SOP number	**55.006**	Version	**6.0**
Title	**Selection and Periodic Review of IBs and SmPCs in CTIMPs for Clinical Management**		

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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 NHSGGC staff with sponsor responsibilities. Chief Investigators may be provided with a copy (marked as an uncontrolled copy) of this SOP for their information. CRUK CTU, Glasgow follow SOPs within its own QA system. The Pharmacovigilance manager, R&I Governance manager and other members of the pharmacovigilance committee have oversight of the CRUK SOPs to ensure consistency in approach.

2. Purpose

The purpose of this Standard Operating Procedure is to outline how Investigator's Brochures (IB) and Summary of Product Characteristics (SmPC) will be selected and internally risk assessed on update for clinical trials either sponsored or co-sponsored by NHS Greater Glasgow & Clyde (NHSGGC). This SOP should be read alongside SOP 55.005 as the two processes are interlinked.

3. Procedures

3.1. Background

All clinical trials must have a source document relating to the clinical use of the Investigational Medicinal Product(s) (IMP(s)). This document must also contain listings of adverse reactions based on observed events that will be used to inform the Reference Safety Information (RSI) for a trial. These listings are contained within the Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC).

While Good Clinical Practice (GCP) dictates that an IB needs to be reviewed at least on an annual basis, the reviewing and updating of SmPCs is the responsibility of the marketing authorisation holder (MAH). The MAH is responsible for updating the SmPC in light of additional information on clinical use or licensing information. The SmPC is a legal requirement for any drugs that are licensed within the EU under Directive 2001/83/EC. Therefore SmPCs may be updated multiple times within the lifetime of a clinical trial.

3.2. SmPC versus IB as supporting clinical information in a clinical trial

The competent authorities such as the MHRA, prefer the use of IBs for the provision of clinical information and the reference safety information wherever possible. An IB may be the only available option when an IMP is an unlicensed medicine within the European Union (EU) member states. It is likely that an IB will be provided by a commercial pharmaceutical company for a drug that is at the pre-licensing or early post-licensing stages. However, for the majority of trials we, as Sponsor, do not have access to the IB(s), particularly for trials with multiple IMPs from different MAHs. Therefore, SmPCs are generally used for reference sources in clinical trials sponsored or co-sponsored by NHSGGC.

Where IBs are used it is preferable that the commercial pharmaceutical company responsible for the development of a medicine or who hold the Marketing Authorisation assume responsibility for the provision of an IB. This must be agreed on a study by study basis. On occasion, primarily where only one trial of an IMP is in progress, NHSGGC and/or the co-Sponsor may have responsibility for providing safety data sets to directly input into updates to the IB and this must be detailed in the trial contract between the NHSGGC, Co-Sponsor (as appropriate) and the responsible organisation.

While NHSGGC and/or the co-sponsor can provide support and feedback to the manufacturer of an IMP to inform the development of an IB it is not possible for NHSGGC and/or co-sponsor to develop the IB for a clinical trial within the context of the current SOPs.

3.3. Selection of SmPC pre-MHRA CTA submission: general considerations

The regulations require that the SmPC selected should be the one best suited to ensure patient safety, is suitable for developing the RSI, and reflects the intended use of the IMP in the clinical trial. The following considerations should ensure that this criterion is met:

- Where an IMP to be used in a clinical trial has a Marketing Authorisation in the UK, but where the protocol allows any brand of the IMP with a Marketing Authorisation in the UK to be administered to the trial participants, a reference SmPC should be selected. For multi-national studies involving other EU countries, a UK SmPC should be selected wherever possible.
- Wherever possible, the SmPC should be available on the electronic Medicines Compendium (eMC) website as the website generally includes a narrative of changes made which facilitates tracking of updates (www.medicines.org.uk/emc). The MHRA website also lists SmPCs available in the UK, but there is no associated update tracking functionality (http://www.mhra.gov.uk/spc-pil/).

