Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Clinical Research and Innovation Office

STANDARD OPERATING PROCEDURE

Pharmacovigilance

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Standard Operating Procedure: Clinical Research and Innovation Office (CRIO)

Pharmacovigilance

This SOP has been produced in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004, all subsequent amendments, the UK policy framework for health and social care research and with reference to the European Commission Communication CT3 dated 11 June 2011.

Background

Pharmacovigilance refers to the science and activities relating to the detection, assessment, understanding and prevention of adverse events/drug related problems.

This SOP focuses on the pharmacovigilance arrangements when Sheffield Teaching Hospitals NHS Foundation Trust accepts sponsorship of a CTIMP (Clinical Trial of an Investigational Medicinal Product) and, where CRIO acts as Sponsor without a CTRU or CRO providing full project management support.

It should be noted that where project management of a CTIMP is provided by a third-party organisation (CTRU or CRO) they will follow their own project management processes, including those for pharmacovigilance. In these cases, whilst the principles and definitions described in this SOP will still apply, the specific processes and responsibilities described here will largely be replaced by processes described in the CTRU/CRO's own SOPs.

Index

1. Acronyms

AE	**Adverse Event**
AR	**Adverse Reaction**
CI	**Chief Investigator**
CRF	**Case Report Form**
CRIO	**Clinical Research and Innovation Office**
CTIMP	**Clinical Trial of Investigational Medicinal Product**
DSUR	**Development Safety Update Report**
eMC	**Electronic Medicines Compendium**
HRA	**Health Research Authority**
IB	**Investigator Brochure**
ICSR	**Individual Case Safety Report**
IMP	**Investigational Medicinal Product**
IRAS	**Integrated Research Application System**
ISF	**Investigator Site File**
MAH	**Marketing Authorisation Holder**
MHRA	**Medicines and Healthcare products Regulatory Agency**
NIMP	**Non-Investigational Medicinal Product**
PI	**Principal Investigator**
PVG	**Pharmacovigilance**
R&D	**Research and Development**
REC	**Research Ethics Committee**
RMS	**Research Management System (CRIO Database)**
RSI	**Reference Safety Information**
SAE	**Serious Adverse Event**
SAR	**Serious Adverse Reaction**
SmPC	**Summary of Product Characteristics**
SOP	**Standard Operating Procedure**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
TMF	**Trial Master File (for single site STH sponsored CTIMPs, the TMF/ISF is referred to as this will be one and the same)**

2. Definitions

Pharmacovigilance	The science and activities relating to the detection, assessment, understanding and prevention of adverse events/drug related problems
Investigational Medicinal Product (IMP)	An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial including products already with a marketing authorisation.
Non-Investigational Medicinal Product (NIMP)	Products that are not the object of investigation (i.e. other than the tested product, placebo or active comparator) may be supplied to participants in a trial and used in accordance with the protocol. For instance, some clinical trial protocols require the use of medicinal products such as support or rescue/escape medication for preventative, diagnostic or therapeutic reasons and/or to ensure that adequate medical care is provided for the participant. They may also be used in accordance with the protocol to induce a physiological response (for example certain allergens in respiratory trials). These medicinal products do not fall within the definition of an IMP and are called NIMPs. NIMPs will usually have a marketing authorisation and will be used according to the authorised conditions. See https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/imp_03-2011.pdf for further information about NIMPs.
Adverse Event (AE)	Any untoward medical occurrence in a participant occurring within the defined trial reporting period (usually from the point at which informed consent is provided), including occurrences which are not necessarily caused by or related to any medicinal product that has been administered.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.
Serious Adverse Event (SAE)	Any adverse event or adverse reaction that a. results in death b. is life threatening[1] c. requires inpatient hospitalisation or prolongation of existing hospitalisation d. results in persistent or significant disability or incapacity e. consists of a congenital anomaly or birth defect. Note - Some medical events may jeopardise the participant or may require an intervention to prevent one of the above characteristics or consequences. Such events (hereinafter referred to as 'important medical events') should also be considered as 'serious' in accordance with the definition.
Serious Adverse Reaction (SAR)	Any adverse reaction that is classed in nature as serious and where there is evidence to suggest a causal relationship between the drug and the adverse event.

[1] Life-threatening in the definition of an SAE or SAR refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe

Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any adverse reaction that is classed in nature as serious and which is not consistent with the Reference Safety Information (RSI) for the medicinal product in question a. In the case of a licensed product, the RSI within the summary of product characteristics (SmPC) for that product b. In the case of any other investigational medicinal product, the RSI within the Investigator's Brochure (IB) relating to the trial in question. Note – to fulfil the definition of SUSAR, there must be suspicion of a causal relationship between the event and the IMP
Causality	The likelihood of a relationship between an AE and an IMP, allowing an event to be classified as either an event or a reaction. A "causality assessment" is required when an SAE occurs and may be required for non-serious AEs. A "causal relationship" implies that there is a reasonable possibility (based on an assessment of the temporal relationship with the IMP, and information from the medical history, concurrent disease and concomitant medication) that the drug has in some way caused the event. A causality assessment of an event will lead to one of the following categories being identified: 1. Reasonable possibility of causal relationship to a study drug A clinical event, including laboratory test abnormality, with temporal relationship to trial treatment or IMP administration which makes a causal relationship a reasonable possibility. The causal relationship may be definite, probable or possible. It may or may not be possible for the event to have been caused by other concomitant medication or a concurrent clinical condition. In any of these scenarios, the event will be counted as "related" for notification purposes 2. Unrelated or unlikely to be related to a study drug A clinical event including laboratory test abnormality with temporal relationship to trial treatment or IMP administration, that makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation. There is no evidence of any causal relationship to the study IMP. Or there is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication) but there is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment). 3. Not assessable – data to follow. In this case, the event will be reported as a SAR until/unless a negative relationship to the IMP has been confirmed

Expectedness	When a serious adverse event has a plausible causal relationship to a study drug (see 'Causality'), leading to the event being classified as a "reaction", the current approved Reference Safety Information (RSI) must be utilised to identify if the reaction is expected for this IMP, i.e. if this is a known effect listed in the RSI. The expected reactions listed in the RSI should be described using MedDRA Preferred Terms (PTs). If a SAR adds additional information about the specificity and /or severity of an expected reaction, this will be considered unexpected. For example if the RSI includes hepatitis, a SAR of fulminant hepatitis is unexpected.
Important Medical Events	Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition of serious. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.
Death	Where death is reported as an outcome of a SAR, this should be expedited as a SUSAR as fatal events are to be considered unexpected unless stated in the RSI as otherwise. Where death is due to progression of disease, this is an SAE, the event is disease progression, and the outcome is death. This is therefore not to be considered a SAR and cannot be a SUSAR. If the CI believes that the disease progression leading to death was caused by an IMP, then disease progression is an SAR and a SUSAR report is required.
Day '0'	The day CRIO receives first notification of a written SAE report (by email).
Urgent Safety Measures	An urgent safety measure is a procedure not defined by the protocol that is put in place prior to authorisation by the Sponsor, MHRA, REC and CRIO in order to protect clinical trial participants from any immediate hazard to their health and safety. During the course of a Clinical Trial involving an IMP, new safety information in the form of a Serious Adverse Event or information received from an external source may necessitate an immediate change in the study procedures or a temporary halt to the study in order to protect clinical trial participants from any immediate hazard to their health and safety. If time does not allow for an amendment to be authorised by the Sponsor, MHRA, Research Ethics Committee (REC), HRA and CRIO (if STH is not acting as Sponsor), this change in procedure can be implemented as an urgent safety measure, by the Investigator, in accordance with the process put in place by the MHRA, and as detailed in this SOP.
Code break	Code break is also known as breaking the blind and involves un-blinding a participant so that the treatment allocation is made known.

Investigator's Brochure (IB)	The IB is a comprehensive document that summarises the known information about an IMP. The purpose of the IB is to compile data relevant to studies of the IMP gathered during clinical trials and as described by ICH GCP "to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures. The IB also provides insight to support the clinical management of the study participants during the course of the clinical trial." The IB is of critical importance throughout the drug development process and is updated with new information as it becomes available. Once the drug has a marketing authorisation in any EU member state, the Summary of Product Characteristics (SmPC) is accepted as an adequate replacement for the IB where the drug is used according to the terms of this authorisation. The Investigator Brochure will contain a list of all known expected adverse reactions – ideally described using the MedDRA Preferred Term (PT). This section is referred to as the Reference Safety Information (RSI). The RSI must be referenced in the case of an SAR to help classify the event with regards to expectedness.
Summary of Product Characteristics (SmPC)	The SmPC is a document that relates to a marketed medicinal product. It contains a description of the product's properties and the conditions attached to its use. It provides information on the following criteria: • Name • Composition • Pharmaceutical form and strength • Licensed Indications • Adverse Reactions • Storage conditions • Holder of marketing authorisation This document is important as it contains the Reference Safety Information (RSI) for the IMP which describes all known expected adverse reactions. The RSI is found is section 4.8. The RSI must be referenced in the case of an SAR to help classify the event with regards to expectedness. The holder of the marketing authorisation of the medicinal product will routinely update the SmPC based on receipt of new information. SmPCs for medicinal products licensed for use in the UK can be found at http://www.medicines.org.uk/emc/
Sponsor Responsibilities	The Sponsor's responsibilities for each study include a. Ongoing safety and evaluation of Investigational Medicinal Products (IMP) being used. b. Keeping detailed written reports of SAEs reported by the Chief or Principal Investigator (CI/PI) and performing an evaluation with respect to seriousness, causality and

	expectedness (such assessments may be delegated to Investigator) c. Reporting SUSARs to the MHRA within given timelines. d. Reporting relevant safety information to the MHRA and Research Ethics Committee (REC) e. Breaking treatment code before submitting expedited reports to the MHRA and REC for specific participants, (delegated as per protocol). Detailed procedure found in SOP C109. f. Submitting the Development Safety Update Report (DSUR) to the MHRA and REC.
SAE reconciliation	The process by which the source data (patient notes) are checked against the report sent to CRIO (and entered onto RMS). This is to ensure accuracy of study data.
NB Investigator classification	Where in this SOP reference to "Investigator" does not specify "Chief" or "Principal", the action will be performed by either the CI at the Lead Site, PI at an additional site – i.e. the Investigator in charge at any given site or a medically qualified and appropriately delegated member of the study team

