updated RSI are adopted immediately, or to wait until the beginning of the next annual reporting period before being adopted.

c. Any change to the RSI must be assessed by the Sponsor, or their delegated representative, against those currently approved, for implications to the trial and the patient population. One of two possible courses of action are appropriate:

- If it is decided that the updated RSI must be taken into consideration immediately then this change in RSI must be submitted to the MHRA as a substantial amendment to the trial at that time. Once approved, the updated RSI **must** be used in any assessment of expectedness of reported SARs. Any update to the RSI that is submitted and approved within the timeframe of the DSUR reporting period may change the assessment of expectedness of SAE/SARs contemporaneously. However, for the purpose of the DSUR, only the RSI approved at the beginning of that reporting period may be used for the assessment of SARS during that period for the completion of data that are submitted as part of the DSUR. This means that' from the point the updated RSI is approved, there may be a cohort of SARS that need to be assessed for expectedness against both the former RSI and the newly approved RSI.

- Alternatively, if it is considered that the updated RSI does not have immediate implications for the trial or the patient population, then the RSI review should be documented but submission of the RSI update to the MHRA as a substantial amendment can be delayed until the beginning of the next DSUR reporting period.

d. It is the responsibility of the Investigator to ensure that the updated RSl is submitted to the MHRA as a substantial amendment for approval prior to the updated RSI being used in the assessment of expectedness (SOP037 Amendments to Research Studies).

e. Following approval of the updated RSI, it is the responsibility of the Sponsor to ensure that the study team and/or additional sites are notified of the substantial amendment and updated RSI, and consequent changes in criteria and assessment of the expectedness of SARs.

6 Risk Management / Liability / Monitoring & Audit

a. The R&D SOP Committee will ensure that this SOP and any future changes to this document are adequately disseminated.

b. The R&D Department will monitor adherence to this SOP via the routine audit and monitoring of individual clinical trials and the Trust's auditors will monitor this SOP as part of their audit of Research Governance. From time to time, the SOP may also be inspected by external regulatory agencies (e.g. Care Quality Commission, Medicines and Healthcare Regulatory Agency).

c. In exceptional circumstances it might be necessary to deviate from this SOP for which written approval of the Senior R&D Manager should be gained before any action is taken. SOP deviations should be recorded including details of alternative procedures followed and filed in the Sponsor and Site Files.

d. The Research and Development Directorate is responsible for the ratification of this procedure.

Further Document Information

Approved by: Managment/Clinical Directorate Group	Research and Development Directorate
Approval date: (this version)	[Current active version approved date]
Ratified by Board of Directors/ Committee of the Board of Directors:	STET
Date:	N/A
This document 'supports: Standards and legislation	Medicines for Human Use (Clinical Trials) Regulations 2004 and all associated amendments. Research Governance Framework for Health and Social Care (2005)
Key related documents:	Trust Research Policy [Insert list of linked or relevant documents to this SOP]

Equality Impact Assessment: Does this document impact on any of the following groups? If YES, state positive or negative, complete Equality Impact Assessment Form available in Disability Equality Scheme document DN192 and attach.

Groups	Disability	Race	Gender	Age	Sexual orientation	Religious & belief	Other
Yes/No	NO	NO	NO	NO	NO	NO	NO
Positive/Negative							

Review date:	March 2026

I certify the contents of this SOP has been reviewed and ratified

DocuSigned by:
Patrick Calvert
81A52758BFFF421...

06-Sep-2023

....

Signed by Dr Patrick Calvert, Clinical Director of R&D — Date