Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Research Department

STANDARD OPERATING PROCEDURE

Pharmacovigilance

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Standard Operating Procedure: Research Department

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

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 the Research Department acts as Sponsor Representative.

This SOP also addresses the requirements of Sheffield Teaching Hospitals NHS Foundation Trust when hosting a Clinical Trial of an IMP, sponsored by an external non-commercial organisation.

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. Therefore many of the processes as defined in this SOP will not apply.

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1. Acronyms

AE	**Adverse Event**
AR	**Adverse Reaction**
CESP	**Common European Submission Portal**
CI	**Chief Investigator**
CRF	**Case Report Form**
CTIMP	**Clinical Trial of Investigational Medicinal Product**
DSUR	**Development Safety Update Report**
eMC	**Electronic Medicines Compendium**
IB	**Investigator Brochure**
ISF	**Investigator Site File**
MHRA	**Medicines and Healthcare products Regulatory Agency**
PI	**Principal Investigator**
PVG	**Pharmacovigilance**
REC	**Research Ethics Committee**
RMS	**Research Management System (R&D 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**

2. Definitions

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 subjects participating 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 subject. 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 http://ec.europa.eu/health/files/eudralex/vol-10/imp_03-2011.pdf for further information about NIMPs.

Adverse Event (AE)	Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.
Serious Adverse Event (SAE)	Any adverse event or adverse reaction that a. results in death b. is life threatening[1] c. requires 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 subject 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.
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
Notable events	If the event is not classed as serious, but is seen as a "notable event" the PI must inform the Sponsor who will report this to the MHRA following the same timelines as for reporting a SUSAR. Notable events may be: 1. an increase in the rate of occurrence of an expected serious adverse event, which is judged to be clinically important 2. post-study SUSARs that occur after the patient has completed a trial

[1] Life-threatening in the definition of an SAE or SAR refers to an event in which the subject 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

	3. a new event, related to the conduct of the trial or the development of the investigational medicinal product (IMP), that is likely to affect the safety of subjects, such as: • a serious adverse event that could be associated with the trial procedures and which could modify the conduct of the trial; • a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease; • a major safety finding (for example, carcinogenicity) from a newly completed animal study; • any anticipated end to a trial or temporary halt for safety reasons where the trial is conducted by the same sponsor with the same IMP in another country; 4. the conclusions or recommendations of a data monitoring committee, where relevant for the safety of subjects The MHRA recommends expedited reporting both to MHRA and the main REC of any information that materially alters the current risk/benefit assessment of the IMP or merits changes in the way the IMP is administered or the overall conduct of the trial.
Day '0'	The day the Research Department receives first notification of a written report (by fax or 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 Research Department in order to protect clinical trial subjects 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 subjects 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) and Research Department (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 (page 11)
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 subjects 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. 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 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 (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 subjects, (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 STH R&D (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 or PI at an additional site – i.e. the Investigator in charge at any given site.

3. Event Reporting for STH Sponsored CTIMPs

3.1 Prior to Sponsor Green Light

1. The Chief Investigator (CI) decides how to record events in the Case Report Form (CRF), source document (patient notes) and Investigator Site File. The CI documents these in the study protocol, following the STH Protocol Guidelines document. The CI will also identify in the protocol the time frame for AE collection. This will usually start following consent and end at a specified time following the last IMP dose. This must be fully justified in the protocol.
2. The CI decides if 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 Research Department (Sponsor) unless there is a reasonable possibility that the IMP could be involved in the causality of the 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 draft protocol passes through the STH Research Department risk assessment processes described in SOP C118.
5. The CI confirms membership of a data monitoring safety committee where necessary and documents this in the protocol.
6. The CI works with the designated R&D Coordinator to complete the online Clinical Trial Application (Via www.myresearchproject.org.uk), including obtaining a study specific EudraCT reference number and obtaining approval from the MHRA as part of STH Sponsor approval requirements.
7. 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.
8. The R&D Coordinator adds the study details to the eSUSAR database (for electronic SUSAR reporting) once Sponsor Green Light has been issued.