3. Event Reporting for STH Sponsored CTIMPs

3.1 Prior to Sponsor Green Light

1. The Chief Investigator (CI) writes the trial protocol, following the HRA protocol template for CTIMPs, adapting section 9 for the Pharmacovigilance requirements of the trial. The CI will ensure this section of the protocol identifies the time frame for AE collection. This will usually start at the point of informed consent and end at a specified time following the last IMP dose, the standard timeframe being 30 days post last IMP dose. This must be fully justified in the protocol.
2. The CI decides if data on non serious AEs will be recorded in the CRF based on whether this information is relevant to the analysis for the study and based on the stage of development of the IMP. Any decision not to record data on non-serious AEs in the CRF and study database must be consistent with the purpose of the study and be documented in the study protocol, with sufficient justification for this decision. Note – all AEs reported by the participants will still need to be recorded in patient notes as per clinical practice regardless of whether the protocol states this data will be recorded in the CRF and study database.
3. The CI decides if any events classed as serious are anticipated for this disease area. These may be excluded from immediate reporting to the Sponsor/unless there is a reasonable possibility that the IMP could be involved in the causality of such an event. The decision to exclude these events from immediate reporting must be documented in the study protocol, with sufficient justification for this decision.
4. The CI decides whether disease progression should be recorded as an SAE or if this will instead fulfil a study outcome or endpoint. The protocol may state for example that this is reported as an SAE only if it is considered more severe than expected in the patient population or if it is considered related to the study drug (this may be due to a lack of efficacy). If there is no specific wording, it is expected that the disease progression, if serious, is treated as any other SAE in the study.
    a. Note - a lack of efficacy in itself is not an adverse event but can cause an adverse event or reaction.

5. Other exceptions from reporting may be considered in the protocol design based on the profile of events seen in the disease area under study, any overlap between study endpoints and events which would otherwise constitute AEs and the safety profile of the IMPs.
6. The following wording is often useful to clarify expected hospitalisations to be exempted from SAE reporting:
    a. Routine treatment or monitoring of the studied indication not associated with any deterioration in condition
    b. Treatment, which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition, e.g. pre-planned hip replacement operation which does not lead to further complications.
    c. Any admission to hospital or other institution for general care where there was no deterioration in condition
    d. Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

7. The draft protocol passes through the STH CRIO risk assessment processes described in SOP C118.
8. The CI confirms membership of a data monitoring safety committee where necessary and documents this in the protocol.
9. The CI works with the trial project manager, Directorate Research Coordinator and designated CRIO Coordinator to complete the online Combined Review Application for MHRA, NHS REC and HRA approval. The team work through steps set out in SOPC118 to complete STH Sponsor Green Light requirements.
10. The PI at each site ensures that local pharmacovigilance responsibilities are recorded in the delegation log which is kept in the local Investigator Site File.

3.2 During active period of study

Where event is an AE or AR

1. The Investigator follows the reporting requirements of the trial protocol, recording the event in the source document and CRF as required.
    a. Where possible, the event should be recorded as a specific diagnosis rather than symptoms.
2. It is recommended that all AEs which are recorded are classified using MedDRA terms at the time of recording. The AE CRF can be amended if required to include a column detailing which version of MedDRA was in use at the time of coding. Alternatively, this information can be collated elsewhere in the TMF/ISF. Coding at the time of the event will prevent a large retrospective coding exercise at the time of results reporting. The MedDRA login details can be provided to the study team by the CRIO Coordinator on request.

3. The CRIO Coordinator will prompt the Investigator for a line listing of recorded AEs and/or ARs on the request of the MHRA.

Where event is an SAE or SAR

1. The Investigator follows the reporting requirements of the trial protocol, recording the event in the source document and CRF as required.
2. The Investigator (or delegate) completes the STH Serious Adverse Event Report Form assessing seriousness, frequency, intensity, relationship to study drug (causality), expectedness (where the relationship is assessed as causal), action and outcome.
    a. Causality assessment decisions must be made by a medically qualified doctor who has been delegated relevant duties in the site delegation log. Where the form has not been completed by a doctor or where the Investigator or delegated clinician signing the form is not medically trained, an appropriately delegated doctor must

countersign the form to indicate that they have reviewed the event details and have performed the assessment.

b. The form should be completed electronically wherever possible to ensure legibility
c. The event, if classed as related to study drug, must be reviewed in accordance with the relevant RSI section of the Sponsor approved version of the IB or SmPC in order to assess expectedness.
    i. All follow up reports for the same event must also use the same version of the RSI for this assessment.
d. Where possible, the event should be recorded as a specific diagnosis rather than symptoms. This assists with the assessment of the event and the MedDRA coding (see below)

3. The Investigator (or delegate) emails the completed, signed SAE Report Form to the STH CRIO within 24 hours of discovery of the event to sth.sae1@nhs.net . The signature can be electronic (e signature or a typed name) or wet ink. The Investigator provides further information on the event when it becomes available, using an additional SAE Report Form and marking these as follow up reports, until the event is resolved.
    a. Where the study team becomes aware of an event but details have not yet been confirmed, this information must still be notified to the STH CRIO within the 24 hours timeframe.
    b. Where the SAE Report Form with an electronic signature is emailed by a delegate and not the signing clinician, the signing clinician (and Investigator if different) must be copied into the email – this provides assurance to CRIO that the Investigator or delegated clinician has reviewed the form that contains their electronic signature.
4. The SAE Report Form is emailed without an Investigator or delegated clinician signature if it is not possible to complete before the 24 hour timeframe. The form is re-sent when the signature for the Investigator or delegated clinician is added.
5. Emails received into the sth.sae1@nhs.net email account will be automatically forwarded to a number of members of CRIO to ensure they are picked up and dealt with quickly. The email account is also checked daily (Monday to Friday) by the Pharmacovigilance Lead or delegated representative to allow for possible issues with the email forwarding system. A spreadsheet is kept within CRIO logging these daily checks and listing the delegation pattern.
6. When an SAE report is received, it is passed to the appropriate CRIO Coordinator or designated individual for action.
    a. Where the appropriate CRIO Coordinator is not available due to annual leave, sickness or working pattern, another CRIO Coordinator will action.
7. The CRIO Coordinator reviews the SAE Report Form for completeness and legibility. The CRIO Coordinator also sense checks the data reported including the event description, seriousness criteria, action taken, outcome and dates, IMP details and dates and causality assessment reported, requesting further information as required, and enters the data onto the RMS SAE page. (Where a study receives a high volume of SAE Report Forms, the CRIO Coordinator should arrange for delegation of data entry with the Research Manager).
    a. As part of the entry to RMS, the CRIO Coordinator uses the MedDRA website to code the event to a specific MedDRA term
    b. The CRIO Coordinator ensures that the correct version of the RSI was used to assess expectedness where applicable and, where the event is categorised as expected, sense checks the RSI term quoted by the Investigator. It should be noted that for follow up reports, or delayed reports, the RSI approved by the MHRA and Sponsor at the time of the occurrence of the event should be used.
    c. Each individual SAE (including initial and all follow up reports) will be allocated an SAE reference. Sub folders within Alfresco section 10.1 will be created using the online Alfresco website and will be given the same reference. The reference will take the format of SAE_[study participant ID reference/number]_[date of event – DDMMMYYYY] (eg. SAE_006_06Sep2021). This reference will be added electronically by the CRIO Coordinator to the SAE Report Form, except in situations where a non-editable pdf of a form has been received in which case this reference will be written on by hand on hard copies.
    d. Where late reporting of an SAE is detected the CRIO coordinator follows this up with the study team to determine the cause of this and to follow non-compliance procedures as necessary.

8. A second CRIO Coordinator Quality Assures (QA) the data entry for discrepancies, making changes where necessary and logging the conduct of this QA in the admin tab of the SAE entry in RMS.
9. The Investigator (or delegate) files all SAE report forms and relevant correspondence in the ISF and updates their SAE log.
10. The CRIO Coordinator files all SAE report forms and relevant correspondence in the R&D Master File and in Alfresco.
    a. Where the R&D reference has been handwritten onto a report, this hard copy will be retaining in the R&D Master File and the document scanned and saved in Alfresco as well as being emailed to the study team for inclusion in the ISF.
11. The CRIO Coordinator updates the trend analysis table for the study and discusses any significant findings with the CI team to identify if any action is required.
12. If, upon further exploration of an SAE report with the study team, it becomes apparent that the event does not meet the criteria for "serious", this can be downgraded by email confirmation from the CRIO Coordinator.
    a. The Investigator (or delegate) files the SAE report form along with the email in the in the TMF/ISF and will update the AE and SAE logs as appropriate.
    b. The CRIO Coordinator will not complete an SAE entry in RMS (or will delete any entry already made) but will note the actions taken in the diary page and file all SAE report forms and correspondence in the R&D Master File and in Alfresco. Any documents filed in the R&D Master File must be clearly labelled as reports that have been downgraded.
13. There is no requirement to report an SAE on Datix unless it also comes under the definition of a patient safety incident.

