Standard Operating Procedure			55.005
Initial Review and Management of Updates to Reference Safety Information			
Version	5.0		
Prepared by	Marc Jones	Signature	Date
Approved by	Caroline Watson	Signature	Date
Released by	Julie Brittenden	Signature	Date

1. SOP Category

NHS GG&C Sponsor Pharmacovigilance

2. Staff Category

Pharmacovigilance (PV) Office
Pharmacovigilance and Safety Manager
R&I Governance
R&I Pharmacy
R&I Coordinators (Sponsor Representative)
Project Managers
Chief Investigators (CIs)

Staff involved in any aspect of pharmacovigilance activity

3. Scope

This procedure applies to the NHS Greater Glasgow and Clyde Research and Development Department and Clinical Research Facility within the Glasgow Clinical Trials Unit (CTU). Chief Investigators may be provided with a copy (marked as an uncontrolled copy) of this SOP for their information. The procedures described below are generally applicable to CRUK; but there are operational differences and as such SOP CRUK-CTU SOP NUMBER: CTU-TCC-PV-004 should be referred to for CRUK trials.

4. Purpose

The purpose of this Standard Operating Procedure is to describe how updates to the Reference Safety Information (RSI) are managed to ensure that the appropriate documentation is in place for the assessment of the expectedness of adverse reactions. This SOP should be read alongside SOP 55.006 as the two processes are interlinked.

5. Procedures

5.1 Background

The Reference Safety Information (RSI) is the information used to assess whether an adverse reaction to an Investigational Medicinal Product (IMP) is expected. The primary source of information for the RSI is contained within the Summary of Product Characteristics (SmPC) and/or the Investigator Brochure (IB) used as a reference document for each IMP in the trial. The primary source of information is the section of the IB or SmPC specifically referencing the adverse reactions considered to be expected for an IMP. For SmPCs this is section 4.8 titled

Undesirable effects; for IBs this is generally section 6.7 labeled undesirable effects or may be explicitly identified as the RSI section elsewhere e.g. Section 5: Effects in Humans. In the majority of trials the SmPC will be the sole source of information for the RSI; however additions can be made to the RSI providing there is sufficient justification for these additions; for example further explanation of expected events can be provided within the RSI cover sheets where event terms are vague or require expansion. Where an IB is in use as the source document for an IMP this will act as the sole source of information.

The RSI is submitted for approval at the time of the CTA application and is clearly identified in Form 55.005B RSI summary) and referred to within the trial protocol. The process for the selection of the reference SmPC is detailed in SOP 55.006: Management of IBs and SmPCs in CTIMPs.

The Glasgow Clinical Trials Unit (GCTU) Pharmacovigilance (PV) Office will provide support for this process as required.

5.2 Initial review of the RSI by the CI and PV Manager

Following selection of a source SmPC or provision of an IB the CI will perform a clinical review of the relevant RSI section. The exact process for this review will differ between SmPCs and IBs and this is detailed below:

5.2.1 Initial Review of SmPC for RSI

Where a SmPC is used to inform the RSI, the requisite level of safety data can be considered sufficient as the SmPC is approved during the marketing authorisation assessment (MAA) process. The Clinical Trial Facilitation Group guidelines require the following additional rules where a SmPC is used to prepare the RSI.

- In general, fatal SARs (Serious Adverse Reaction) listed in the SmPC should not be considered expected following treatment with an IMP, even where previous fatal and life threatening SARs have occurred.
- Where a SmPC does include events that may be fatal it should be clearly stated within section 4.8 that the IMP can cause these fatal events.
- Section 4.8 provides a list of the expected undesirable effects of an IMP. It does not describe the seriousness of the reported events. Therefore a distinction must be made between those effects that would ordinarily be classed an adverse reaction (AR) and those that may result in a SAR.
- Where an IMP is used outside of its licensed indication, consideration should be given as to whether all listed terms within section 4.87 are directly applicable within the indication studied within the trial.

5.2.2 Initial Review of IB for RSI

Where an IMP has not been through the MAA assessment process, 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).

- In general, fatal SARs cannot be considered expected.
- Life threatening SARs may be considered expected, where there is sufficient justification for provided within the IB.
- Adverse reactions should not be included within the RSI section.
- Where an IMP is being developed within multiple medical conditions then ideally the lists of SARs may be in separate tables as the expected SARs may differ. Where the lists of expected SARs has not been listed as separate tables for each medical condition, the CI must review each listed SAR and determine

applicability to the condition being studied. The outcome of this review will be documented within the RSI Summary.

5.2.3 Preparation of RSI Summary Document

The listed terms contained within section 4.8 of the SmPC or the relevant section of the IB for each IMP will be transcribed onto Form 55.005B RSI Summary by the PV Manager along with the frequency of these events. The transcription will be checked by an R&I pharmacist for consistency prior to CI review.

