# STANDARD OPERATING PROCEDURE 17
# Safety
# Part 4: Reference Safety Information

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| V3.0 | 13 Dec 2023 | Very minor changes to text to improve clarity. |
| V2.0 | 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 | |

# STANDARD OPERATING PROCEDURE 17
# Safety
# Part 4 – Reference Safety Information (RSI)

## 1. Purpose and Scope

This Standard Operating Procedure (SOP) describes the procedure for selecting and defining Reference Safety Information (RSI) for assessing the expectedness of Serious Adverse Reactions (SARs) in Clinical Trials of Investigational Medicinal Products (CTIMPs) and managing any changes and associated approvals. Full definitions relating to pharmacovigilance are covered in more detail in Part 1 of this SOP 'Pharmacovigilance for CTIMPs'.

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

If the research project is not sponsored by UoW but is managed by Warwick Clinical Trials Unit (WCTU) and appropriately delegated in the collaboration agreement, this SOP should apply. Where this is not the case, externally sponsored studies should follow the relevant sponsor's own process and document any deviations from the procedure outlined here.

## 2. Definitions

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| **Reference Safety Information (RSI)** | Approved document which defines the Serious Adverse Reactions (SARs) that are expected for the Investigational Medicinal Product (IMP) being administered to subjects in a clinical trial. |
| **Serious Adverse Event (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:<br>1. Results in death,<br>2. Is life-threatening,<br>3. Requires hospitalisation or prolongation of existing inpatients' hospitalisation,<br>4. Results in persistent or significant disability or incapacity,<br>5. Is a congenital anomaly or birth defect,<br>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). |
| **Serious Adverse Reaction (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. |
| **Suspected Unexpected Serious Adverse Reaction (SUSAR)** | A suspected serious adverse reaction that is also unexpected i.e. the nature, frequency or severity of the event is not consistent with the applicable RSI. A SUSAR is therefore a reaction suspected of having a possible causal relationship with the IMP which has not previously been documented in the RSI. |

## 3. Background

The Medicines for Human Use (Clinical Trials) Regulations state that all relevant information about a SUSAR should be reported to the Competent Authority (CA) within 7 days (for life-threating or fatal

events) or within 15 days for all others. For UK trials, the Medicines and Healthcare products Regulatory Agency (MHRA) is the CA.

The RSI is a definitive list of expected SARs for an IMP that serves as the basis for assessing whether SAEs that have been deemed clinically to be potentially related to administration of the IMP, are expected reactions. This helps determine whether an event should be classified as a SUSAR and as a result requires expedited reporting to the CA.

The RSI should be managed in accordance with these regulations so that the safety profile of the IMP can be reviewed by the trial team and the regulatory authority in a way that is consistent.

## 4. Procedure

### 4.1 Responsibilities

All staff working on CTIMPs must ensure that they are familiar with the processes contained within this document. The sponsor has overall responsibility for pharmacovigilance and compliance with the regulations. For University of Warwick (UoW) sponsored CTIMPs, pharmacovigilance activity is delegated to Warwick Clinical Trials Unit (WCTU) but key oversight is maintained by the sponsor's Office in Research and Impact Services (R&IS). For externally sponsored CTIMPs, any delegation of pharmacovigilance responsibilities should made clear in the relevant agreements between the external sponsor and the University of Warwick.

Where WCTU are managing pharmacovigilance, the following responsibilities apply:

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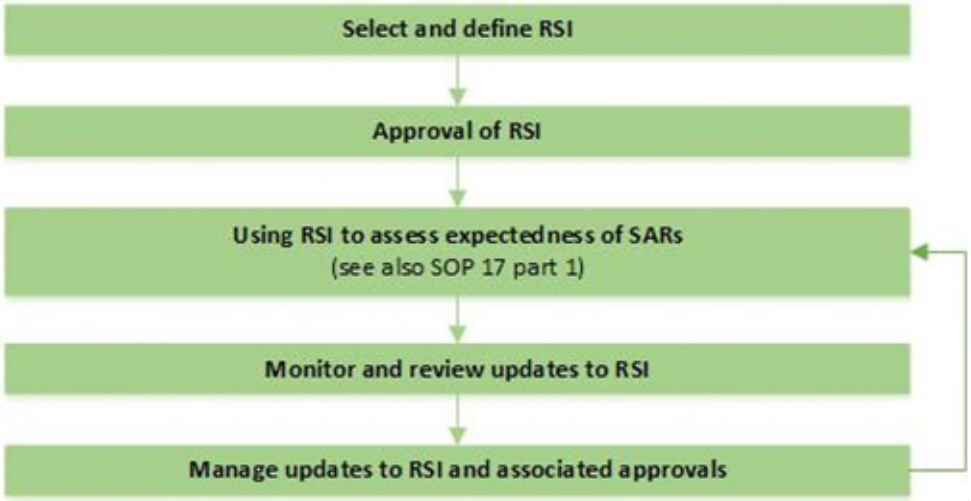
| **Chief Investigator (CI) (or delegate)** | Select appropriate RSI, risk assess any updates to the RSI and obtain relevant approvals for any changes made. These tasks can be delegated to other members of the clinical team, but this delegation should be clearly documented. |
| **Pharmacy Advisor** | Assist the CI in the risk assessment of updates to the RSI. |
| **Trial Manager /Trial Coordinator (TM/TC)** | Ensure the RSI and any subsequent updates are sent to the relevant CAs for approval prior to their use for assessment of SARs. Check for updates to the RSI at intervals specified by the Monitoring Plan. Prepare and submit Developmental Safety Update Reports (DSURs) to the MHRA. |
| **Senior Project Manager (SPM)** | Check agreements and ensure appropriate documentation of pharmacovigilance activity delegated to WCTU. |
| **Quality Assurance (QA) Team** | Chair the initial trial risk assessment and monitoring plan meetings where regularity of checks for updates to the RSI will occur. Review substantial amendments to the MHRA prior to submission to sponsor. |

### 4.2 When?

At the point of trial design and application for Clinical Trial Authorisation (CTA), RSI should be considered. It should be used throughout the trial to assess expectedness of SAEs that are deemed to be related to administration of the IMP by a clinician. The contents and appropriateness of the RSI in the context of the clinical trial should be assessed throughout the safety reporting period for the trial and amended where necessary.

### 4.3 How?

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




### 4.3.1 Select and define RSI

The RSI should be carefully selected, taking into consideration the trial population and whether the IMP will be used within its Marketing Authorisation (MA)/licence. The MA is 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. For products with a MA, there will be a Summary of Product Characteristics (SPC) which details the safety information for the drug in the context of its MA. These documents have standard layouts, and section 4.8 is always the section which lists the expected serious adverse reactions for a drug.

#### 4.3.1.1 Trials that will use the IMP within the MA

If the clinical trial IMP is being used within this intended use, then usually section 4.8 of the SPC can be used as the trial RSI.

#### 4.3.1.2 Trials that will use IMP outside of the MA

For trials where the IMP is being used outside of the MA, then it is common to write bespoke RSI into a section of the Investigator Brochure (IB). RSI contained within an IB would ideally be formatted in the same way as section 4.8 of an SPC which is formatted according to the International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) requirements, however it should include the nature, frequency and severity of expected adverse reactions. Expected adverse reactions should be restricted to those that have been observed upon administration of the IMP more than once and not based on what might be anticipated based on the pharmacological properties of the IMP. Life threatening and fatal SARs are very rarely included in RSI without very clear justification as these are almost always considered 'unexpected'.

If justified sufficiently, clinical trials of an IMP that is being used outside the terms of the MA can use the relevant product's SPC as the RSI if the sponsor does not have access to an IB for the marketed IMP or it can be clearly justified that it remains applicable to the trial population intended. Any justification for the use of RSI must be clear in the CTA application.

#### 4.3.1.3 Trials running in multiple countries or combinations of IMP

Where a trial is running in multiple countries, the RSI should be consistent across them and the selection justified.

Where combinations of IMPs are being used, the RSI should ideally refer to the combination. If this is not available there should be an approved RSI for each IMP being used.

#### 4.3.1.4 Defining RSI

The specific section of the document in which the RSI is located should be referenced in the protocol and the covering letter of the application for CTA so it is clear which parts of the documents should be used for assessing expectedness of SARs. The RSI is not the whole document but the section which contains the definitive list of expected adverse reactions.