Where event is a SUSAR

1. The CRIO Coordinator confirms classification of the event with the CI/PI and facilitates unblinding and reclassification if necessary (see section 7 – Blinded studies)
2. The CRIO Coordinator or designated individual enters the information onto the MHRA ICSR Submission website (see appendix 3) with support from a clinical member of the research team, creating a report for the study, and submits this to the MHRA online; creating a pdf copy that is sent to the REC by email along with a completed safety report form[2]:
    a. Within 7 days of receipt if the SUSAR is life threatening or fatal, where day 0 is the day that CRIO receives the SAE Report Form from the Investigator. Follow up information must be provided within a further 8 days.
    b. Within 15 days if the SUSAR is not life threatening or fatal, where day 0 is the day that the Sponsor receives the SAE Report Form from the Investigator. Follow up information must be provided when it is made available.
3. The CRIO Coordinator or designated individual ensures that all Investigators (at STH and additional sites) using the suspect IMP are informed of SUSARs related to it including those Investigators using the IMP in all studies where STH is acting as Sponsor. This information will be sent to the Investigator by email with a request for confirmation of receipt.
4. The CRIO Coordinator or designated individual ensures that the manufacturer of the IMP is notified of the SUSAR where appropriate.
5. The CRIO Coordinator or designated individual files the SAE Report Form and SUSAR pdf report in the R&D Master File and an electronic copy in Alfresco.
6. The CRIO Coordinator updates the trend analysis table for the study and discusses any significant findings with the CI team to identify if any action is required.
7. The CRIO Coordinator makes a copy of the SUSAR report and up to date study specific trend analysis available to the Director of R&D.
8. The Director of R&D on behalf of the Sponsor and in consultation with the CI assesses the SUSAR and makes a decision as to whether the study should be temporarily halted or terminated based on the risk.

[2] Where the study was approved via Combined Review the MHRA will communicate directly with the REC on receipt of the SUSAR report and it does not require additional emailing to them.

a. If the study is temporarily halted the CRIO Coordinator or designated individual informs the MHRA, REC and HRA immediately and at least within 15 days from when the trial is temporarily halted. The notification should be made as a substantial amendment using the IRAS amendment tool and must clearly explain what has been halted (e.g., stopping recruitment and/or interrupting treatment of participants already included) and the reasons for the temporary halt. To restart a trial that has been temporarily halted, the CRIO Coordinator and CI should make the request as a substantial amendment using the IRAS amendment tool and providing evidence that it is safe to restart the trial.

b. If the study is terminated, the MHRA and Ethics Committees should be notified within 15 days of this decision, using the end of trial declaration form, a link to which is available on the MHRA website https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#end-of-trial (or for trials previously submitted using Combined Review using the End of Trial notification facility within the project in the Combined Review part of IRAS) and including a brief explanation of the reasons for ending the trial.

9. If a SUSAR occurs in any study sponsored by STH, the "SUSAR occurred?" box must be ticked on the MHRA subtab of the Regulatory tab in RMS for that study. This will only be ticked once irrespective of the number of SUSARs that may occur in order to allow for sponsor oversight reporting. This applies to STH sponsored CTIMPs managed both in house and by external third parties (CRO/CTRUs).

Upgrade and Downgrade of report to MHRA and REC

1. If follow up information becomes available that indicates that a previously non-reportable event has become reportable (SUSAR) the report will be expedited to the MHRA and REC. Day 0 for the expedited report will be the date follow up information was received.
2. If follow up information is received by CRIO that an expedited report is no longer reportable after reporting it to the MHRA and REC, follow up information should state that the event has been downgraded and reasons given. No further follow up information shall be sent to the MHRA and REC.

SUSARs arising from the comparator drug, placebo or NIMP

In the case of a SUSAR arising from a comparator drug, the Sponsor is also obliged to report to the MHRA and REC. In addition, the Sponsor must inform the marketing authorisation holder of the comparator drug and inform them of the notification to the MHRA.

Events associated with a placebo will usually not satisfy the criteria for an Adverse Reaction and therefore will not be subject to expedited reporting. However, where SUSARs are associated with placebo, the Sponsor must report this to the MHRA and REC.

If a SUSAR arising from a NIMP is likely to affect the safety of the trial participants, this should be reported to the MHRA, REC (and HRA as required) as an Urgent Safety Measure, a substantial amendment, or via a notification to terminate the study early, as applicable.

If the SUSAR is definitely attributed to the NIMP and is not considered to be related in any way to an IMP and is not likely to constitute a hazard to the safety of other trial participants, it should not be reported to the MHRA. However, standard safety reporting should be considered (yellow card scheme) and/or reporting to the REC as an event related to a study procedure (see below).

In the case of a SUSAR arising from:

a. a suspected interaction between a NIMP and an IMP, or
b. either a NIMP or IMP and cannot be attributed to one of these,

the event should be reported to the MHRA and REC.

SAEs related to a study procedure

SAEs occurring in studies which do not involve an IMP, or where an event is related to a study procedure in a CTIMP must be reported to NHS REC, where in the opinion of the CI the event was:

- "related': that is, it resulted from administration of any of the research procedures;

and

- 'unexpected': that is, the type of event is not listed in the protocol as an expected occurrence.

Reports of SAEs that are both related and unexpected should be submitted to the NHS REC within 15 days of the CI becoming aware of the event, using the HRA SAE Form. The form can be found on the HRA Progress and Safety Reporting page: http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/

In non CTIMP studies, reports of SAEs to the REC should be copied to the CRIO Coordinator for information only.

Where an event is related to a study procedure in a CTIMP, the CRIO Coordinator will review the report prior to submission and ensure that relevant safety information is included in the subsequent DSUR.

Where the study is multicentre and the event occurs at a PI site, the PI should report the event to the CI who will inform the REC as described above.

The CI should also inform PIs at other Participating Sites of any "related" and "unexpected" SAEs.

Reporting SUSARs during periods of extended leave

During periods of extend leave within CRIO (e.g. Christmas period) a designated CRIO Coordinator will be available to check the SAE email account and action as necessary. Shorter breaks such as weekends and Bank Holidays do not require this process to be put in place.

Resolution of reported SAEs

The CRIO Coordinator ensures that all events reported for a CTIMP are followed to resolution, as indicated by RMS. This should be checked at least annually at the time of the DSUR preparation.

In order to ensure that all reported SAEs have reached a resolution the following must have occurred:

1. The event will have been recorded in as specific a diagnosis as possible based on the information available to the study team
2. Reported SAEs will have been classed as related or unrelated to an IMP
3. If the SAE is classed as related, it will be further categorised as expected or unexpected.
4. Either:
    a. the event has an end date and an outcome, or
    b. in the case of long term SAEs that are not expected to complete before the study ends, following agreement from the CI they are noted as stabilised in the event details tab on RMS (and marked as either "Recovering", "Not Recovered" or "Recovered with Sequelae") but have no end date. An example of this could be a diagnosis of cancer, or possibly an event that is not long term but may continue beyond the involvement of the participant in the study if deemed appropriate by the CI (i.e there are no benefits to the safety of the participant or the study data to continue to follow up the event).

Once the 4 steps above have been completed, the box “follow up complete” can be marked in RMS indicating no further follow up action is required with regards to this event.

Where an ongoing event has been confirmed as not requiring further follow up, the date field “outcome assigned date” will be completed (instead of the event end date field) to identify the date it was agreed by the sponsor that further follow up was not required.

When the study ends, unresolved events will be dealt with as follows:

1. The CRIO Coordinator requests confirmation from the study team that all available data has been provided regarding the event.
2. If the event is ongoing, but it is agreed that further follow up is not required, the event is marked as “follow up complete” and an “outcome assigned date” added to RMS.
3. If the event is ongoing and it is agreed that follow up should continue, the CRIO Coordinator will ensure communication continues with the study team until an outcome can be assigned.
4. Where the causality of an event could not be determined before the end of the study, it should be followed up until this has been confirmed and an outcome assigned.

4. Performing Trend Analysis for STH Sponsored CTIMPs

Identification of any safety trends is the responsibility of the CI along with the Data Monitoring Committee where applicable. Safety trends may involve increased severity or frequency of certain events.
CRIO will also maintain a small trend analysis table, populated with all reported SAEs, which will enable the CRIO Coordinator to flag up any potential trends to the CI. This table will identify an increase in frequency of serious adverse events but will not be able to necessarily identify an increase in severity.

