UNIVERSITY OF WARWICK

STANDARD OPERATING PROCEDURE 17 Part 4

Reference Safety Information (RSI)

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Revision Chronology:	**Effective date:**	**Reason for change:**
4.0	11 May 2026	Biennial review: SOP updated to align with key requirements of ICH-GCP E6(R3) for RSI content and review, and with terminology and processes introduced by the updated UK Clinical Trial Regulations. Text streamlined and transferred to the new SOP template. Clarified that a dedicated RSI within the Investigator Brochure is required when the IMP is used outside its MA.
3.0	13 Dec 2023	Very minor changes to text to improve clarity.
2.0	11 Oct 2021	Biennial review: Update to new SOP template. Addition of template to record reviews and implementation of RSI changes. Minor changes to text.
V1.0	4 July 2019	

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CONTENTS

1 Purpose and Scope

This SOP outlines the process for selecting, defining and updating Reference Safety Information (RSI) used to determine the expectedness of Serious Adverse Reactions (SARs) in Clinical Trials of Investigational Medicinal Products (CTIMPs). Definitions relating to pharmacovigilance are provided in SOP 17 Part 1:Pharmacovigilance for CTIMPs.

It is applicable to all staff working on University of Warwick (UoW) sponsored CTIMPs.

For externally sponsored studies managed by WCTU, this SOP applies where pharmacovigilance responsibilities have been delegated. Where no such delegation exists, teams must follow the external sponsor's own processes.

2 Acronyms

CA	Competent Authority
CI	Chief Investigator
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigation Medicinal Product
DSUR	Developmental Safety Update Report
EMC	Electronic Medicines Compendium
IB	Investigator Brochure
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
PIS	Patient Information Sheet
QA	Quality Assurance
R&IS	Research and Impact Services
RSI	Reference Safety Information
SAE/SAR	Serious Adverse Event/Reaction
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SPM	Senior Project Manager
SUSAR	Suspected Unexpected Serious Adverse Reaction
TM/TC	Trial Manager/Trial Coordinator
TMF	Trial Master File
TMG	Trial Management Group
UoW	University of Warwick
WCTU	Warwick Clinical Trials Unit

3 Definitions

RSI	Approved document which defines the SARs that are expected for the IMP being administered to participants in a clinical trial.

SAE	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product, which does not necessarily have a causal relationship with this treatment but fulfils one or more of the following criteria: 1. Results in death, 2. Is life-threatening, 3. Requires hospitalisation or prolongation of existing inpatients' hospitalisation, 4. Results in persistent or significant disability or incapacity, 5. Is a congenital anomaly or birth defect, 6. Requires medical intervention to prevent one of the above, or is otherwise considered medically significant by the investigator (e.g. participant safety is jeopardised).
SAR	All untoward and unintended responses to an IMP related to any dose administered. This is an SAE for which there is reason to suspect that it may be caused by the administration of the IMP.
Marketing Authorisation	Approval granted by a CA for a drug for which sufficient evidence of quality, efficacy and safety profiles have been demonstrated for a particular intended use. An MA is also known as a licence.

4 Background

Under the Medicines for Human Use (Clinical Trials) Regulations, SUSARs must be reported to the CA within seven days for life-threatening or fatal events and 15 days for all other SUSARs. For UK CTIMPs, the MHRA is the CA.

The RSI is a definitive list of expected SARs for an IMP and is the basis for assessing whether SARs are expected reactions or should be classed as a SUSAR requiring expedited reporting to the CA.

Management and timely review of the RSI ensure that the IMP's safety profile is consistently interpreted by the trial team and regulators, supporting reliable benefit–risk assessment throughout the trial.

5 Responsibilities

All staff working on CTIMPs must be familiar with the content of this SOP. The sponsor retains overall responsibility for pharmacovigilance and ensuring compliance with the regulations governing safety reporting and management of RSI. For UoW sponsored CTIMPs, pharmacovigilance activity is delegated to WCTU but key oversight is maintained by the sponsor's Office in R&IS. For externally sponsored CTIMPs, any delegation of pharmacovigilance responsibilities must be made clear in the relevant agreements between the external sponsor and UoW.