- If the IMP is unlicensed in the UK, but licensed in an EU member state then the SmPC from another member state should be used where an IB is unavailable. Consideration must be given by sponsor as to how regular updates will be available in the English language. The 'European public assessment reports' (EPARs) listed on the EMA website http://www.ema.europa.eu/ are a comprehensive list of all medicines licensed via the centralised European route. The Irish Competent Authority (www.hpra.ie) or medicines.ie (http://www.medicines.ie/) are alternative sources of English language SmPCs, should an IMP not be licensed in the UK but licensed in Ireland.
- For studies with IMPs that are licensed in the USA but subsequently imported from the USA, the MHRA have previously accepted Prescribing Information provided by the FDA (Federal Drugs Administration). These are accessible from the FDA website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/). However, the use of such reference documents must be carefully assessed due to the inherent difficulties of ensuring that any updates can be identified within a reasonable time frame.
- An IMP may not always be used or presented in the same form as detailed in the SmPC. It is still desirable that a SmPC is used rather than an IB developed wherever possible. If the use of the IMP will differ from the licensed indication(s), additional information should be provided in the protocol summarising the relevant non-clinical and clinical data that support the clinical use of the IMP in the trial. For example, in the UK, the only licensed form of ketamine is as an injection for use during anaesthesia (Ketalar®). For use of oral ketamine capsules in palliative pain management, it was acceptable to use the Ketalar® SmPC with additional information in the protocol to support use. IMP may also be licensed for a specific indication e.g. ovarian cancer and be used in clinical trials for an unrelated cancer e.g. brain cancer

3.4. Selection of SmPC pre-MHRA CTA submission: Reference Safety Information

When selecting a SmPC/IB to act as a reference document for the trial, consideration must be given to the format and content of the RSI section of the document. The Clinical Trial Facilitation and Coordination Group released a Q and A document in November 2017 that forms the basis of a set of guidelines for the format and content of a RSI; the MHRA has released additional guidance taking into account this documentation, updates to the clinical trials regulations, and the update of ICH GCP to version 3. Detailed information relating to the RSI is contained within SOP 55.005.

3.5. Post-MHRA approval

Once the CTA has UK regulatory approval, the process for SmPC and IB checks will commence. R&I pharmacy will also either conduct or ensure that a check is made for IB updates if more than one year has passed since the IB submitted for the CTA was issued.

3.6. Process to check for SmPC/IB updates

SmPCs will be checked on an approximately monthly basis by R&I pharmacy for all clinical trials commencing from the Developmental International Birth Date (DIBD) until the end of trial is reached, as defined in the study protocol. A record of the check and actions taken will be made using Form 55.006A SmPC Tracker for Sponsored/Co-Sponsored Clinical Trials and Form 55.006B IB Tracker for Sponsored/Co-Sponsored Clinical Trials stored within the trial specific SmPC/IB folders within R&I Pharmacy. For SmPCs listed on the eMC website, tracking will be based on the date updated to eMC rather than the date of text revision detailed in section 10 of the SmPC. For all other SmPC or equivalent documents the date of revision will be used (See also figure 1).
Updates to IBs will be checked on the 1 year anniversary or thereabouts of the IB version retained within the sponsor file.

If a SmPC ceases to be updated to eMC or equivalent and a new reference SmPC is required, then this should be discussed with the relevant pharmacovigilance officer as it may be necessary to change the RSI in place for trial. The process for updating the RSI is documented in SOP 55.005.

3.7. Clinical management of participants

This is the responsibility of the local investigator. The investigator must refer to the most up to date version of the SmPC/IB to inform clinical decisions. For IBs this will always be the latest version of the IB that has been approved by the MHRA and distributed to the investigator by the Sponsor. For SmPCs, this will be the current version available from the Marketing Authorisation Holder as located on the EMC website (www.medicines.org.uk/emc) or, where unavailable via this website, provided by Sponsor pharmacy. Study specific requirements (e.g. in international studies) should be detailed in the protocol

3.8. 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 R&I Pharmacist and changes with any relevancy to the study reviewed by the Chief Investigator (as per GCTU SOP 55.005) 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 locations

Where changes will have no foreseeable impact on the conduct of the clinical trial, the R&I Pharmacist may make the decision not to circulate the updated SmPC to the Chief Investigator. The PV officer will be informed in each instance. The following are typical examples:

- **administrative change to SmPC:** Example - change to Marketing Authorisation Holder address
- **product specific change to a reference SmPC:** Example - location is permitted to use any brand of paclitaxel but in the selected reference SmPC there is a change to the shelf-life
- **update relating to a different patient group:** Example - SmPC updated with information on paediatric use but clinical trial is in an older adult population

The reviewing clinical trial pharmacist will be professionally responsible for the decision not to inform the CI.