1. The CRIO Coordinator receives SAE report by email.
2. The CRIO Coordinator enters the SAE data onto RMS.
3. The CRIO Coordinator populates the Trend Analysis template, located in the CRIO departmental drive (studies <STH16999) or Alfresco, section 10.1 Pharmacovigilance/SAEs Pharmacovigilance/SAE reports (studies >STH17000)
4. The CRIO Coordinator scrutinises the table.
5. If a trend is observed
    a. The CRIO Coordinator reports the finding to the CI.
    b. The CI acknowledges if any additional reporting is necessary.
    c. If no additional reporting to the MHRA is necessary, the CRIO Coordinator files the correspondence.
    d. If additional reporting to the MHRA is necessary, the CI in conjunction with the Director of R&D discusses the need for any protocol amendments to be made or discontinuation of the study.
    e. The CI implements the amendment process
6. If no trend is observed
    a. The CRIO Coordinator continues to update the Trend Analysis Template until the conclusion of the study

Where actions have been taken based on the review of Trend Analysis, details are included in the annual DSUR and final report

5. Urgent Safety Measures for STH Sponsored CTIMPs

1. The CRIO Coordinator receives confirmation of a change in study procedure including full details of the information received by the CI and the decision making process leading to the implementation of the urgent safety measure.
2. The CI (on behalf of CRIO) immediately (ideally within 24 hours and no later than 3 days) contacts the Clinical Trial Unit at the MHRA on 020 3080 6456 to discuss the issue with a medical assessor.
    a. Information you will be asked for on the call:
        - EudraCT number or IRAS number of; a. The trials for which USM action has been taken, b. Other ongoing trials with the same Investigational Medicinal Product(s) (IMP(s)) c. Trials run by a different Sponsor affected by the USM action
        - The affected IMP(s) – commercial or developmental names
        - Nature of the safety concern and whether it has been reported as a SUSAR
        - Which USMs have been taken and when
        - The number of UK participants who are currently receiving the IMP, the number of participants who received it and the number affected by the USM
        - Contact details in case of further questions

3. The CI liaises with the CRIO Coordinator to notify the MHRA and the REC of the measures taken by email within 3 days of the measures being taken to clintrialhelpline@mhra.gov.uk (as advised by the medical assessor). An amendment submission to the MHRA, REC and HRA will also be required.
4. The substantial amendment should include a covering letter detailing the measures taken, the reason for them and the safety scientist contacted, an IRAS amendment tool, and supporting documentation. This must be submitted within 2 weeks of the measures being taken.
5. The substantial amendment should be submitted using the IRAS amendment portal and MHRA Submissions or via the combined review part of IRAS if the study was originally submitted via combined review.
6. If a study is temporarily halted for any reason, (stops recruitment of new participants and/or interrupts the treatment of participants already included in the trial), the CRIO Coordinator must notify the MHRA , REC and HRA as soon as possible and not later than 15 days as a substantial amendment using the IRAS amendment tool and clearly explain what has been halted (e.g. stopping recruitment and/or interrupting treatment of participants already included) and the reasons for the temporary halt. Substantial amendments relating to temporary halts should be submitted via the IRAS amendment portal and MHRA Submissions or via the combined review part of IRAS if the study was originally submitted via combined review.
7. To restart a study that has been temporarily halted, the CI in collaboration with the CRIO Coordinator should make the request as a substantial amendment using the IRAS amendment tool and providing evidence that it is safe to restart the study. The study may not recommence until the REC has given a favourable opinion, the HRA has approved the amendment and the MHRA has not raised grounds for non-acceptance of the recommencement within 35 days of them receiving a valid submission.

6. Pregnancy in STH Sponsored CTIMPs

Although pregnancy does not meet the definition of an SAE, if a pregnancy ends with a negative outcome for the mother or child/foetus, this will be classed as an SAE and reported as such. This could include miscarriage (where this fits in with the definition of serious) congenital abnormalities or birth defects. The study protocol must include information regarding how to deal with pregnancy during a clinical trial, including whether follow up procedures are required to identify any congenital disorders caused by the IMP. It may be possible to determine the risk to a pregnancy using current

safety information. Some IMPs may have a known long term safety issue in which case the follow up of the child may be extended as per the protocol.

It should also be noted that where a drug interaction led to decreased efficacy of hormonal contraception, this should be noted in the DSUR and reported to the Marketing Authorisation Holder (MAH).

1. CI identifies whether the IMP to be used holds a risk of causing a negative outcome on pregnancy.
    a. If there is a risk, the study protocol should exclude women of child-bearing potential, or the inclusion criteria should list the use of 2 methods of contraception in order for a female of child-bearing potential to be consented.
    b. The CI should consider whether the IMP may cause a negative outcome on pregnancy in female partners of male participants and describe appropriate methods of contraception to be used if there is a risk.

2. For CTIMP studies including women of childbearing potential and/or those where a risk to pregnancy in a female partner of a male participant is identified, a 'Pregnancy reporting form' should be included in the template case report form/data capture tool at the time of development prior to study recruitment.
    a. If follow up of the pregnancy will be required as per protocol, consent must be obtained from the mother and so follow up information sheet and consent forms for this purpose should be approved by the HRA and REC.

3. Where the manufacturer of an IMP is involved in the protocol design, they may stipulate the above whether or not the IMP poses a risk to pregnancy.

4. With the exception of a study where pregnancy is an outcome measure, any pregnancy of a female participant (or the female partner of a male participant where such pregnancies are identified by the protocol as being at risk from the IMP) should be notified by the Investigator to CRIO by providing either the study pregnancy reporting form from within the case report form if one is used, or alternatively the STH template pregnancy reporting form within 24 hours of notification to the study team. This is sent by email to sth.sae1@nhs.net
    a. The pregnancy must be followed up until conclusion, again submitting either an updated case report form or updated pregnancy reporting form.

5. On receipt of a pregnancy report form, the CRIO Coordinator will review the form and the study protocol and liaise with the CI and study team to ensure that they are putting the appropriate follow up processes in place.
6. The CRIO Coordinator adds a reminder onto the STH CTIMP subtab of the Regulatory tab in RMS with a reminder date of the proposed due date.
7. The CRIO Coordinator adds a tick to the box marked "Pregnancy occurred" on the MHRA subtab of the Regulatory tab in RMS if not already ticked. This allows for an RMS search of CTIMPs where at least one pregnancy has occurred during the trial.
8. On receiving the RMS reminder, the CRIO Coordinator contacts the CI to request an update.
    a. The CI will ensure that the pregnancy is followed up and that an outcome is detailed on the pregnancy reporting form and provided to the CRIO Coordinator
9. If the pregnancy resulted in any negative outcomes that would fulfil the definition of an SAE, the CI will report this to CRIO as an SAE using the STH SAE Report Form template.

7. Blinded studies (STH Sponsored CTIMPs)

In the case of a blinded study, it is advantageous to retain the blind for all participants prior to the analysis of the study results. However, when an SAE may potentially be a SUSAR or judged reportable to the Regulatory authorities on an expedited basis for any other reason, the Investigator must break the blind for that specific participant only.

The event is assessed by the PI or delegate for seriousness, causal relationship to study drug and expectedness making the assumption that the event has been caused by one of the IMPs (or NIMPS). If the event appears to be a SUSAR and may be causally related to a blinded IMP, then the blind should be broken by the responsible party, as detailed in the protocol, for the participant prior to reporting. The event should then be considered for re-classification in the light of the unblinding information as for example, events occurring in association with the placebo are unlikely to be classed as an adverse reaction and would therefore usually be reclassified as an SAE.

Where possible the blind should be maintained for the trial participant and those researchers who are responsible for data analysis and interpretation of the results at the end of the study.

The Investigator and CRIO Coordinator use SOP C109 to ensure code break procedures are followed correctly.

8. Annual Safety Reporting for STH Sponsored CTIMPs

In addition to the expedited reporting required for SUSARs, sponsors are required to submit a safety report to the MHRA and REC, once a year throughout the life of the clinical trial or on request.

The format used for the annual safety report is that of the Development Safety Update Report (DSUR). An STH template document is available.

DSURs should be provided at yearly intervals from the date of the first CTA approval from the MHRA and should be submitted within 60 days of this date. Where more than one clinical trial is conducted using the same IMP, a single combined DSUR should be produced, using the CTA anniversary of the first approved study. The DSUR period of the other studies will then fall in line with the date of the first study. This may lead to one study having more than one reporting period anniversary date if more than one IMP is being used. This should be carefully tracked to ensure reporting is fulfilled as required for each IMP.

The aim of the DSUR is to describe concisely all new safety information relevant for one or several clinical trial(s) and to assess the safety of participants included in these studies.

The DSUR should include the following:

Part 1: Analysis of the participants' safety in the concerned clinical trial(s) with an appraisal of its ongoing risk to benefit ratio
Part 2: A line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the concerned trial(s), including all serious adverse reactions from third countries during the reporting period.
Part 3: An aggregate summary tabulation of serious adverse events that occurred in the concerned trial(s) during the reporting period.