3.2 During active period of study

Where event is an AE or AR

1. The Investigator follows the guidance of the study specific protocol, recording the event in the source document and CRF as required.
   1.1 Where possible, the event should be recorded as a specific diagnosis rather than symptoms.

2. The R&D Coordinator will prompt the Investigator for a line listing of recorded AE and/or AR on the request of the MHRA.
3. 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 Investigator Site File. All AEs must be entered into the EudraCT database using this coding as part of the final study results reporting process. 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 R&D Coordinator on request.

Where event is an SAE or SAR

1. The Investigator follows the guidance of the study specific 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 expectedness, seriousness, frequency, intensity, relationship to study drug, action and outcome.
    a. Causality assessment decisions must be made by a medically qualified doctor. Where the form has not been completed by a doctor or where the PI signing the form is not medically trained, a 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 medication, 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.
    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 a scanned copy of the completed, signed SAE Report Form to the STH Research Department within 24 hours of discovery of the event on SAE@sth.nhs.uk (ensuring that the word “SAE” is included in the email subject field) or if not possible faxes it to 0114 22 65937. 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 Research Department within the 24 hours timeframe. This may be via a phone call if there is not enough information available to populate the SAE Report Form.
4. The SAE Report Form is emailed or faxed without an Investigator signature if it is not possible to complete before the 24 hour timeframe. The form is re-sent when the signature for the Investigator is added.
5. The SAE@sth.nhs.uk email account is checked twice daily (Monday to Friday) by the Pharmacovigilance Lead or delegated representative
6. An assigned R&D representative checks the fax machine twice daily, according to the assignment procedure arranged within Research Department.
7. When an SAE report is received, it is passed to the appropriate R&D Coordinator or designated individual for action.
8. The R&D Coordinator reviews the SAE Report Form for completeness and legibility, 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 R&D Coordinator should arrange for delegation of data entry with the Research Manager).
    a. As part of the entry to RMS, the R&D Coordinator uses the MedDRA website to code the event to a specific MedDRA term
9. A second R&D Coordinator Quality Assures (QA) the data entry for discrepancies, making changes where necessary.

10. The Investigator (or delegate) files all SAE report forms and correspondence in the ISF and updates their SAE log.
11. The R&D Coordinator files all SAE report forms and correspondence in the R&D Master File and in Alfresco if an electronic copy has been received.
12. The R&D Coordinator updates the trend analysis table for the study and reports any significant findings to the MHRA following the requirements of the MHRA for notable event reporting (See page 10)
13. 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 R&D Coordinator.
    a. The Investigator (or delegate) files the SAE report form along with the email in the in the ISF and will update the AE and SAE logs as appropriate.
    b. The R&D 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

    16. 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 R&D Coordinator confirms classification of the event with the CI/PI and facilitates unblinding and reclassification if necessary (see section 7)
2. The R&D Coordinator or designated individual enters the information onto the eSUSAR website (see appendix 3) , 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:
    a. Within 7 days of receipt if the SUSAR is life threatening or fatal, where day 0 is the day that the Research Department 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 R&D 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 their preferred method of contact, i.e. fax or email with a request for confirmation of receipt.
4. The R&D Coordinator or designated individual ensures that the manufacturer of the IMP is notified of the SUSAR.
5. The R&D Coordinator or designated individual files the SAE Report Form and eSUSAR pdf report in the R&D Master File and an electronic copy in Alfresco.
6. The R&D Coordinator updates the trend analysis table for the study and reports any significant findings to the MHRA following the requirements of the MHRA for notable event reporting (See page 11)
7. The R&D 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.
    a. If the study is temporarily halted the R&D Coordinator or designated individual informs the MHRA and the REC 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 notification of amendment form available on the EudraCT: European Clinical Trials website and clearly explain what has been halted (e.g. stopping recruitment and/or interrupting treatment of subjects already included) and the reasons for the temporary halt. To restart a trial that has been temporarily halted, the R&D Coordinator and CI should make the request as a substantial amendment using the notification of amendment form 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 available from the EudraCT: European Clinical Trials website and including a brief explanation of the reasons for ending the trial.