The review process will be documented as above and the relevant correspondence filed in the sponsor and investigator site files.

The GCTU or CRUK/CTU pharmacovigilance officer (as appropriate) will be included in all relevant correspondence.

3.9. Following review

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

3.9.1. No impact on clinical management, risk- benefit or RSI e.g. administrative change only.

Action for SmPCs: No action required where a SmPC is used as a source document.
Action for IBs: Where an IB is used as the source information it should be distributed to locations as the last version with a statement stating there is no impact. The communication should also advise locations on where to access and/or file the revised document and how to supersede the previous version.

3.9.2. Change impacting on clinical management without changes to risk- benefit and/or RSI

Actions for SmPCs:

- If the opinion of the CI is that the updated information should be circulated to locations, 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. The communication will advise locations on the impact of the change, where to access and file the updated clinical information and that the RSI remains unchanged.

- The study protocol, patient information sheet or other study documents may need to be amended in order to manage the identified change in clinical management. Where required, a substantial modification will be prepared and submitted to Regulatory Authority/ Ethics Committee as appropriate.

- The approved document will normally continue to serve as the RSI but, on a case-by-case basis, the RSI may be amended. See SOP 55.005.

Actions for IBs:

- Where an IB is used as the source information it should be distributed to locations as the last version with a statement advising locations of the impact of the change, a copy of the IB, and whether the updated IB will replace the current RSI. The communication should also advise locations on where to access and/or file the revised document and how to supersede the previous version.

3.9.3. Change impacting on risk-benefit with or without impact on clinical management and/or RSI

Actions for both IBs and SmPCs:

- If the opinion of the CI updated information indicates a change that will impact on the risk-benefit ratio of the trial, the Research Governance Manager, Lead Clinical Trials Pharmacist, PV Officer and R&I Coordinator will be alerted by the R&I Pharmacist. The Research Governance Manager and Lead Clinical Trials Pharmacist will consider if any immediate action is required to ensure participant safety and develop an action plan and timeline to resolve the issue e.g. protocol amendment, urgent safety measure etc.

- A substantial modification to manage the identified change in risk-benefit will be submitted to Regulatory Authority/Ethics Committee. In addition to the substantial modification, changes may also be required to the study protocol, patient information sheet and other study documents.

- Once the substantial modification is approved, confirmation of continued R&I management approval will be granted as per standard procedure.

- A notification of the revision of the SmPC/IB will be circulated detailing changes in the risk-benefit assessment and actions taken in response. For SmPCs a link to the relevant SmPC page will be included, for IBs a copy of the IB will be included. A cover letter or e-mail will be circulated to locations providing information on the reasons for a change in the risk-benefit assessment and actions taken. The communication should also advise locations on where to access and/or file the revised document and how to supersede the previous version. 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.

- Where an update to the RSI is required please see SOP 55.005.

3.9.4. Change to RSI with no impact on risk benefit or clinical management
Actions:
See SOP 55.005 for changes to the RSI

3.10. Advising Study Teams of updates to the IB/SmPC

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.

The PV Office in liaison with R&I Pharmacy will advise the Project Manager, Trial Coordinator or CI that an update is required and provide the appropriate documentation for distribution.

