SOP number	**55.005**	Version	**6.0**
Title	**Management of Reference Safety Information for Clinical Trials of IMPs (including ATMPS)**		

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SOP category	NHS GG&C Sponsor Pharmacovigilance

Staff category

Staff Category	R	A	C	I
R&I Pharmacovigilance	X			
R&I Research Governance Manager		X		
R&I Innovation Lead				X
Sponsor Research Co-Coordinators				X
Project Managers				X
Industry Collaboration Project Manager				X
R&I Pharmacy			X	
R&I Monitoring				X
Chief Investigator			X	
R&I Director				X

1. Scope

This procedure applies to all Clinical Trials of Investigational Medicinal Products (CTIMPs) Sponsored by the NHS Greater Glasgow and Clyde (NHSGGC) Research and Innovation Department. The SOP is applicable for all NHSGGC staff with responsibility for creating and reviewing the RSI. This SOP applies to Chief investigators, and other clinicians delegated this responsibility who may not be employees of NHSGGC.

2. Purpose

The purpose of this Standard Operating Procedure is to describe how to manage the Reference Safety Information (RSI) and ensure that the appropriate documentation is in place for the assessment of the expectedness of adverse reactions by either the CI, Sponsor PV and Safety manager, or Sponsor Clinical Trial Pharmacists. The SOP takes into account guidance provided by the Clinical Trial Facilitation Group (CTFG) and MHRA. The SOP should be read alongside SOP 55.006 Selection and Periodic Review of IBs and SmPCs in CTIMPs for Clinical Management as the two processes are interlinked.

3. Procedures

3.1. Background

The Reference Safety Information (RSI) is used to assess whether an adverse reaction to an Investigational Medicinal Product (IMP) or Advanced Therapy Medicinal Product (ATMP) is considered expected. The primary source of information for the RSI is contained within the Summary of Product Characteristics (SmPC) or Investigator Brochure (IB) used as a reference document for each IMP in the trial. In general, the IB is in place prior to marketing authorisation of the IMP and is managed by the originating manufacturer and the SmPC is the document released by a manufacturer following market authorisation used to inform clinical management.

For SmPCs this is section 4.8 titled Undesirable effects; for IBs there must be a specific section titled Reference Safety Information, generally within section 6: Effects in Humans.

The RSI for each IMP used in trial must be submitted for approval at the time of the CTA application and only approved versions may be used for the assessment of expectedness.

The management of the RSI differs markedly depending on the source documents and as such procedures will be split between IB and SmPC sections.

In the majority of trials sponsored and co-sponsored within NHSGGC, the SmPC will be the sole source of information for the RSI for licensed IMPs as Sponsor does not have access to the IB. However, additions can be made to the RSI providing there is sufficient justification and evidence for these documented in Form 55.005B RSI Summary and the trial risk assessment. Where an IB is provided by a pharmaceutical partner as the source document for an IMP, this will act as the sole source of information.

3.2. Initial preparation of an RSI: Investigator Brochure

The preference of the competent authorities, such as the MHRA, is for IBs to be used as the RSI for clinical trials. The principal reason being that listings of adverse reactions within IBs are subject to strict guidelines as set out by the Clinical Trial Facilitation Group (CTFG) and guidance provided by the MHRA. Where an IMP has not been through the Marketing Authorisation Application (MAA) assessment process, an IB will always be used. An IB may also be used where the MAH is directly involved in the clinical trial. As Sponsor we may be asked to directly contribute by the Marketing Authorisation Holder (MAH) to the development of the RSI section of the IB and all considerations below must be taken into account. Where this is the case responsibilities of both parties must be clearly defined within the contract and any appendices. For IBs provided by Glasgow University, SOP 21.027 (Development and Maintenance of an Investigator's Brochure for IMP/ATIMPs owned by Co-Sponsor) should be referred to. In all scenarios the latest approved version of the IB should be used to inform the RSI.