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 the Research Department that an expedited report is no longer reportable the report will still be expedited, however 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, study procedure, placebo or NIMP

In the case of a SUSAR arising from a comparator drug or study procedure, 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 and REC 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 and REC. However, standard safety reporting should be considered (yellow card scheme).

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.

Reporting SUSARs during periods of extended leave

During periods of extend leave within Research Department (e.g. Christmas period) a designated R&D Coordinator will be available to check the SAE email account and fax machine and action as necessary.

Resolution of reported SAEs

The R&D 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 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

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 R&D 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 R&D 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.

Where a notable event occurs

1. The R&D Coordinator receives notification of a notable event via email or fax from the Investigator.
2. If a potential notable event is identified from assessing trend analysis within the Research Department, the R&D Coordinator contacts the CI and PI (where applicable) to confirm if this should be reported as a notable event.
3. The R&D Coordinator reports the event to the MHRA (using the CESP system) and REC (by email) following the same timelines for reporting a SUSAR, using the Serious Adverse Event Form, checking the ‘notable event’ box under project details.
4. The R&D Coordinator or designated individual files the Report Form in the R&D Master File.
5. The R&D Coordinator sends a copy of the Report Form to each Investigator for inclusion in the ISF.

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.
The Research Department will also maintain a small trend analysis table, populated with all reported SAEs, which will enable the R&D 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 R&D Coordinator receives SAE report by email or fax.
2. The R&D Coordinator enters the SAE data onto RMS.

3. The R&D Coordinator populates the Trend Analysis template, located in the Research Department departmental drive (studies <STH16999) or Alfresco, section 10.1 Pharmacovigilance/SAEs Pharmacovigilance/SAE reports (studies >STH17000)
4. The R&D Coordinator scrutinises the table.
5. If a trend is observed
    a. The R&D 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 R&D 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 R&D Coordinator continues to update the Trend Analysis Template until the conclusion of the study
    b. Details of the Trend Analysis are included in the annual DSUR and final report.

5. Urgent Safety Measures for STH Sponsored CTIMPs

1. The R&D 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 Research Department) immediately (within 24 hours) contacts the Clinical Trial Unit at the MHRA on 020 3080 6456 to discuss the issue with a safety scientist. If the MHRA needs more information a medical assessor will contact the CI.
3. The CI liaises with the R&D Coordinator to notify the MHRA and the REC of the measures taken by email (as advised by the safety scientist) an amendment submission 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, a Notification of Amendment Form, and supporting documentation.
5. The substantial amendment should be submitted to the MHRA using the CESP system.
6. If a study is temporarily halted for any reason, (stops recruitment of new subjects and/or interrupts the treatment of subjects already included in the trial), the R&D Coordinator must notify the MHRA and the REC as soon as possible and not later than 15 days as a substantial amendment using the notification of amendment form and clearly explain what has been halted (e.g. stopping recruitment and/or interrupting treatment of subjects already included) and the reasons for the temporary halt. Substantial amendments relating to temporary halts should be submitted to the MHRA via the CESP system.
7. To restart a study that has been temporarily halted, the CI in collaboration with the R&D Coordinator should make the request as a substantial amendment using the notification of amendment form 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, a congenital anomaly or birth defect does. The study protocol must include information regarding how to deal with pregnancy during a

clinical trial, including follow up procedures to identify any congenital disorders caused by the IMP.

If the IMP used holds a risk of causing a negative outcome on pregnancy, the study 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.
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.

For CTIMP studies including women of child bearing 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.

The Research Department can provide template pregnancy follow up information sheets and consent forms that can be submitted with the IRAS application.

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 the Research Department using the STH template pregnancy reporting form within 24 hours of notification. The pregnancy must be followed up until conclusion, again submitting an updated pregnancy reporting form. It may be possible to determine the risk on the 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. Consent must be provided by the Mother for this follow up.

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 also reported to the Marketing Authorisation Holder (MAH).

If the 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

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 for seriousness, expectedness and causal relationship making the assumption that the event has been caused by one of the IMPs (or NIMPS). If the event appears to be a SUSAR, 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 those researchers who are responsible for data analysis and interpretation of the results at the end of the study.