Where WCTU are managing pharmacovigilance, the following responsibilities apply:

CI (or delegate)	• Select appropriate RSI and assess updates. • Lead risk assessment of RSI changes and secure required approvals. • Delegation to clinical team members is permitted if documented.
Pharmacy Advisor	• Support the CI in evaluating the clinical relevance and impact of proposed RSI updates.

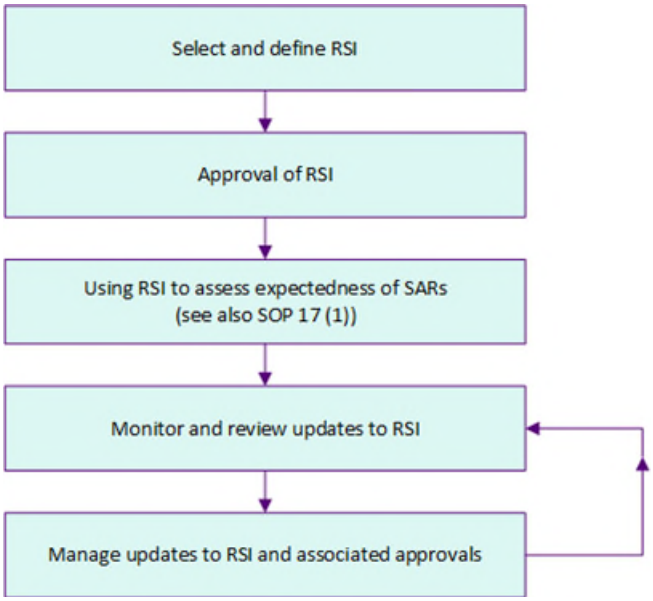
	• Provide specialist input into the safety profile, including frequency/nature of reactions where a bespoke RSI will be implemented.
TM/TC	• Submit RSI and any approved updates to MHRA before use for expectedness assessment. • Check for RSI updates. • Prepare and submit DSURs to the MHRA ensuring consistency with the RSI used during the reporting period.

6 When

RSI must be identified during trial design and submitted as part of the CTA. The RSI forms the reference point for assessing the expectedness of SARs throughout the trial. SUSARs need to be reported to the MHRA only in the timelines outlined in Section 4 of this SOP. The RSI must be used consistently during the safety reporting period to determine whether an event should be classified as a SUSAR requiring expedited reporting. Its content and continued suitability must be reviewed regularly (at least annually) and updated when relevant new safety information becomes available.

7 How

Below is a flow chart summarising the selection and management of RSI. Further information relating to each element can be located below:



7.1 Select and define RSI

The RSI must be selected, taking into consideration the trial population and whether the IMP will be used within or outside its Marketing Authorisation (MA). Any justification for the selected RSI must be documented in the CTA application.

For authorised products, and in some other circumstances where justified, section 4.9 of the SPC will normally be used as the RSI. When the IMP is used outside its licensed indication, section 4.8 of the RSI may be used where an IB is not available or where the SmPC is still appropriate for the trial population.

For trials where the IMP is used outside its MA and there is no justification for use of the SPC, a bespoke RSI must be included within a section of the IB. RSI contained within an IB must:

- Contain a list of adverse reactions
- Include frequency and nature of each reaction
- Serve as the reference for determining expectedness and the need for expedited SUSAR reporting.

Expected adverse reactions should be restricted to those that have been observed more than once in human exposure and not inferred solely from pharmacology. Life threatening or fatal SARs should only be included when strongly justified, as these are generally considered ‘unexpected’.

7.1.1 Trials running in multiple countries or combination of IMP

For multi-country trials, the same RSI must be used across all participating countries, with clear justification for its selection to ensure consistent expectedness assessments and regulatory reporting obligations.

For trials using multiple IMPs or IMP combinations, the RSI should ideally describe the combined safety profile. If no combination RSI exists, an approved RSI must be in place for each individual IMP, and expectedness should be assessed against all relevant RSIs.
Where different doses or concentrations are used, a separate RSI may be needed if safety profiles differ meaningfully or if justified by the risk assessment.