### 4.3.2 Approval of RSI

The RSI which will be used in the trial will need to be defined appropriately as per section 4.3.1.4 above and submitted to the MHRA (and any other CAs for where the trial will be run) during application for CTA. This is the version that must be used for assessing expectedness of SARs. No other version should be used unless approved by the MHRA or relevant CA via submission of a subsequent substantial amendment.

### 4.3.3 Using RSI to assess expectedness of SARs

As per part 1 of this SOP 'Pharmacovigilance for CTIMPs', there should be an individual delegated to assess expectedness on behalf of the sponsor. This will typically be the TM/TC or the CI. Expectedness assessment by this individual 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 to the trial office after 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 details on DSUR submission please see SOP 5 Part 3 'Communication with approval bodies'.

### 4.3.4 Monitor and review updates to RSI

The trial risk assessment or monitoring plan should define how regularly the TM/TC should check for updates to the document which contains the RSI. If not, it should be reviewed prior to submission of the DSUR on an annual basis. If the IMP risks are high according to the trial risk assessment, then consideration might be made for doing this more regularly e.g., 6 monthly or quarterly. This should be documented in the monitoring plan.

SPCs can be found on the Electronic Medicines Compendium (EMC) or MHRA websites:
https://www.medicines.org.uk/emc
https://products.mhra.gov.uk/

If there have been changes to the section of the SPC or IB which is being used as the RSI, then these should be risk assessed by the CI/clinical delegate and the pharmacy advisor if possible. They should consider if the changes are relevant and will affect the population being looked at and decide if these changes need to be implemented for the purposes of expectedness assessment. If not, then the current approved RSI can continue to be used. An updated SPC or IB will not automatically lead to an updated RSI. Any decisions made and the rationale should be documented and available in the TMF. It is important that anyone conducting expectedness assessment on behalf of the sponsor is aware which RSI is the current approved version.

### 4.3.5 Manage updates to RSI and associated documents

If changes to the section of the document containing the RSI are deemed to be relevant to include in the trial RSI then any updates are required to be submitted to the MHRA (and any other relevant CAs) as a substantial amendment. Formatting changes or modifications to exposure rates that do not result in a change in the frequency category to which the reaction has been assigned do not require a substantial amendment.

Considerations must be given as to whether the protocol or Patient Information Sheets (PIS) /Consent Forms/Risk Assessment/Monitoring Plan require updating in line with the changes to the RSI. For

example, are any additional exclusion criteria or any additional monitoring steps required which will need to go into the protocol?

It is recommended that a record is kept of all reviews, the decisions, and any subsequent implementation dates for the RSI. A template (T63) is available to download to record these details in the TMF. The Trial Management Group (TMG) Decision log can aid the documentation.

#### 4.3.5.1 Timing of submission for approval and implementation of new/updated RSI

Ideally any updates made to the RSI would be submitted for approval via a substantial amendment in line with the DSUR submission i.e., at the end of the reporting period. The same RSI should ideally be used throughout the full DSUR reporting period to ensure that expectedness assessments are carried out consistently. Updates to the RSI can be done earlier if felt necessary; any changes to the RSI made part way through a reporting period need to be made clear in the DSUR report.

Approval from the CA in all member states that are involved in the trial is required prior to implementation of new RSI to assess expectedness. The implementation date is usually the date of approval and should be recorded clearly in the TMF. Where expectedness assessment is delegated to WCTU by the sponsor, the RSI does not need to be contained in the Investigator Site File (ISF).

#### 4.3.5.2 Updates to other sections of the document containing the RSI

If a new version of the IB or SPC is released but no changes have been made to the section that lists the expected adverse reactions, no changes to the RSI will be required. However, updates to other sections within the IB or SPC should be considered from the point of view of any need for changes to the protocol, consent form or patient information sheet as a result.

If a new version of the IB or SPC is published, this may be made available to trial pharmacists and/or nurses without approval. Only the RSI needs to be approved if changes are made.

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

## List of abbreviations

| | |
|---|---|
| CA | Competent Authority |
| CI | Chief Investigator |
| CTA | Clinical Trial Authorisation |
| CTIMP | Clinical Trial of Investigational Medicinal Product |
| DSUR | Developmental Safety Update Report |
| 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 |