



STANDARD OPERATING PROCEDURE FOR MANAGING REFERENCE SAFETY INFORMATION AND THE ASSESSMENT OF EXPECTEDNESS IN CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS

SOP NUMBER:	TASC SOP71 v1
AUTHOR:	Joana Rocha
EFFECTIVE DATE:	30 Sept 2026
REVIEW DATE:	30 Sept 2028

1. PURPOSE

This Standard Operating Procedure (SOP) describes the procedure for documenting Reference Safety Information (RSI) updates and the managing of the RSI in the assessment of expectedness of adverse reactions (ARs) in Clinical Trials of Investigational Medicinal Products (CTIMPs) which are sponsored or co-sponsored by the University of Dundee (UoD) and/or NHS Tayside (NHST) where NHST has been delegated the responsibility for Pharmacovigilance (PV).

2. SCOPE

This SOP applies to members of staff associated with and managing CTIMPs that are sponsored or co-sponsored by the UoD or NHST.

The Sponsor pharmacovigilance procedure complies with the requirements of the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 (SI 538) and the principles of GCP.

Pharmacovigilance may be delegated to a third party, but the process and reporting duties must be agreed between the Sponsor and third party before the trial commences with the responsibilities clearly documented.

The delegation of PV activities does not remove the Sponsor's overall responsibility for oversight of those activities.

3. RESPONSIBILITIES

Investigator (Chief Investigator {CI} or delegate):

- will ensure, alongside Sponsor, that the RSI is clearly defined in the trial protocol.
- is responsible for risk assessing all changes in the RSI and checking if any changes have an impact on the risk/benefit of the trial and submit this for Sponsor review.
- will ensure modifications relating to Summary of Product Characteristics (SmPC)/Investigator Brochure (IB) are notified to and approved by Sponsor.

Uncontrolled when printed. Please visit the [TASC website](#) for the latest version of this SOP.

Sponsor approval does not replace the requirement for regulatory approval/notification where applicable.

Sponsor (Research Governance):

- will ensure, alongside the Investigator, that the RSI is clearly defined in the protocol.
- will consider and document the implications of any RSI changes.
- will review any proposed modifications and confirm the appropriate classification and regulatory pathway for the modification.

TASC Pharmacovigilance:

- will ensure only the approved RSI will be used in Tayside Pharmacovigilance System.
- will document changes to SmPCs and IBs
- will annually check updates for SmPCs and IBs.

TASC Medical Reviewer (TASC Pharmacovigilance Committee Members):

- will assess expectedness for all reported serious adverse reactions (SARs) on the Tayside Pharmacovigilance System.

4. PROCEDURE

4.1 Background

4.1.1 The RSI is used for the assessment of the expectedness of suspected SARs that occur in clinical trials. It forms part of the clinical trial authorisation (CTA) and should be clearly defined in the study protocol.

4.1.2 The RSI is located in the SmPC and/or in the IB for the trial Investigational Medicinal Products (IMPs). The RSI should be a list of expected SARs and their frequencies. Only the RSI approved by the licensing authority (Medicines and Healthcare products Regulatory Agency {MHRA} or others) can be implemented during the study. Any changes to RSI may only be implemented after the Sponsor modification process is complete.

4.2 RSI Submission

The RSI can be submitted in the following formats:

- For IMPs with a Marketing Authorisation (MA)
 - For an IMP with MA in the United Kingdom/Great Britain or European Member States, the RSI should be the section 4.8. 'Undesirable Effects' of the appropriate SmPC.

Uncontrolled when printed. Please visit the [TASC website](#) for the latest version of this SOP.

The latest version of an SmPC should be the version submitted to the licensing authority (MHRA or others), unless otherwise justified.

Note: If more than one MA is in place with different SmPCs, the CI should justify the selection of the most appropriate to use as source for the RSI.

- For IMPs without MA
 - The RSI should be clearly specific and separated in a section within the IB and should clearly outline expected SARs for regulatory reporting.

4.3 SmPC and IB updates

4.3.1 The CI is responsible for checking if any changes have been made to the RSI that have an impact risk/benefit of the trial (i.e. the addition of new events). The CI will advise the Sponsor of any potential impact on the trial.

4.3.2 TASC Pharmacovigilance will check annually for any updates to the SmPC or IB.

4.3.3 Changes to RSI can be made that include new or removed expected adverse events, or newly released SmPC/IB with no new adverse events listed or removed. These changes can impact the trial Development Safety Update Reports (DSURs). Please refer to the TASC SOP on preparing a DSUR.