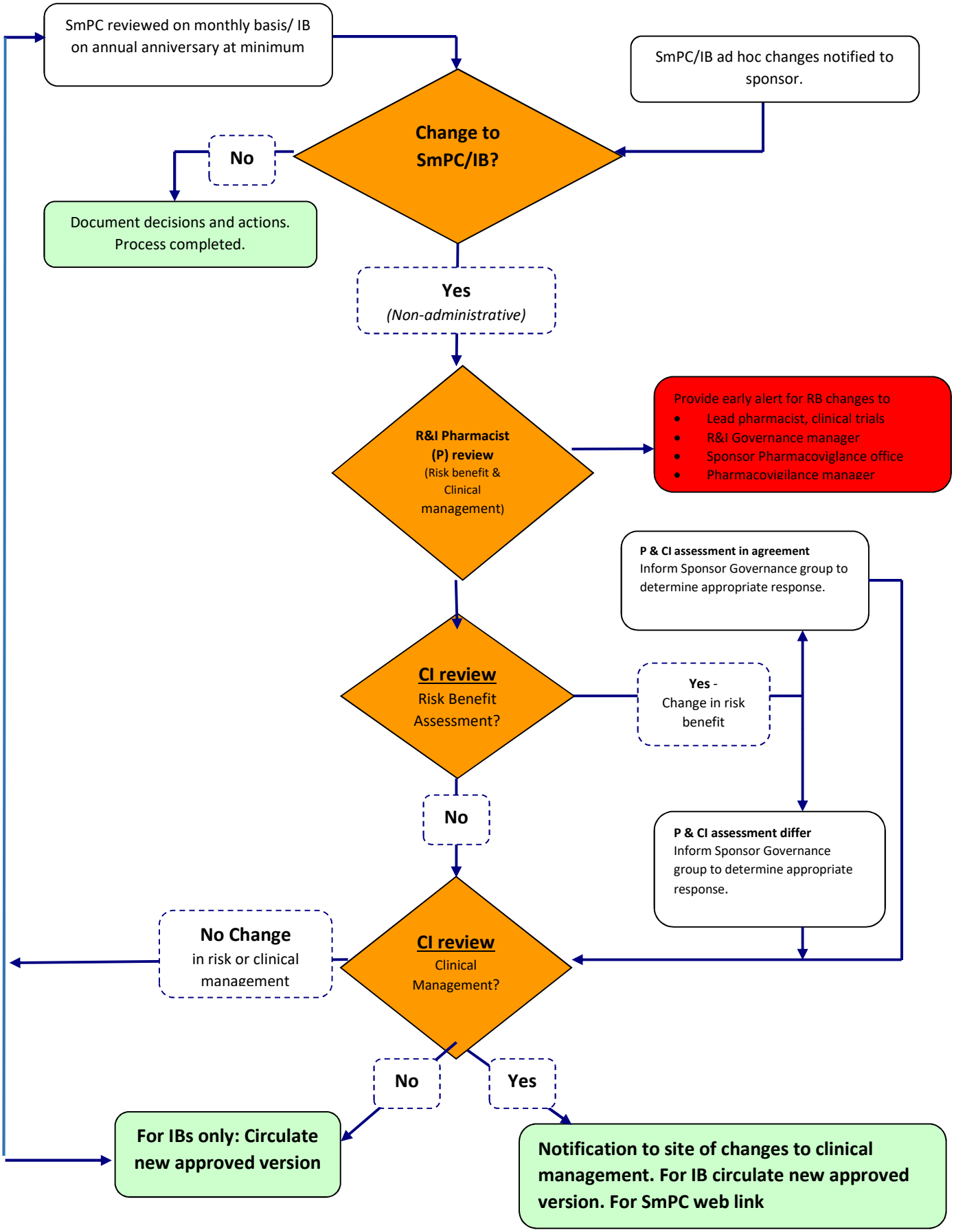
IB/SmPC may be circulated in one of three formats:

- Physical hard copy:
- Stored electronically for locations to review or download: e.g. on study web-portal.
- Circulation via electronic means: e.g. via e-mail or CD-ROM.

The version of the IB/SmPC submitted as part of the CTA will be circulated as part of the initial document set for approval at investigator locations and will be prefixed with Form 55.006C Reference Clinical Information Front Sheet Summary informing locations of where to check for updates to clinical management etc.

Revisions to this document will be circulated as appropriate for the trial (e.g. web portal updated or circulated in paper format) along with any e-mail locations providing information on the reasons for a change. The communication should also advise locations on where to access or file the revised document and how to supersede the previous document. See Figure 1 below for process diagram.