The Investigator and R&D 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 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.

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 subjects included in these studies.

The DSUR should include the following:

Part 1: Analysis of the subjects' 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 http://ec.europa.eu/health/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf

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 R&D Coordinator identifies if the DSUR will cover one or multiple STH sponsored CTIMPs
3. The R&D 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, R&D 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 R&D Coordinator
    a. The format of the DSUR should be MS Word, in order for the R&D Coordinator to amend if necessary and then produce a pdf for submission.
5. The R&D Coordinator combines DSURs where more than one CTIMP is involved, ensuring that all studies are adequately described
6. The R&D Coordinator reviews the SAEs noted in the report and compares this to the record on RMS.
    a. If any discrepancies arise, the R&D Coordinator discusses this with the CI or delegated individual to ensure both parties hold accurate records
    b. The R&D Coordinator also uses this opportunity to request updates on any SAEs that do not have a final resolution.
7. The R&D 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 R&D Coordinator submits the DSUR to the MHRA via the CESP system (selecting "regulatory activity G0042 – Developmental Safety Update Reports" when uploading).
9. The R&D 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/
10. The R&D 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 the Research Department
11. The R&D Coordinator enters the date that the report was sent the MHRA and REC into RMS
12. The R&D Coordinator ensures that a hard copy of the report is filed in the R&D Master File
13. The R&D Coordinator provides a copy to the CI for inclusion in the Investigator Site File

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. In this notification, the sponsor should include an analysis of subject safety along with line listings of SARs or suspected SARs and summary tables, if appropriate.

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 drugs. 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.

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

If the DSUR is due before recruitment has started, a letter explaining that no recruitment has taken place and therefore there are no safety issues to report can be submitted to the MHRA and REC in place of a full DSUR.

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.

9. Study closure of STH Sponsored CTIMPs

1. The CI or delegated individual notifies the R&D 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 R&D Coordinator submits the end of study declaration 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 R&D Coordinator completes the end of study declaration form as found on the HRA website: http://www.hra.nhs.uk/resources/during-and-after-your-study/end-of-study-notification-clinical-trials-of-investigational-medicinal-products-ctimps-eudract-form/ with assistance from the CI or delegated individual if required

4. The R&D Coordinator submits the end of study declaration to both the MHRA (via the CESP system) and the REC who provided the original favourable opinion (electronically by email)
5. The R&D 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 Investigator Site File. A copy is also saved on the Research Department departmental drive or Alfresco system as applicable
6. 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
7. The R&D Coordinator in collaboration with the CI or delegated individual ensures that the end of trial study report is submitted to the REC by email within one year of the end of the study.
    a. There is no standard format for final reports. As a minimum, it should include whether the study achieved its objectives, the main findings, and arrangements for publication or dissemination of the research, including any feedback to participants
8. The CI or delegated individual in collaboration with the R&D Coordinator ensures the upload of the end of trial summary results to EudraCT as per the commission's guidelines on posting and publication of result-related information. http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-10/2012_302-03/2012_302-03_en.pdf
    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.gsi.gov.uk once the result-related information has been uploaded to EudraCT, with 'End of trial : result-related information: EudraCT XXXX-XXXXXX-XX' as the subject line

10. Investigator Brochure (IB) or Summary of Product Characteristics (SmPC)

The Investigator Brochure (IB) forms part of the MHRA CTA application. This should be prepared from all available information and evidence that supports the rationale for the proposed clinical trial and the safe use of the investigational medicinal product (IMP) in the trial and be presented in the format of summaries. Guidance on the preparation of an IB can be found within GCP E6 (R1) Section 7: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf
The Summary of Product Characteristics (SmPC) will replace the IB if the IMP is authorised in any EU Member State and it is used according to the terms of the marketing authorisation. Where an IMP has a marketing authorisation and is not being used in accordance with the terms of the authorisation, the SmPC should be complimented with a summary of relevant non-clinical and clinical data that supports the use of the IMP in the trial. This may be addressed through the use of the IB, or a summary document.