- Updates to the RSI including an update to section 4.8 of the SmPC will be considered a **substantial modification**.
- Changes to the format of the RSI that do not involve a change in the content will be considered a **minor modification**.

4.3.4 All SmPC/IB updates will be assessed and managed in accordance with the TASC SOP on Management of Modifications. This documentation will be filed in the Trial Master File (TMF).

4.4 RSI Changes

If changes have been made and are significant and/or are relevant to the trial or participant population, the CI must risk assess how those changes affect the RSI and submit the review to Sponsor.

The RSI assessment outcome scenario:

- **No changes to RSI (no new events listed or events removed)**

The trial CI and Sponsor will document the RSI has not changed and does not require a substantial modification before the new SmPC/IB is used. All assessments and decisions will be documented and filed in the TMF.

Uncontrolled when printed. Please visit the [TASC website](#) for the latest version of this SOP.

Or

- **New events listed in RSI**

The CI must risk assess the updated RSI version against the current approved RSI version and update Sponsor of any required changes.

The CI or delegate will complete the Sponsor modification process and **must not** implement the new SmPC/IB until the modification is reviewed and approved.

A risk benefit assessment needs to be provided by the CI in the submission of the modification to the licensing authority (MHRA or others). The new SmPC/IB version must not be implemented before the modification is approved by the licensing authority (MHRA or others).

TASC Pharmacovigilance will control and track the change process which can demonstrate when the RSI was approved by the licensing authority (MHRA or others) and implemented by Sponsor.

- **New events listed in RSI (mid DSUR period)**

The CI must risk assess the updated RSI version against the current approved RSI version and update Sponsor of any required changes. If changes are minimal (i.e. not relevant to ongoing trial or patient population) Sponsor may determine that the current approved RSI will continue to be used for the purpose of reporting Suspected Unexpected Serious Adverse Reactions (SUSARs) for the remainder of the DSUR period.

The CI or delegate must complete the Sponsor modification process stating that the new RSI will not be implemented until the end of the current DSUR period.

TASC Pharmacovigilance will control and track the change process which can demonstrate when the RSI was approved by the licensing authority (MHRA or others) and implemented by Sponsor. This documentation will be filed in the TMF.

4.5 Expectedness Assessment

4.5.1 The Sponsor is responsible for ensuring expectedness assessment is undertaken. This activity is delegated to the TASC Medical Reviewer under the Sponsor PV arrangements.

4.5.2 The TASC Medical Reviewer will use the RSI version contained in the SmPC or IB which has been approved at the time of the event. This will determine whether an event should be classified as a SUSAR and require expedited reporting. Please refer to the TASC SOP on reporting Serious Adverse Events.

4.5.3 The TASC Medical Reviewer is responsible for reviewing and assessing Expectedness (when applicable) of all reported SARs on the Tayside Pharmacovigilance System.

Uncontrolled when printed. Please visit the [TASC website](#) for the latest version of this SOP.

4.5.4 For a reaction to be categorised as **expected** the reaction must be clearly listed in the RSI.

ARs may be classed as either:

- **Expected:** the AR is consistent with the information on adverse effects of the study drug listed in the RSI. An expected AR must be an event previously observed and documented.
- **Unexpected:** the AR is not consistent with the information on adverse effects of the study drug listed in the RSI. (An AR may be also described as unexpected if it has occurred with greater frequency or severity that might otherwise have been expected.)

5. ABBREVIATIONS & DEFINITIONS

AR	Adverse Reaction
CI	Chief Investigator
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
DSUR	Development Safety Update Report
IB	Investigator's Brochure
IMP	Investigational Medicinal Product
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
NHST	National Health Service Tayside
PV	Pharmacovigilance
RSI	Reference Safety Information
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SOP	Standard Operating Procedure
TMF	Trial Master File
UoD	University of Dundee

6. ASSOCIATED DOCUMENTS & REFERENCES

None

7. DOCUMENT HISTORY

Version Number:	Reviewed by (job title):	Effective Date:	Details of editions made:
1	Joana Rocha (PV Monitor)	30/09/2026	New

Uncontrolled when printed. Please visit the [TASC website](#) for the latest version of this SOP.

8. APPROVALS

Approved by (job title)	Date
Dr Steve McSwiggan, Senior R&D Manager NHS Tayside	24 Sept 2026
Dr Valerie Godfrey (TASC Quality Assurance Manager) on behalf of TASC Clinical Research Guidelines Committee	24 Sep 2026