3.11. Figure 1


SmPC reviewed on monthly basis/ IB on annual anniversary at minimum
SmPC/IB ad hoc changes notified to sponsor.
Change to SmPC/IB?
No
Document decisions and actions. Process completed.
Yes
(Non-administrative)
R&I Pharmacist (P) review
(Risk benefit & Clinical management)
Provide early alert for RB changes to
Lead pharmacist, clinical trials
R&I Governance manager
Sponsor Pharmacovigilance office
Pharmacovigilance manager
P & CI assessment in agreement
Inform Sponsor Governance group to determine appropriate response.
CI review
Risk Benefit Assessment?
Yes - Change in risk benefit
No
P & CI assessment differ
Inform Sponsor Governance group to determine appropriate response.
No Change
in risk or clinical management
CI review
Clinical Management?
No
Yes
For IBs only: Circulate new approved version
Notification to site of changes to clinical management. For IB circulate new approved version. For SmPC web link

3.12. Response times

If the CI fails to respond to requests for the review of the risk-benefit assessment or impact on clinical management within a reasonable time frame, a reminder e-mail will be sent. Failure to respond will be escalated to the R&I governance manager.

If, in the assessment of the pharmacist, patient safety is potentially affected by an update then a different follow-up approach will be utilised. The Lead Pharmacist, Clinical Trials and R&I Governance Manager will be alerted and an action plan developed to ensure that Chief Investigator input is obtained within a timely basis.

Once all actions are complete the event should be considered as closed with critical correspondence filed in the R&I file

3.13. Filing of SmPC updates and associated documents

Sponsor File: Pharmacy Section

The SmPC/IB approved at the time of CTA prefixed with Form 55.006C Reference Clinical Information Front Sheet will be stored in the Sponsor File. Any updates to this document will be added to the file along with correspondence relating to the review.

Investigator File

This should contain the current version of the IB and associated correspondence. Superseded versions of the IB should be retained by the investigator. Where stored outside of the investigator site file, a file note should be in place stating the location of the documentation.

For SmPCs all correspondence relating to updates of clinical management, along with any circulated information should be filed accordingly.

Pharmacy Site File

Pharmacy locations will retain the current and superseded versions of the IB in the appropriate section of the pharmacy site file. Pharmacy locations are not required to retain the current and superseded versions of the SmPC within the pharmacy site file but may choose instead to insert a file note stating the location of the current working version of the SmPC and where information on the current clinical use is located e.g. the electronic Medicines Compendium.

4. Referenced documents

- Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'). Eudralex volume 10 (11.06.2011) Accessed 11.09.2012 CELEX:52011XC0611(01):EN:TXT.pdf
- Good Clinical Practice (July 1996) Eudralex volume 10 Accessed 11.09.2012. EudraLex - Volume 10 - Public Health - European Commission
- Directive 2001/83/EC. Of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to Medicinal Products for Human Use. Accessed 11.09.2012. CELEX:32001L0083:EN:TXT.pdf
- Form 55.006A SmPC Tracker for Sponsored/Co-Sponsored Clinical Trials
- Form 55.006B IB Tracker for Sponsored/Co-Sponsored Clinical Trials
- ICH Harmonised Guideline For Good Clinical Practice E6(R3)
- CTFG QA Document – Reference Safety Information (2017)
- 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
- Form 55.006C Reference Clinical Information Front Sheet
- SOP 55.005 Management of Updates to Reference Safety Information

5. Related documents

- SOP 55.005 Management of Updates to Reference Safety Information
- Form 55.006A SmPC Tracker for Sponsored/Co-Sponsored Clinical Trials
- Form 55.006B IB Tracker for Sponsored/Co-Sponsored Clinical Trials
- Form 55.006C Reference Clinical Information Front Sheet

6. Document history

Version	Date	Description	Retrospective Implementation
1.0	27/08/2013	Release of 1st Version	No
2.0	15/07/2016	Reviewed and released as part of SOPs reorganisation process. SOP category changed and SOP renumbered (previously 18.017). New template (v1.4). 'Prepared by' changed to Caroline Watson, 'Approved by' and 'Released by' changed to Julie Brittenden. Minor clarifications.	No
3.0	19/12/2018	Changes to scope, SmPC selection section, post MHRA approval section, flowchart and various minor clarifications.	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	Update to actions following review and update of IB/SmPC and filing requirements.	No
6.0	03/03/2026	Updated to separate from RSI process following MHRA updates to guidance	No