3.2.1. Listings within an IB

The Clinical Trial Facilitation Group have provided guidelines regarding the listing of undesirable effects within the RSI section of the IB (most commonly section 5 or 6). When reviewing an IB or creating listings for an IB the following rules must be taken into account:

- Adverse reactions should not be included within the RSI section
- Events must be listed using MedDRA preferred terms (PTs)
- Number of observed events per number of exposed subjects should be included
- Evens cannot be aggregated, broad terms such as infection should be avoided unless there have been observances of that exact term
- In general, fatal Serious Adverse Reactions (SARs) cannot be considered expected

- Life threatening SARs may be considered expected, where there have been multiple observances of the SAR and sufficient justification for provided within the IB. For example, a life-threatening reaction may be considered acceptable in the treatment of acute stroke or for drugs used as chemotherapy but unlikely to be considered acceptable in a drug used to manage asthma.

Further consideration is required when an IMP is being developed within multiple medical conditions or where an IMP is repurposed for use in a new medical condition. Observed events in oncology participants will not necessarily be the same as observed events in heart failure participants for example. In such scenarios the lists of SARs may need to be split into separate tables for each medical condition. Where the lists of expected SARs has not been listed as clearly defined RSI tables for each medical condition, the CI must review each listed SAR and determine applicability to the condition being studied. The review itself and the outcome of this review will be documented within the RSI Summary.

There may be IMPs with no observed serious adverse reactions and therefore no expected events. In such scenarios the RSI must explicitly state this. For example "No SARs are considered expected by the sponsor for the purpose of expedited reporting of SUSARs and identification of SUSARs in the "Cumulative summary tabulation of serious adverse reactions" in the DSUR for the IMP". Note: There may be observed serious adverse reactions in some medical conditions but not in others and this must be reflected in the RSI.

Where a provided IB does not have an RSI conforming to the above requirements, this must be raised with the CI and the manufacturer/MAH. If NHSGGC or a co-sponsor working with NHSGGC have a contract with the MAH this requirement must be included to support NHSGGC in its Sponsor responsibilities regardless of whether an IB or SmPC is utilised for the development of the RSI.

3.3. Initial preparation of an RSI: Summary of Product Characteristics

SmPCs form the basis of the RSI in the majority of IMPs used in clinical trials sponsored by NHSGGC. Unlike IBs, listings of adverse events in section 4.8 of the SmPC do not necessarily comply with the CTFG and MHRA guidance. The principle differences are as follows:

- Adverse reactions can be included within the listings without clear indication
- The listed adverse reactions do not necessarily use MedDRA PTs
- Event terms may be pooled. For example an IMP may result in multiple reported infection types such as upper respiratory tract infections, lower respiratory tract infections, UTIs, pneumonia, flu etc. In some SmPCs these terms would be pooled using the term "Infection"
- Life-threatening events can be considered expected where the benefit/risk ratio is considered justifiable
- Fatal serious adverse reactions may be considered expected where it's stated that such events have been reported and the benefit/risk ratio is considered justifiable.

Despite the differences in how adverse events are listed, guidance released by the MHRA states that the CTFG guidelines must be applied in terms of the listing of adverse reactions and the assessment of expectedness of adverse reactions (see SOP 50.019).

Taking the above into account, it is clear that SmPCs are not ideal for use as the reference safety information in clinical trials, particularly those for older IMPs. Therefore, additional steps are

required to create a trial specific RSI suitable for use in assessing expectedness when an IB is unavailable.

3.3.1. Creation of a trial specific RSI

The creation of a trial specific RSI requires a thorough review of Section 4.8 of the tabulated list of adverse reaction within the selected SmPC for each IMP by the Sponsor PV and Safety Manager, the CI and other clinical members of the TMG involved in development of the trial protocol. The Sponsor PV and Safety Manager, the CI, and Sponsor pharmacist (providing an accuracy check) sign off the final RSI summary to document the review process. The latest version of the SmPC for each IMP should be obtained. These can usually be downloaded from the Electronic Medicines Compendium (https://www.medicines.org.uk/emc) and this will be used to create the RSI summary.

The review process is as follows:

Frequency of events

Where a SmPC is used as the RSI and information has been obtained via post marketing surveillance as well as clinical trials, it can be considered acceptable to consider these events expected if the IMP is used within the same or a similar indication to those indicated within the SmPC. The rationale for considered events to be expected should be detailed within the RSI Summary.

If the IMP is used outside its licensed indication, the RSI must be based on clinical experience within the relevant disease area and therefore events of unknown frequency may not be considered expected without justification of the inclusion for each event.