Full details of what to include in an annual safety report can be found in Section 8 of "CT-3" – Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use – June 2011 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52011XC0611(01)&from=EN

1. RMS flags up the imminent requirement of the submission of the DSUR for a study (1 month in advance of the CTA anniversary date)
2. The CRIO Coordinator identifies if the DSUR will cover one or multiple STH sponsored CTIMPs
3. The CRIO Coordinator sends the template DSUR document to the CI(s) or delegated individual of all studies for which the report will cover requesting return of the completed document(s) – where there are multiple STH sponsored CTIMPs using the same IMP, CRIO Coordinator

should complete the generic parts of the DSUR as far as possible in advance in order to avoid duplicated work by CIs

4. The CI or delegated individual returns the completed DSUR within the timeframe specified by the CRIO Coordinator
    a. The format of the DSUR should be MS Word, in order for the CRIO Coordinator to amend if necessary and then produce a pdf for submission.
5. The CRIO Coordinator combines DSURs where more than one CTIMP is involved, ensuring that all studies are adequately described
6. The CRIO Coordinator reviews the SARs noted in the report and compares this to the record on RMS.
    a. If any discrepancies arise, the CRIO Coordinator discusses this with the CI or delegated individual to ensure both parties hold accurate records
    b. The CRIO Coordinator also uses this opportunity to request updates on any SAEs that do not have a final resolution.
7. The CRIO Coordinator requests review of the DSUR by the Pharmacovigilance Leads as required – this is recommended for the first DSUR submission for a study.
8. The CRIO Coordinator submits the DSUR to the MHRA via the MHRA Submissions Portal or via the combined review part of IRAS if the study was originally submitted via combined review.
9. The CRIO Coordinator sends an electronic copy the report to the REC who provided the original favourable opinion by email, along with the completed CT safety report form that is found on the HRA website: http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/
    a. Note – if the combined review part of IRAS is used for submission, a separate email to the REC is not required.
10. The CRIO Coordinator saves a copy of the report and cover letter in the appropriate section of the electronic file for the study – either on the departmental drive or in the Alfresco system, depending on when the study was first registered with CRIO.
11. The CRIO Coordinator enters into RMS the date that the report was sent to the MHRA and REC
12. The CRIO Coordinator ensures that a hard copy of the report is filed in the R&D Master File
13. The CRIO Coordinator provides a copy to the CI for inclusion in the TMF/ISF

In the case of short term studies (less than 1 year), a DSUR will not be expected. However, notification of the end of trial is required. The end of trial report should include an analysis of participant safety along with line listings of SARs or suspected SARs and summary tables..

A DSUR should cover one IMP. A separate DSUR is not required for NIMPs, Placebos or comparator drugs. However, relevant safety information of the above mentioned drug types (NIMP, placebo or comparator) should be addressed in the DSURs of the investigational drug(s).
If more than one IMP is being used in a study, it is possible to provide a rationale for submitting one DSUR for the study rather than per IMP. This could occur where it is unlikely that further studies will include one of the IMPs. This should be reviewed carefully as different Clinical Directorates may have cause to design studies using the same IMP. It could also be the case for a double blinded trial of more than two IMPs where it would not be possible to split the safety data.

Wherever possible, during the setup of the CTIMP, the CRIO Coordinator should try to negotiate a single DSUR with a commercial manufacturer, allowing STH to provide safety data for inclusion in the manufacturer's DSUR – note this would only be applicable should the manufacturer be sponsoring clinical trials of their own using the IMP.

A DSUR should be submitted each year until the end of the study is declared to the MHRA and REC. The definition of the end of study should be made clear in the protocol. Within a year of declaring the end of study, a final study report will be sent to the MHRA and REC and this should include any safety data that has come to light since the last DSUR submission. A full DSUR submission is not required at this time.

Where it is known that a DSUR is to be the last submitted (because the study is due to end), this can be acknowledged in the DSUR or the cover letter.

Shortened DSUR available for Notification Scheme approved trials

This is suitable for individual trials authorised under the Notification Scheme which are not part of a multi-study development programme. Also Phase IV national (UK only) trials of licensed products that commanded a low fee from the MHRA, and where all participants have completed treatment and are only in follow-up will also be suitable for submission of a short format DSUR. As an alternative to producing a full DSUR for these trials you may use the Health Research Authority Annual Progress Report.
Please indicate in your cover letter that this is an Annual Progress Report (APR) in lieu of a full DSUR and include the EudraCT number (if applicable) and CTA reference number. You should include a list of all serious adverse reactions in section 6 of the APR.

9. Study closure of STH Sponsored CTIMPs

1. The CI or delegated individual notifies the CRIO Coordinator that the study has ended as per the definition of end of study detailed in the protocol or that it has terminated early and the reasons behind this.
2. The CRIO Coordinator submits the end of study declaration along with a cover letter to the MHRA and REC within 90 of the end of the study, or within 15 days if the study was terminated early (for safety reasons rather than failure to recruit or recruitment completed)
    a. Further information regarding the reasons behind the early termination must also be submitted if applicable
3. The CRIO Coordinator completes the end of study declaration form as found on the MHRA website: https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#end-of-trial with assistance from the CI or delegated individual if required
4. The CRIO Coordinator submits the end of study declaration to both the MHRA (via the MHRA Submissions Portal) and the REC who provided the original favourable opinion (electronically by email)
5. For CTIMPs submitted through combined review, the end of trial form can be completed and submitted to the MHRA in the combined review part of Integrated Research Application System (IRAS). This automatically submits the notification to the REC and MHRA.
6. The CRIO Coordinator ensures that a copy of the declaration is filed in the R&D Master File and provides a copy to the CI for inclusion in the TMF/ISF. A copy is also saved on the CRIO departmental drive or Alfresco system as applicable.
7. The CRIO Coordinator updates the Regulatory tab in RMS to show that the EoT declaration has been submitted.
8. Once the declaration of the end of study form has been received by the MHRA, only the end of trial study report will be accepted. It is not possible to submit any further amendments at this stage
9. The CRIO Coordinator in collaboration with the CI or delegated individual ensures that a final report is submitted to the REC and HRA within 12 months of the end of the study.
    a. If the study was originally submitted via combined review, the final report form in the combined review part of Integrated Research Application System (IRAS) should be completed and submitted.
    b. All other studies should use the webform found on the HRA website

10. The CI or delegated individual in collaboration with the CRIO Coordinator ensures the upload of the end of trial summary results to the public register where the trial is registered (ISRCTN or clintrials.gov) for those trials that ended on or after 31 December 2020. For trials ending prior to 31 December 2020, results must be posted on EudraCT as per the commission's guidelines on posting and publication of result-related information. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52012XC1006(01)&from=EN
    a. It is not a requirement for this clinical trial summary report to be sent to the MHRA directly as well, however a short confirmatory email should be sent to CT.Submission@mhra.gov.uk once the result-related information has been uploaded to EudraCT, with End of trial: result-related information: EudraCT XXXX-XXXXXX-XX' and/or IRAS ID XXXXXXX as the subject line

10. Reference Safety Information (RSI)

10.1 General Information

The Reference Safety Information (RSI) is a list of known side effects and their frequency of occurrence, i.e which reactions are expected for that IMP within a clinical trial.

This list of expected reactions facilitates the assessment of causality when a SAR occurs in a clinical trial, and determines which SARs require expedited reporting as a SUSAR.

The RSI is contained either in

- a clearly defined section of the Investigator Brochure (IB) or
- section 4.8 of the Summary of Product Characteristics (SmPC) where the IMP has a Marketing Authorisation and is being used within the terms of this MA

Only the RSI that is approved for use in the study should be used to assess the expectedness of a SAR. For example, an SmPC should never be taken directly from the EMC website to use in the assessment as this may not be the approved version of the document for the study. The version control management of the RSI must be documented in the R&D Master File and TMF/ISF as well as in the CRIO RMS database.

Any amendment to the RSI requires a substantial amendment to the MHRA and HRA. An amendment fee applies – see the MHRA website for current fee.

Where an SmPC contains the RSI for a study, it should be noted that section 4.8 also lists non serious reactions. Should a reaction occur that is contained in this list, but the severity is such that the event is classed as serious, then this would be unexpected and subject to expedited reporting as a SUSAR.

For the purposes of expedited reporting, the version of **the RSI approved by the MHRA and endorsed by the Sponsor at the moment of occurrence of the SAR applies**. This version must also be used for any follow ups of the same SAR.

10.2 RSI Version Management

The RSI should remain consistent during a reporting period (the period between CTA anniversary dates and the time period for DSUR reports)

Occasionally, the RSI may be updated during this time period, for example if there are significant changes that are deemed relevant. However, this should be avoided wherever possible.

Changing the RSI during a reporting period may lead to the same event being reported differently during the same period. For example, an event that was classed as a SUSAR using the original RSI may be downgraded to a SAR in a new version. This causes inconsistency in the reporting of identical events during the reporting period which is why a change in RSI should be avoided.

For the purposes of the DSUR line listing, all events classified as reactions must be assessed using the RSI that was in place at the beginning of the reporting period[3]. This ensures consistent reporting of

[3] Note – the “RSI in place at the beginning of the reporting period” does not always mean the RSI that has approval on the anniversary date. This would be the case if the RSI was to remain unchanged by the Sponsor. However, at the time of submission of the DSUR for the previous reporting period, the Sponsor may also submit an amendment to change the RSI. Therefore, although it may take a number of weeks for this new RSI to be approved by the MHRA and implemented by the Sponsor,

events within the DSUR report (Note, this may lead to events being reassessed and reclassified at the time of drafting the DSUR – the line listing must contain detailed information regarding any changes to the classification of an event).

It should also be noted that a change to the safety information for any IMP would require an assessment of whether study participants need to be informed and reconsented.