The Sponsor will normally be responsible for creating and updating the IB. However in the case of non-commercially sponsored CTIMPs, it is often possible to obtain permission to submit an IB created by a commercial Marketing Authorisation Holder (MAH) for a different study that they sponsor. Any authorisations that are put in place to allow use of this document should be submitted as part of the MHRA CTA application.

Only one SmPC or IB should be in place at any one time for a study for each IMP involved.

Only the IB or SmPC approved for use in the study by the Sponsor should be filed in the Investigator Site File and used by the research team.

The IB or SmPC contains the Reference Safety Information (RSI) for an IMP, which forms the basis for expectedness for adverse events and facilitates the assessment of causality. A list of known side effects and their frequency of occurrence are described – in the SmPC this is section 4.8.

Ideally the RSI used to assess events (i.e. the version approved by the MHRA and endorsed by the sponsor) should stay 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 events in the DSUR which is why a change in RSI should be avoided.

For the purpose of SUSAR reporting the version of the RSI as endorsed by the Sponsor at the moment of occurrence of the SUSAR applies.

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. This ensures consistent reporting of 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).

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.

10.1 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 R&D 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 R&D Coordinator identifies one SmPC that will be used for the study. A copy of the SmPC is retained in the R&D Master File, CI Investigator Site File and in the PI Investigator Site Files where the study is multi-centre.
3. 1 month prior to the CTA anniversary date, RMS notifies the R&D Coordinator of the imminent requirement to prepare the DSUR – and therefore to ascertain whether an amendment to the SmPC will be required.
    a. The R&D Coordinator reviews the EMC website for updates to the SmPC
        i. If there is a new SmPC with no RSI updates (section 4.8), this version can be implemented on the CTA anniversary date and be used as the SmPC for the next reporting period – this should be noted clearly in the DSUR
        ii. 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) an amendment is prepared and submitted to the MHRA via CESP and also to the HRA to allow for the new SmPC to be implemented - in parallel with the DSUR submission.
        iii. If there is a new SmPC with updated RSI that is not relevant to the study population, the previously Sponsor-approved version can be used for the new reporting period. This must be approved by the CI and detailed in the R&D Master File, CI Investigator Site File and PI Investigator Site Files where the study is multi-centre. This must also be justified in the next DSUR where RSI versions are detailed.
        iv. If there has been no update to the SmPC, the current version can be used for the new reporting period
4. 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”: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:082:0001:0019:en:PDF this requires submission to the MHRA, REC and HRA as a substantial amendment.

5. If the R&D Coordinator is made aware of an update to the SmPC in the middle of the reporting period that amends the RSI or 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. This however should be avoided as described above in order to retain consistency. 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 would be classed as SUSARs with the original SmPC may then be classed as SARs. 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 SmPC should be re iterated in the report, ensuring that downgraded events are clearly noted because no formal SUSAR report would have been submitted at the time.

6. Any substantial amendment to the SmPC must be accompanied by a new risk:benefit assessment statement and an updated protocol where required.
7. A copy of the updated SmPC is retained in the R&D Master File, CI Investigator Site File and in the PI Investigator Site Files where the study is multi-centre.
8. Any update to the SmPC must be logged in the amendment section of the study tracking sheet – either noted as an amendment or an "update" if no amendment was submitted. It must be clear which version of the document is to be used.
9. The MHRA tab on RMS must be updated to show the version and date of the Sponsor approved SmPC (use the date of revision of text)
10. If the CI or Sponsor becomes aware of any new safety information, this must be fed back to the MAH.