Pooled or broad terms

The listings of adverse reactions should be reviewed to check for terms that are clearly pooled e.g. infection, rashes, anaphylactoid reactions or that are too broad e.g. cardiac arrhythmias, events related to the nervous system, embolism which may lead to corresponding consequences in the organs concerned.

For these broad terms, the CI will be asked to list those events that would be considered expected in preferred terms. For example, for infection the CI may choose to list urinary tract infection, upper respiratory tract infection etc. as infections that would be considered expected in participants exposed to the IMP. These will be listed in the RSI summary under the relevant term.

While the PV and Safety Manager and Clinical Trial Pharmacists may lead on the preparation of data etc., the CI must be involved in the process. Other clinicians named within the protocol may also be aid in the creation of the RSI. Form 55.005B RSI Summary documents the decision making and the final RSI will be signed by the CI, Sponsor Pharmacovigilance and Sponsor Pharmacy.

Creation of a tabulated list of adverse reactions for a trial specific RSI

Section A of Form 55.005B should be populated following the review process. Each listed term must be checked to ensure that MedDRA Preferred Terms (PTs) are listed rather than Lower Level Terms where possible. For those broader or pooled terms that are not PTs, the “Further information” column may be completed to indicate an expanded list of terms considered expected. Where additional information is provided within the footnotes of SmPC section 4.8 this should also be added to the “Further information” column. The expected seriousness for each listed event should also be indicated within the table.

Section B should contain all assumptions, justifications and detail any supporting information used to create the trial specific RSI and acknowledging the limitation of using a SmPC to inform the RSI.

3.4. Submission of RSI for approval: SmPCs and IBs

In general, a copy of Form 55.005B RSI summary will be produced for each IMP. However, if appropriate, multiple IMPs may be included within one RSI summary. The CI, Sponsor Clinical Trial Pharmacist and Sponsor PV and Safety Manager must sign off each RSI summary sheet. Form 55.005B is attached as a front sheet to the reference IB/SmPC and together submitted to the MHRA for approval as the confirmed RSI.

3.5. Review and Assessment of Changes to the RSI

The RSI for any investigational medicinal product involved in a clinical trial must stay consistent during each DSUR reporting period.

Prior to the preparation of a DSUR, the reference SmPC/IB for each IMP should be reviewed by the PV and Safety Manager for updates to the relevant undesirable effects section. In addition a literature review or trial safety data may be required if this was used in the original creation of the RSI. Should there be an addition or a removal of a listed SAR, an increase in the frequency of an expected fatal and/or life threatening event, or a currently listed SAR is amended to include fatal or life threatening, then an update to the RSI is required.

The process for the review of the source SmPC/IB for changes to the RSI is closely related to the process of review of updates to the source SmPC/IB that may impact on the clinical management of trial participants. Should one process identify the need for a substantial amendment then a parallel review for the other should be carried out contemporaneously; where an IB is used as the RSI this will always be the case.

The timing of the checks where a SmPC is used as the RSI is flexible but at a minimum checks should be carried out circa three months before the end of the current RSI reporting period to allow time for the submission of a substantial amendment and to obtain Competent Authority approval.

The review and assessment of the RSI can be timed to occur with the submission of any other substantial amendments to the protocol e.g. changes due to updates in clinical information impacting on the benefit/risk of the trial, a substantial change to the RSI section, or a change in the source SmPC/IB used for clinical information.

Any study specific proposals for an alternative approach to the updating of the RSI (e.g. in a short duration study using an IB when changes do not impact on the risk-benefit assessment of the study) should be detailed in the CTA application and approved by the MHRA.

Any study specific requirements (e.g. in international studies) should be detailed in the protocol.

3.6. Assessment of updates to the SmPC/IB

Updates to the SmPC or IB approved for use in a trial will be reviewed and assessed by the Sponsor Clinical Trial Pharmacist and changes with any relevancy to the study reviewed by the Chief Investigator (as per GCTU SOP 55.006) to determine whether the updates have resulted in any change to:

- The overall risk – benefit assessment of the study
- The clinical management of participants in the trial sufficient to warrant circulation of the amended IB/SmPC to study sites

The CI will be included in all relevant correspondence generated by the review of the RSI. The Sponsor Clinical Trials Pharmacist will be copy in the PV and Safety Manager for information.