10.3 RSI Management Process - STH Sponsored CTIMP where an SmPC is to be used

1. When the CTIMP protocol is written, the CI identifies which brand of the IMP will be used, allowing the CRIO Coordinator to identify the appropriate SmPC for inclusion in the MHRA CTA application from the Electronic Medicines Compendium website: http://www.medicines.org.uk/emc

2. Where any one of a number of brands of the IMP may be used, the CRIO Coordinator identifies one SmPC that will be used for the study.

3. Where a new study plans to use an IMP already under investigation in a different STH sponsored CTIMP, the version of the SmPC approved for use in the first study will be submitted as part of the CTA application in order to align the RSI for both studies and to allow a combined DSUR to be created.

4. On receipt of approval from the MHRA, the CRIO Coordinator ensures that the approved version of the document is filed in the R&D Master File, TMF/ISF and Alfresco. The CRIO version control tracker is also updated as well as the information retained in RMS.

5. 1 month prior to the CTA anniversary date, RMS notifies the CRIO Coordinator of the imminent requirement to prepare the DSUR – and therefore to ascertain whether an amendment to the SmPC will be required.

6. The CRIO Coordinator reviews the EMC website for updates to the SmPC

    a. If there is no new version of the SmPC, or a new version of the SmPC with no RSI updates (section 4.8), no change is made to the SmPC in use as the RSI and the previous version will continue to act as RSI going forward into the new reporting period – this should be noted clearly in the DSUR and in the diary page on RMS.
    b. If there is a new SmPC with updated RSI that is relevant to the study population (and does not simply involve a format/wording change) a substantial amendment[4] is prepared and submitted to the MHRA and HRA via the IRAS amendment portal and MHRA Submissions to allow for the new SmPC to be implemented and thereby include the RSI for the next reporting period- in parallel with the DSUR submission. The amendment should take into account any changes to the risk:benefit and include changes to the protocol and patient facing documents as required.
        - If the study was originally submitted via combined review then this part of IRAS should be used instead of MHRA Submissions
    c. If there is a new SmPC with updated RSI that is not relevant to the study population, the previously approved version can be used for the new reporting period. This must be confirmed by the CI and detailed in the R&D Master File, TMF/ISF and noted in

this is considered the RSI in place at the beginning of the period. Please see the CTFG Q&A example RSI control diagram in appendix 4

[4] A change in RSI is a change in the risk:benefit and so should always be classed as a substantial amendment. This change might not necessitate an update to the protocol or patient documents, but it must be made clear that this has been assessed by the Sponsor and Investigator when preparing the amendment.

the diary page on RMS. This must also be justified in the next DSUR where RSI versions are detailed.

7. If, on review of the EMC website any changes other than those to the RSI have been made to the SmPC that fulfil the definition of substantial as per the European Guidance “CT-1”: EUR-Lex - 52010XC0330(01) - EN - EUR-Lex (europa.eu) this requires submission to the MHRA, REC and HRA as a substantial amendment.

8. If the CRIO Coordinator is made aware of an update to the SmPC in the middle of the reporting period that amends the RSI in a way that affects the study, or otherwise falls under the definition of substantial, this can be submitted to the MHRA as a substantial amendment at that time. It must be made clear that this is an amendment in the middle of a DSUR reporting period. However, a change in the RSI should be avoided if possible as described above in order to retain consistency and to avoid having to reassess events for the purposes of the DSUR at the end of the reporting period.

9. If the CRIO Coordinator is made aware of an update to the SmPC in the middle of the reporting period that does not change the RSI, or the changes to the RSI are minimal or not relevant to the study population, then the RSI may remain unchanged for the remainder of the reporting period. An amendment may then be submitted to update the RSI at the time of the DSUR submission if required.

10. Any substantial amendment to the SmPC must be accompanied by a new risk:benefit assessment statement and an updated protocol where required.
    a. It is important to decide whether the existing protocol is sufficient to mitigate the risk of the occurrence of any new known reactions or if any additional actions need to be implemented (including changes to the eligibility criteria, additional safety monitoring or updates to the PIS and consent forms).

11. Where an amendment to update RSI is required a copy of the updated SmPC is retained in the R&D Master File, TMF/ISF and filed in Alfresco.

12. Any update to the SmPC submitted as an amendment must be logged in the amendment section of the study version control tracking sheet.

13. The MHRA tab on RMS must be updated to show the version and date of the approved SmPC (use the date of revision of text if present).

14. If the CI or Sponsor becomes aware of any new safety information, this must be fed back to the MAH.

10.4 RSI Management Process - STH Sponsored CTIMP where an IB is to be used

1. When the CTIMP protocol is written, the CI identifies whether a commercial IB can be used with approval from a commercial MAH, or if there is the necessity to create an IB in house.
2. If the commercial IB is used, the CRIO Coordinator liaises with the commercial MAH to obtain all relevant documentation for inclusion in the MHRA CTA application.

3. If the IB is written in house, this is drafted by the CI with support from the CRIO Coordinator where applicable, and submitted as part of the IMP Dossier.

4. 1 month prior to the CTA anniversary date, RMS notifies the CRIO Coordinator of the imminent requirement to prepare the DSUR – and therefore to ascertain whether an amendment to the IB will be required.

5. The CRIO Coordinator contacts the commercial MAH to identify if there are any updates to the IB
    a. If there is a new IB with no RSI updates, and no amendment required, this version can be implemented on the CTA anniversary date and be used as the IB for the next reporting period – this should be clearly noted in the DSUR and in the diary page on RMS. The document should be saved in the R&D Master File, TMF/ISF and Alfresco. The document version tracker must be updated to note this as a sponsor only amendment.

    b. If there is a new IB with updated RSI that is relevant to the study population, (and does not simply involve a format/wording change) an amendment is prepared and submitted to the MHRA and HRA via the IRAS amendment portal and MHRA Submissions to allow for the new IB to be implemented in parallel with the DSUR submission
        1. If the study was originally submitted via combined review then this part of IRAS should be used instead of MHRA Submissions

    c. If there is a new IB with updated RSI that is not relevant to the study population, this version can be implemented without submission of an amendment at the beginning of the new reporting period. This must be approved by the CI and filed in the R&D Master File, TMF/ISF and Alfresco. The document version tracker must be updated to note this as a sponsor only amendment. This must also be justified in the next DSUR where RSI versions are detailed.

    d. If there has been no update to the IB, the current version can be used for the new reporting period.

6. On the anniversary of the MHRA CTA, the annual DSUR is prepared by the CI with assistance from the CRIO Coordinator where required (unless agreement is in place with the commercial MAH that they will submit a single product DSUR using STH CTIMP data).

7. The updated IB and all relevant amendment paperwork is retained in the R&D Master File, TMF/ISF and Alfresco.

8. If the CRIO Coordinator is made aware of an update to a commercial IB in the middle of the reporting period, this can be submitted to the MHRA as a substantial amendment at that time, as long as the MHRA has previously assessed the IB. It must be made clear that this is an amendment in the middle of a DSUR reporting period. However, ideally we would not implement the updated IB until the start of the next DSUR reporting period. The exception would be if the updated IB contains significant new safety information (rather than the addition of new minor side effects).
    a. If an amendment is submitted in the middle of the reporting period, there may be a change in expectedness of events, for example events that we classed as SUSARs with the original IB may then be classed as SARs for the next part of DSUR period. For the purposes of the DSUR, all events must be classified using the RSI in place at the start of the reporting period. The change in the commercial IB, should be reiterated in the DSUR, confirming that the updated IB has been assessed by the MHRA and ensuring that downgraded events are clearly noted because no formal SUSAR report was submitted at the time.
9. Any substantial amendment to the IB must be accompanied by a new risk:benefit assessment statement and an updated protocol where required.
    a. It is important to decide whether the existing protocol is sufficient to mitigate the risk of the occurrence of any new known reactions or if any additional actions need to be implemented (including changes to the eligibility criteria, additional safety monitoring or updates to the PIS and consent forms).

10. Where STH is in control of the IB, it is recommended by the MHRA that any changes to the RSI that could be made in the middle of the DSUR reporting period are retained and submitted as

a substantial amendment to the IB alongside the DSUR submission in order to align the DSUR and RSI.

11. Any amendment to an IB that is controlled by STH is submitted in track changes format.

12. If substantial amendments other than to the RSI section are made to the IB (for example a change in the toxicology or risk:benefit assessment), an amendment can be submitted at any time during the DSUR reporting period. Implementing this new IB has no impact on the assessment of events as the RSI remains the same.

13. If the CI or Sponsor becomes aware of any new safety information for a study where the IB is controlled by a commercial MAH, this must be fed back to them.

Note: in both cases, when amending the RSI in parallel with the DSUR submission, the date of approval of a new version of RSI for expedited reporting will be different from the date of implementation of a new version of RSI for the new DSUR period because there will be a time delay between the end of the DSUR period and MHRA and Sponsor approval of a new RSI (within IB or SmPC) i.e. a new version will only be approved perhaps 1-3 months into the new DSUR period because it was submitted in parallel with the DSUR.

During this transitional period, should a SAR occur, the RSI already approved (the previous year) would be used for the expectedness assessment for expedited reporting. This could lead to a SUSAR report. However, the same event may occur again a few months later and be assessed using the newly approved RSI and be reported expeditiously only as a SAR. Hence the requirement in the next DSUR to review all SARs that have occurred within the full reporting period for the line listing and fully explain any discrepancies.