For a SmPC, the CI will be required to clinically review these listings and assign the level of seriousness that would be expected for each term. For example; some listed terms such as nausea would be unlikely to result in hospitalisation and therefore would only be expected to be reported as an adverse reaction. Should nausea be assessed as related to the IMP result in hospitalisation this would be classed as an unexpected serious adverse reaction. Other listed terms such as myocardial infarction are usually life threatening, and often fatal and could therefore be considered expected should the benefit-risk ratio be favourable.

For an IB the listings within the RSI Summary do not require CI review (all listed events are SARs, and should not ordinarily be expected to be life threatening or fatal), unless there is an indication within the IB that a listed term may be life threatening. In such cases the clinical trial protocol must be updated to include risk minimization measures and this should be reflected within the RSI Summary.

Where a SmPC is the primary source for the RSI there may be further information regarding the expected SARs for the IMP(s) used within the trial obtained from additional sources such as EPARs or FDA prescribing information. Should the CI believe there is sufficient evidence then these expected SARs may be added to the RSI providing that sufficient justification for their inclusion is provided within the protocol and is referenced within the RSI Summary.

Following CI review, checks are carried out by the PV manager to ensure that the RSI summary is in line with the regulatory guidance regarding reference safety information.

This form along with the associated source SmPC or IB will be submitted to the MHRA and the two documents will act as the RSI for each IMP.

5.3 Review and Assessment of Changes to the RSI

The RSI for any IMP 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 manager for updates to the relevant undesirable effects section. 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.
The most up to date version of the SmPC/IB must be available to the investigator to inform clinical decisions. For IBs this will be the version approved with the CTA unless new version of the IB has been approved in which case this will be the updated version. For SmPCs this will be the current version available from the Marketing Authorisation Holder. These can usually be located on the electronic Medicines Compendium: http://www.medicines.org.uk/emc/
Any study specific requirements (e.g. in international studies) should be detailed in the protocol.

5.4 Review and assessment of updates to SmPC/IB

Updates to the SmPC or IB approved for use in a trial will be reviewed and assessed by the Clinical Research 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 review process will be documented as part of the DSUR tracking process and the relevant correspondence filed in the sponsor and investigator site files.

The CI will be included in all relevant correspondence generated by the review of the RSI, R&I pharmacy will be copied in for information.

5.5 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 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 Pharmacovigilance Manager and R&I 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 should be updated for each IMP and submitted along with the source SmPC/IB to the MHRA as part of the amendment. An e-mail will be circulated to sites following approval of the amendment informing them that the RSI has been updated and the new RSI will be in place for the next DSUR reporting period and stating the reason for the change. For some trials where sites are carrying out assessments of expectedness, sites may be asked to supersede older versions of the RSI at the time of the new DSUR reporting period. For trials where the Sponsor and CI assess expectedness this is for information only, as Sponsor has responsibility for all SAR expectedness assessments. RSI version control is a sponsor responsibility only.

This will be undertaken by the Project Manager, Trial Coordinator or CI as appropriate for the trial in liaison with the PV Office and R&I Pharmacy.

5.6 Clinical management of participants

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

5.7 Filing of RSI documents

Sponsor File: Pharmacovigilance Section

As the PV section of the sponsor file (Non- CRUK/CTU trials) is currently held within the PV Office in the Robertson Centre for Biostatistics, the approved RSI and any updates and related correspondence will be stored in this file.

Investigator Site File

For trials where expectedness is assigned by local investigators this should contain all current and superseded versions of the RSI with cover sheets and associated correspondence.

For trials where expectedness is assigned by the Sponsor and CI the RSI documentation should be filed as per other amendments. As the Sponsor has responsibility for all expectedness assessments, responsibility for RSI version control is a Sponsor responsibility only.

Pharmacy Site File

Pharmacy are not required to retain the current and superseded versions of the RSI within the pharmacy site file but should insert a file note stating the location of the Reference Safety Information.

6. Related documents

1. EUDRALEX Volume 10 Clinical trials guidelines http://ec.europa.eu/health/documents/eudralex/vol-10/ (Accessed 20.06.16)

2. Medicines and Healthcare products Regulatory Agency, Good *Clinical Practice Guide,* UK: TSO, 2012.

3. http://www.ct-toolkit.ac.uk/ (Accessed 20.06.16)

4. The Medicines for Human Use (Clinical Trials) Regulations (UK SI 1031) and amendments

5. CTFG QA Document – Reference Safety Information

7. Referenced documents

GCTU SOP 55.001: Pharmacovigilance in Clinical Trials of Investigational Medicinal Products (Glasgow Clinical Trials Unit)
Form 55.005B: Template RSI Summary
GCTU SOP 55.002 Preparation and submission of the Development Safety Update Report
GCTU SOP 55.006 Selection and Periodic Review of IBs and SmPCs in CTIMPs for Clinical Management
CRUK-CTU SOP NUMBER: CTU-TCC-PV-004: Managing Updates to Trial Reference Safety Information

8. Document History

Version	Date	Description
1.0	14/11/13	Initial creation
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.
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
4.0	27/05/2021	Updated in line with CTFG guidelines, MHRA inspection findings, and Sponsor PV discussions.
5.0	18/11/2021	Further updates and clarifications on actions following a change to RSI and filing of RSI documentation.