3.7. Following review of the RSI

The actions required following review will depend on the outcome of that review. Several scenarios are possible:

1. **No impact on RSI e.g. administrative change only.**
   Action:
   The currently approved document will continue to serve as the RSI.
2. **Change to RSI**
   Actions:
   Following review of changes to the RSI during the reporting period, professional judgment by the Chief Investigator, in collaboration with the Sponsor PV and Safety Manager and Sponsor Clinical Trial Pharmacists, will be used to determine whether an update to the RSI for the trial is appropriate or whether the approved RSI should remain in place. This will depend on study specific circumstances.

   Where the RSI is to be updated, this requires a substantial amendment (the amendment should clearly highlight what is being used as the RSI (a specific section in the IB or SmPC) and the changes made to the RSI. If the change to the RSI is being made to align with the DSUR reporting period then it is acceptable to submit the amendment in advance of the DSUR in order to ensure a smooth transition to the updated RSI at the appropriate date. It is advised that this is clearly highlighted as being the situation in the covering letter for the amendment.

   Where a change to the RSI has occurred, Form 55.005B RSI Summary will be updated for each IMP as per section 3.3.1 and submitted along with the source SmPC/IB to the MHRA as part of the amendment.

3.8. Clinical management of participants

This is the responsibility of the local investigator and is detailed in SOP 55.006.

3.9. Filing of RSI documents

Sponsor File: Pharmacovigilance Section

The initial approved RSI(s) for the trial and any updates along with all related correspondence will be stored in the relevant section of the Sponsor PV section of the TMF.

4. Referenced documents

- SOP 55.001: Pharmacovigilance in Clinical Trials of Investigational Medicinal Products (Glasgow Clinical Trials Unit)
- Form 55.005A: Template Reference Safety Information Front Sheet
- Form 55.005B: Template RSI Summary
- SOP 55.002 Preparation and submission of the Development Safety Update Report
- SOP 55.006 Selection and Periodic Review of IBs and SmPCs in CTIMPs for Clinical Management
- SOP 21.027 Development and Maintenance of an Investigator's Brochure for IMP/ATIMPs owned by Co-Sponsor
- CRUK-CTU SOP NUMBER: CTU-TCC-PV-004: Managing Updates to Trial Reference Safety Information

5. Related documents

- EUDRALEX Volume 10 Clinical trials guidelines https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en (Accessed 16/01/2026)
- ICH Harmonised Guideline For Good Clinical Practice E6(R3)
- http://www.ct-toolkit.ac.uk/
- The Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments
- CTFG QA Document – Reference Safety Information
- https://www.gov.uk/guidance/clinical-trials-for-medicines-collection-verification-reporting-of-safety-events?utm_medium=email&utm_campaign=govuk-notifications&utm_source=clinical-trials-for-medicines-collection-verification-reporting-of-safety-events&utm_content=confirmation#reference-safety-information-rsi dated 25/06/25 and updated 01/10/25

6. Document history

Version	Date	Description	Retrospective Implementation
1.0	14/11/2013	Initial creation	No
2.0	15/07/2016	Reviewed and released as part of SOPs reorganisation process. SOP category changed and SOP renumbered (previously 18.016). New template (v1.4). Changes to Section 5.5 and 5.6 to clarify process. 'Prepared by' changed to Caroline Watson, 'Approved by' and 'Released by' changed to Julie Brittenden. Robertson Centre for Biostatistics removed from Staff Category and R&D Pharmacy added (section 2). References to other documents updated to reflect current structure.	No
3.0	19/12/2018	Updated the document with changes to the review process for updated SmPC, changes to the Pharmacy Site file and to reflect changes in practice. Changes in applicable staff categories	No
4.0	27/05/2021	Updated in line with CTFG guidelines, MHRA inspection findings, and Sponsor PV discussions.	No
5.0	18/11/2021	Further updates and clarifications on actions following a change to RSI and filing of RSI documentation.	No
6.0	03/03/2026	Updated in line with MHRA guidance and ICH GCP E6 R3	No