10.5 Retention of the IB or SmPC in the Pharmacy File

Where an IB is in use for an IMP, a hard copy of the IB that contains the sponsor endorsed RSI should be kept in the Pharmacy File – if a hard copy is not available, a file note will be present to indicate the location of the document. Superseded copies should be clearly marked as such.

Where an SmPC is in use for an IMP, a file note will be present in the Pharmacy File that contains the EMC link for the current MHRA approved SmPC. Where the SmPC is not available electronically, a hard copy will be kept in the Pharmacy File, but this will be clearly labelled as not for use as RSI.

The file note that contains the EMC link to the SmPC will also indicate that RMS lists the details of the document that is in use as RSI. An electronic copy of the document containing the RSI can also be found in Alfresco.

11. SAE Reconciliation

As part of the process of study specific monitoring, Serious Adverse Event reports will be reconciled against the participant source data.
The CRIO Coordinator will obtain sufficient template SAE reconciliation forms (1 per event) to use when performing a monitoring visit and use these to cross check the data recorded at source against the data reported to CRIO. The STH CRIO monitoring SOP will be followed with regard to reporting of findings.

12. Oversight of Pharmacovigilance managed by site or third party organisation (ie CTRU) of STH Sponsored CTIMPs

Where STH acts as Sponsor for a multicentre CTIMP, project management of the study must generally be provided by a third party organisation (CTRU or CRO). The CI must ensure that funding for this is included in the grant.

The third party organisation will follow their own project management processes, including those for pharmacovigilance. Therefore many of the processes as defined in this SOP will not apply. This may include processes for SAE reporting, SUSAR reporting, DSUR development and pregnancy reporting.

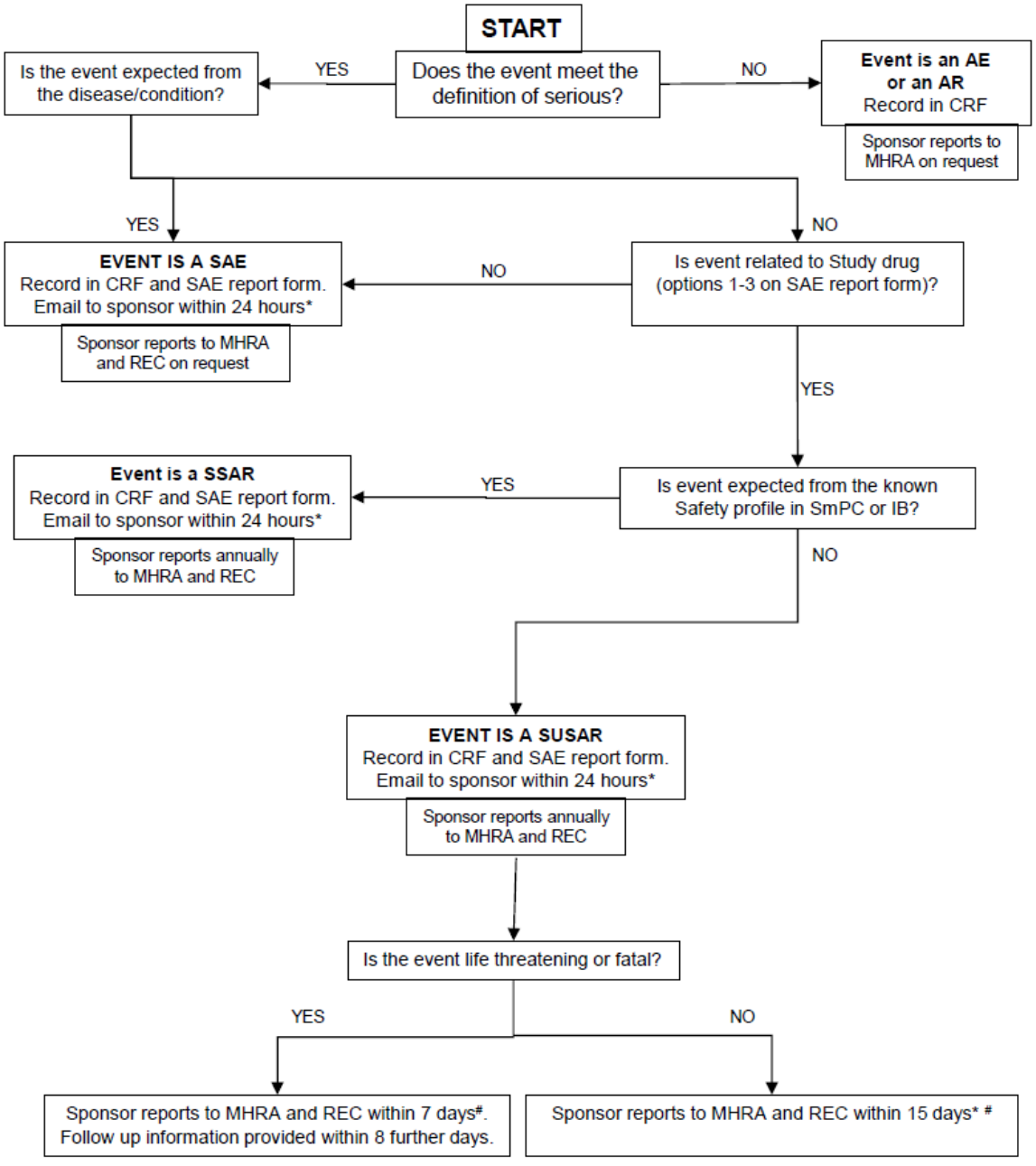
1. The CRIO Coordinator and CI ensure that the delegated aspects of pharmacovigilance have been documented within the study agreement, to be signed by all parties – this should include receipt of SAE reports by sites, all interaction with sites to collect the necessary follow up data, coordination of reports to be considered by the data monitoring committee (or equivalent group) and trend analysis. Other activities such as responsibility for SUSAR submissions should be discussed and agreed on a case by case basis
2. If the third party organisation is not registered with the UKCRC (http://www.ukcrc-ctu.org.uk/), the CRIO Coordinator should review the pharmacovigilance SOPs and SAE reporting template of the third party organisation to ensure these are satisfactory (discuss with colleagues and CRIO pharmacovigilance and monitoring leads)
3. Once the study has begun, the CRIO Coordinator should be copied in to annual SAE line listings (incorporated in the DSUR), copies of SUSAR reports and any other reports as applicable.
4. Entry into RMS of SAEs is not required as these will be recorded by the third party organisation
    a. Although SAEs including SUSARs will not be entered into the RMS Serious Adverse Events tab, if a SUSAR occurs in any study sponsored by STH, the “SUSAR occurred?” box must be ticked on the MHRA subtab of the Regulatory tab in RMS for that study. This will only be ticked once irrespective of the number of SUSARs that may occur in order to allow for sponsor oversight reporting.
5. The CRIO Coordinator or designated individual will file all paperwork received in the R&D Master File

13. SAE & SUSAR reporting for studies where STH does not act as Research Governance Sponsor

SAEs and SUSARs occurring in studies where STH does not act as research sponsor must be reported following the reporting procedures required in the Sponsor’s protocol and in any research manual or study specific SOP provided by the Sponsor. It is not necessary to report SAEs or SUSARs occurring to STH participants in these studies to the STH CRIO, but an SAE log must be maintained by the STH PI within their ISF. SUSARS that occur to patients outside of STH do not need to be reported to the CRIO but may be reported to the PI for information as per the Sponsor’s protocol. If a report is sent to the STH CRIO, it can be logged on the RMS diary page and filed in Alfresco, however no further action is required.
There is no requirement to report an SAE on Datix unless it also comes under the definition of a patient safety incident.

Appendix 1: Adverse Event Flowchart

Sheffield Teaching Hospitals NHS Foundation Trust
Research Department
Adverse Event Flowchart



Version 4.2

*Follow up report to be sent to sponsor when additional information is available until event is resolved.

#Where day 0 is the day that the report arrives in the Research Department from the PI.

Appendix 2: Study Specific Trend Analysis Template

	Number of occurrences
Event (MedDRA term)	
Total	

How to use:
When a new SAE is entered onto RMS, use the MedDRA term to tally the event in the correct cell of the table.