7.1.2 Defining RSI

The exact section of the document that contains the RSI must be clearly referenced in both the protocol and the CTA submission (including the covering letter), so regulators and trial staff can easily identify the material used to assess the expectedness of SARs.

The RSI refers only to the specific section listing the definitive expected adverse reactions, not the entire IB or SPC.

7.2 Approval of RSI

No updated RSI may be implemented unless it has been formally approved by the MHRA or relevant CA through a subsequent modification, ensuring continued compliance with ICH-GCP E6(R3) requirements for RSI content and use in expedited reporting.

7.3 Using RSI to assess expectedness of SARs

As outlined in SOP 17 Part 1, the Sponsor should delegate an individual to assess expectedness on behalf of the sponsor. This will typically be the TM or CI. Expectedness assessment must be done using the RSI which was approved for use at the time of the event even if the event or subsequent follow-up was submitted implementation of a new RSI. All events that are listed in the DSUR to the MHRA should be assessed in this way and no event should be re-classified retrospectively following the implementation of a new RSI. For DSUR submission processes, refer to SOP 5 Part 3 'Communication with approval bodies'.

7.4 Monitor and review updates to RSI

The trial risk assessment or monitoring plan should specify how often the TM/TC should check for updates to the document containing the RSI. If no interval is defined, the RSI must be reviewed at least annually, and prior to submission of the DSUR. If the IMP risks are high according to the trial risk assessment, a more regular review should be considered. This should be documented in the monitoring plan. It is a good idea to align this assessment with a Trial Management Meeting.

SPCs can be found on the EMC or MHRA websites:

https://www.medicines.org.uk/emc

https://products.mhra.gov.uk/

If updates occur to the relevant sections of an SPC or IB, the CI (or clinical delegate), supported where possible by the Pharmacy Advisor, must risk assess the changes to determine whether they should be adopted for expectedness assessments. An updated SPC or IB does not automatically mean the RSI must be updated; only clinically relevant changes should trigger a revised RSI. All decisions and the rationale for adopting or not adopting changes must be clearly documented in the TMF. Staff responsible for expectedness assessment must always know which RSI version is currently approved to ensure consistent and accurate SUSAR determination.

7.5 Manage updates to RSI and associated documents

If changes to the section of the document containing the RSI are considered relevant to the trial population or safety profile, updates must be submitted to the MHRA (and any other relevant CAs) as a substantial modification before implementation.

Changes limited to formatting or numerical exposure updates that do not alter the frequency category of any reaction do not require regulatory approval.

Following any RSI update, the trial team must evaluate whether related documents require revision e.g. the protocol, PIS/consent materials, risk assessment, or monitoring plan to ensure safety measures, exclusion criteria, or monitoring requirements remain accurate. A record of all RSI reviews, decisions,

rationales, and implementation dates must be maintained in the TMF. T63 (RSI Implementation Log) can be used for this purpose.

7.5.1 Timing of submission for approval and implementation of new/updated RSI

Where possible, RSI updates should be submitted for approval in line with DSUR timing, allowing consistent expectedness assessments throughout the reporting period. However, updates may be submitted earlier where clinically necessary; if implemented between DSURs, the DSUR must clearly identify the date the new RSI took effect and the events assessed under each version. A new RSI must not be used until approval has been granted by all relevant Competent Authorities. The implementation date should be documented in the TMF. Where expectedness assessment has been delegated to WCTU, the RSI does not need to be stored in the ISF, provided the TMF clearly identifies the current approved version.

7.5.2 Updates to other sections of the document containing RSI

If a new version of the IB or SPC is released but the RSI section remains unchanged, the RSI itself does not need updating or re-approval. However, updates in other sections (e.g., new safety findings, pharmacology, dosing, contraindications) must be reviewed by the CI and trial team to determine whether the protocol, PIS/consent materials, or monitoring requirements require amendment.

New IB/SPC versions may be shared operationally with pharmacists or site nurses without regulatory approval, but RSI changes always require approval before use for expectedness assessment.

Further information on RSI and the regulatory requirements can be found via the following link: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf

8 Templates

T63 RSI Implementation Log