10.2 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 R&D 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 R&D Coordinator where applicable, and submitted as part of the IMP Dossier.
4. 1 month prior to the CTA anniversary date, RMS notifies the R&D Coordinator of the imminent requirement to prepare the DSUR – and therefore to ascertain whether an amendment to the IB will be required.
    a. The R&D Coordinator contacts the commercial MAH to identify if there are any updates to the IB
        i. If there is a new IB with no RSI updates, 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
        ii. 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 via CESP and also to the HRA to allow for the new IB to be implemented in parallel with the DSUR submission
        iii. 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 detailed in the R&D Master File, CI Investigator Site File and PI Investigator Site Files where the study is multi-centre. This must also be justified in the next DSUR where RSI versions are detailed.
        iv. If there has been no update to the IB, the current version can be used for the new reporting period

5. On the anniversary of the MHRA CTA, the annual DSUR is prepared by the CI with assistance from the R&D Coordinator where required (unless agreement is in place with the commercial MAH that they will submit a single product DSUR using STH CTIMP data).
6. The updated IB is retained in the R&D Master File, Investigator Site File and copies provided to all other relevant parties, such as PIs where the study is multicentre.
7. If the R&D 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 re iterated 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.

8. Any substantial amendment to the IB must be accompanied by a new risk:benefit assessment statement and an updated protocol where required.
9. 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.
10. Any amendment to an IB that is controlled by STH is submitted in track changes format.
11. 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.
12. Any update to the IB must be logged in the study tracking sheet – either as an amendment or an “update”. It must be clear which version of the document is to be used.
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, 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 on eSUSAR. 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 for the line listing and fully explain any discrepancies.

10.3 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 reference should be made to RMS for the document that is in use as RSI. An electronic copy of the document containing the RSI can also be found in Alfresco.

11. 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.

1. The R&D 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 trend analysis
2. If the third party organisation is not registered with the UKCRC (http://www.ukcrc-ctu.org.uk/), the R&D Coordinator should review the pharmacovigilance SOPs and SAE reporting template of the third party organisation to ensure these are satisfactory (discuss with colleagues and Research Department pharmacovigilance and monitoring leads)
3. Once the study has begun, the R&D Coordinator should be copied in to annual SAE line listings (incorporated in the DSUR), 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
5. The R&D Coordinator or designated individual will file all paperwork received in the R&D Master File

12. SAE reporting for non CTIMPs where STH acts as Research Governance Sponsor

SAEs occurring in studies which do not involve an IMP 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 R&D Coordinator for information only.

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.

13. SAE & SUSAR reporting for CTIMPs 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 Sponsor's protocol guidance. It is not necessary to report SAEs or SUSARs occurring to STH participants to the STH Research Department, but an SAE log must be maintained by the STH PI within their Investigator Site file. If a report is sent to the STH Research Department, it can be logged on the RMS diary page and filed in Alfresco, however no further action is required.