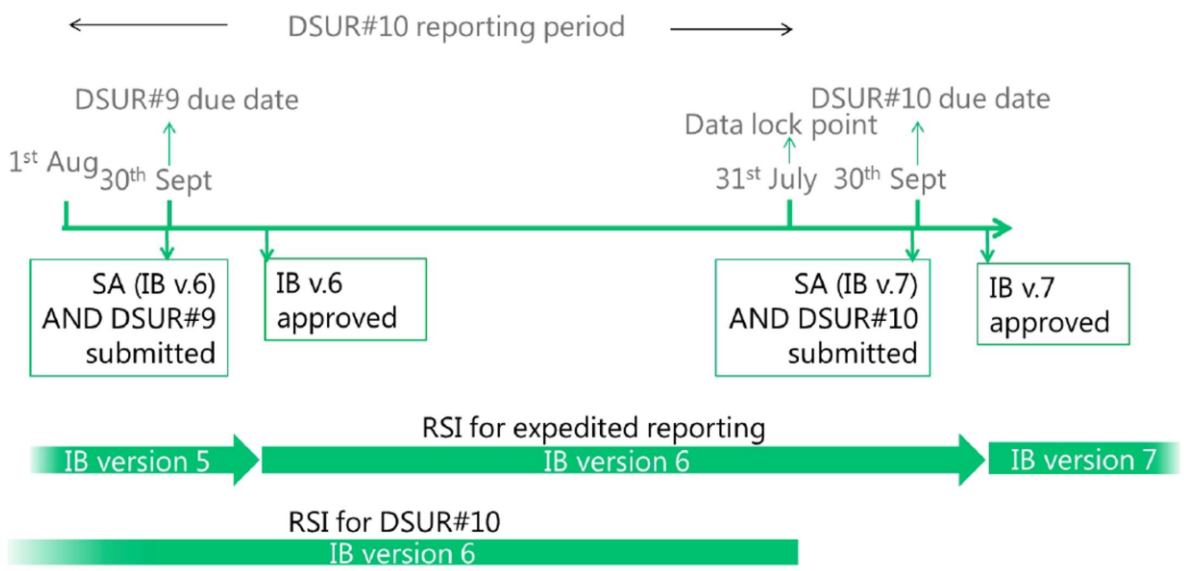
A trend will be seen where one event seems to be reported more frequently than expected, using information from IB/SmPC /safety information (Number of occurrences).
This table will be tailored to suit the study. For example in most cases only one site (STH) would be listed as a multicentre study should involve a CTRU and therefore pharmacovigilance activities would be delegated. However where STH is responsible for the pharmacovigilance at more than one site, an extra column should be added so that it would be possible to identify if one site were reporting more or less SAEs than other sites. This could also indicate a trend, whereby reporting procedures were not being adequately followed at a site.

Appendix 3: SUSAR Reporting – ICSR Submissions

Website: https://icsrsubmissions.mhra.gov.uk/login

- Full details of how to use the submission website are found in the User Reference Guide and FAQ documents that are located in Alf 1, section 10.2
- CRIO Coordinators can request a unique login to access the website.
- Logins deactivate after 6 months and so are only requested when a CRIO Coordinator has SUSAR reporting responsibilities for an approved study.
- Reactivation can be requested by emailing ICSRtesting@mhra.gov.uk
- External staff who have responsibility for submitting SUSARs on behalf of STH will need to contact the MHRA (ICSRtesting@mhra.gov.uk) to be added to the STH organisational list.
- When creating a report , it should be noted that the “Sender’s Safety Report Unique Identifier” field follows the format of (Country Code)-(Company)-(text) e.g. GB-COMPANY1-2394. So for an STH SUSAR, the following numbering has been agreed: GB-SHEFFTEAHOSP-STH12345/1 (where 1 after the STH reference denotes the number of the SUSAR for that study).

Appendix 4: CTFG Q&A example RSI control diagram



Appendix 5: Associated Documents

	Document	CRIO Network Location	Website	RMS	Created by
1	STH Serious Adverse Event report form	S:\General\Research Governance\Pharmacovigilance\Adverse Events	Yes	No	AP
2	STH AE flowchart	S:\General\Research Governance\Pharmacovigilance\Adverse Events\SAE flowchart	No	No	AL/AP
3	STH Adverse Event CRF page	S:\General\Research Governance\Pharmacovigilance\Adverse events	Yes	No	AP
4	STH Concomitant Medications CRF page	S:\General\Research Governance\Generic Case Report Form\Data Collection Tool\original generic forms	No	No	AL
5	DSUR template	S:\General\Research Governance\Pharmacovigilance\Annual safety reports	No	No	N/A
6	MHRA DSUR cover letter	S:\General\Research Governance\Pharmacovigilance\Annual safety reports	No	No	AP
7	Pregnancy reporting form	S:\General\Research Governance\Pharmacovigilance\Pregnancy	Yes	No	AL/AP
8	Trend analysis template	S:\General\Research Governance\Pharmacovigilance\Trend Analysis	No	No	AP

Appendix 6: Note Regarding RMS Updates

It should be noted that in July 2015 the SAE Report Form and associated fields on the RMS database were updated with regards to describing the relationship of an SAE to the study drug. The available responses were amended from:

- Related
- Not Related
- Not Assessable

To:

- Definite
- Probable
- Possible
- Unlikely
- Unrelated
- Not Assessable - data to follow

For this reason, SAEs already logged in RMS required mapping to a new category of relationship.
It was decided that all SAEs logged as Not Related would be mapped to Unrelated, and all SAEs logged as Related would be mapped to Probable.

It should be noted that in September 2017 the SAE Report Form and associated fields on the RMS database were updated with regards to SAE outcomes describing the status of the participant following the event. The available responses were amended from:

- Recovered
- Improved
- Unchanged
- Deterioration
- Persisted
- Death

To:

- Recovered
- Recovering
- Not recovered
- Recovered with sequelae
- Fatal
- Unknown

A mapping exercise was undertaken and all events recorded mapped easily to the new outcomes.

It should be noted that in January 2022, the SAE Report Form and associated fields on the RMS database were updated with regards to describing the relationship of an SAE to the study drug. The available responses were amended from:

- Definite
- Probable
- Possible
- Unlikely
- Unrelated
- Not Assessable - data to follow

To:

- Reasonable possibility of causal relationship to a study drug
- Unrelated or unlikely to be related to a study drug
- Not Assessable – data to follow

Historic entries in RMS have not been affected by this change; allowing previously entered data regarding causality to be viewed. However going forwards only the new categories can be chosen.

Appendix 7: SOP revisions and history

SOP number	Effective date	Reason for change	Author
THIS SOP			
C117 V3.0		• Addition of information to the definitions section including causality, expectedness and death • Update to remove references to CESP and include references to MHRA submissions portal, IRAS amendment portal and the combined review IRAS system • Update to the STH SAE reporting email address • Updated information regarding PI sign off of SAE reporting forms to allow electronic sign off • Updates to RSI section to enhance clarity • Addition of new appendix 4 – CTFG Q&A example RSI control diagram • Update to EudraCT reporting • Update to SUSAR reporting • Change of reference – R&D to CRIO • Other clarifications and formatting changes Also to note – changes have been made to the SAE reporting form and other supporting pharmacovigilance related documents to improve the quality of data that is collected by study teams.	AP
C117 V2.2	01 Nov 2018	• Update to change the MedDRA coding to note the written term rather than the numerical code for events due to this being required for EudraCT reporting rather than the numerical code	AP
C117 V2.1	01 Sep 2018	• Update to opening statement to replace the Research Governance Framework with the UK policy framework for health and social care research • Update to Index page numbers • Update to section 3.1 regarding the protocol design • Update to section 3.2 to indicate that MedDRA login details will be provided on request for coding of events • Update to section 3.2 to clarify the timeframes for following up events to resolution • Update to section 3.2 to confirm when a Datix form is required • Repositioning of section regarding SAE resolution in section 3.2 • Update to section 4 to clarify that Trend Analysis is the responsibility of the CI and DMC • Updates to section 6 to clarify the pregnancy reporting process • Update to section 9 to clarify that EudraCT results reporting is primary the responsibility of the CI with support from the Research Coordinator • Update to section 10 to confirm that an update to the RSI within an SmPC or IB may not necessarily require an amendment to the	AP

		document in use for the study if there is no impact on patient safety or if the risk:benefit assessment is not affected • Update to section 10 to retract the previous process of reviewing the SmPC/IB version 2 months ahead of DSUR cut off. Any amendments will now be submitted in parallel with the DSUR submission • Addition of section 10.3 to describe the process of IB/SmPC retention in the Pharmacy File • Update to appendix 2 – trend analysis table to facilitate completion • Removal of appendix 4 – MedDRA log in details • Update to appendix 5 regarding changes to RMS – change to the list of outcomes to match those used by eSUSAR	
C117 V2.0	01 Jan 17	• Update to acronyms • Update to definitions • Update to section 3.1 regarding AE recording • Updates to section 3.2 regarding reporting of SAEs and the use of CESP • Updates to section 5 regarding notification of MHRA of Urgent Safety Measures • Clarification in section 6 • Updates to section 8 regarding submission of DSURs via CESP • Removal of section 9 – study closure. • Major updates to section 10 regarding the update of SmPCs and IBs • Update to section 11 to indicate trend analysis should be undertaken by third party organisation • Update to appendix 2 – trend analysis table • Addition of appendix 4 – MedDRA login details	AP
C117 V1.4	01 July 15	• Update to section 3.2 regarding review of incomplete SAE entries on RMS. • Update to section 5 to reflect a change in the MHRA requirements for Urgent Safety Measure reporting. • Update to section 6 regarding the management of pregnancy in STH Sponsored CTIMPs • Clarification in section 8 regarding DSUR periods where more than one study is included in a DSUR • Updates regarding changing NRES guidance to HRA guidance with associated weblinks – including the requirement to email documentation to RECs rather than send hard copies • Clarification in section 13 related to STH R&D role in externally sponsored CTIMP SAEs • Amendment to file paths for associated documents	AP

PREVIOUS SOPs			
C117 V1.3	01 Oct 14	• Clarification of sections 8 & 10 – annual safety reporting and the use of SmPC and IB.	AL/AP
C117 V1.2	01 Jun 14	• Addition of Appendix 3: eSUSAR registration • Addition of section 14: SAE reconciliation	AL/AP
C117 V1.1	07 Jan 14	• Overhaul of procedure and Incorporation of SOPs: A122, A123, B101, B108, B113, B121, B130, C111, C112, C115	AL/AP
C117 V1.0	11 Oct 13	n/a	AL/AP