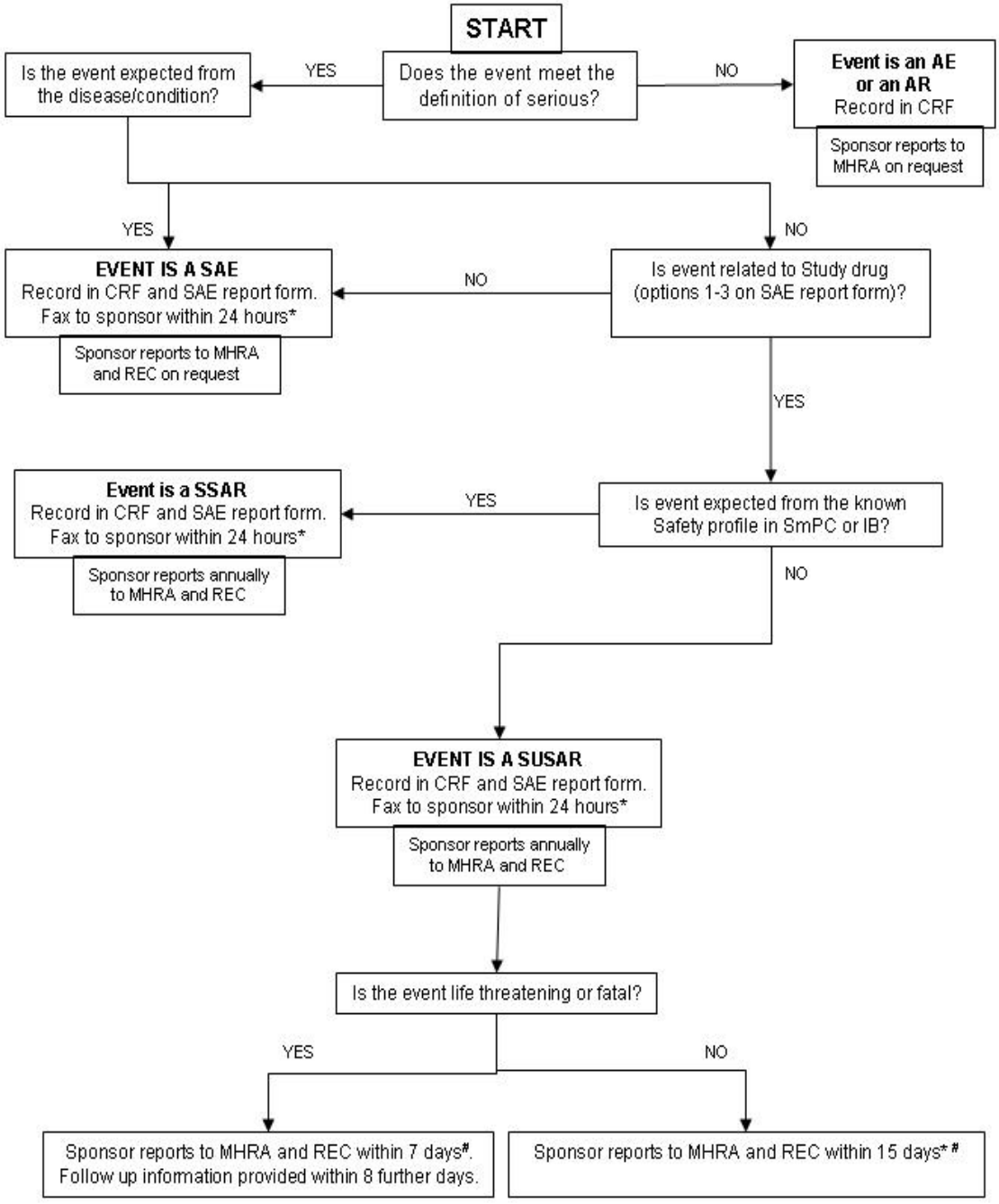
There is no requirement to report an SAE on Datix unless it also comes under the definition of a patient safety incident.

14. SAE Reconciliation

As part of the process of study specific monitoring, Serious Adverse Event reports will be reconciled against the participant source data.
The R&D 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 R&D. The STH R&D monitoring SOP will be followed with regard to reporting of findings.

Appendix 1: Adverse Event Flowchart

Sheffield Teaching Hospitals NHS Foundation Trust
Research Department
Adverse Event Flowchart



Version 4.1

*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

STH XXXXX		Number of occurrences
Event	MedDRA Term	
	Total	

How to use:
When a new SAE is entered onto RMS, use the MedDRA term/event 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: eSUSAR website

Website: https://esusar.mhra.gov.uk/

- All R&D co-ordinators have a unique login to access the eSUSAR website.
- For new members of staff, a login is created by PVG lead.
- A back-up central log of username and passwords (on a password protected spreadsheet) is retained by the PVG lead.
- At study authorisation, R&D Coordinator will inform PVG lead and a new study entry will be made onto eSUSAR.
- All R&D Coordinators have access to all studies on eSUSAR, however, it is the responsibility of the assigned R&D Coordinator to enter details of the SUSAR within the timelines specified by the Clinical Trials Regulations and outlined in section 3.2 of this SOP.
- Where the assigned R&D Coordinator is not available, the PVG lead will perform this activity.

Appendix 4: Associated Documents

	Document	Research Department 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	No	No	AP

		reports			
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
9	SAE Reconciliation Form	S:\General\Research Governance\Monitoring documents	No	No	AL

Appendix 5: 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.

Appendix 6: SOP revisions and history

SOP number	Effective date	Reason for change	Author
THIS SOP			
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 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	AP
C117 V2.0	01 Jan 17	• Update to acronyms	AP

		• 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	
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