Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Research Department

STANDARD OPERATING PROCEDURE

Pharmacovigilance

SOP History	*Replaces: A122, A123, B101, B108, B113, B121, B130, C111, C112, C115*
SOP Number	*C117*
Created	*STH Research Department (AL/AP)*
Superseded	*B108, v1.8*
Version	*1.1*
Date	*07 Jan 2014*
Related SOPs	C108 Sponsorship C109 Code Break
Approved by	*Research Manager*

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 and the Research Governance Framework 2005 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.

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1. Acronyms

AE	**Adverse Event**
AR	**Adverse Reaction**
CI	**Chief Investigator**
CRF	**Case Report Form**
CTIMP	**Clinical Trial of Investigational Medicinal Product**
DSUR	**Development Safety Update Report**
IB	**Investigator Brochure**
ISF	**Investigator Site File**
MHRA	**Medicines and Healthcare products Regulatory Agency**
PI	**Principal Investigator**
PV	**Pharmacovigilance**
REC	**Research Ethics Committee**
RMS	**Research Management System (R&D Database)**
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. These medicinal products do not fall within the definition of an IMP and are called 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 information about the medicinal product in question a. In the case of a licensed product, the summary of product characteristics (SmPC) for that product b. In the case of any other investigational medicinal product, 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 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;

[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

	• 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 10)
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.

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 describes all known expected adverse reactions. The SmPC should be referenced in the case of an SAE to help classify the event. 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.
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 Research Governance Authorisation

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.
2. The CI decides if any events classed as serious are expected for this disease area. These should be excluded from immediate reporting and documented in the study protocol, with sufficient evidence for this decision.
3. The CI documents delegated responsibilities of event reporting in the Investigator Site File.
4. The CI confirms membership of a data monitoring safety committee where necessary and documents this in the protocol.
5. For a multi-centre study, 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.
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 Research Governance approval requirements..
7. The R&D Coordinator adds the study details to the eSUSAR database (for electronic SUSAR reporting) once Research Governance Authorisation 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 CRF and source document as required by the protocol.
2. The R&D Coordinator will prompt the Investigator for a line listing of AE and/or AR on the request of the MHRA.

Where event is an SAE or SAR

1. The Investigator follows the guidance of the study specific protocol, recording the event in the CRF and source document.
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. The form should be completed electronically wherever possible to endure legibility
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 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.
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).

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 9)
13. The R&D Coordinator ensures all events are followed to resolution, as indicated by RMS.

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, 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 or post:
    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 9)
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 (eg 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 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.

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.

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 and REC 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

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 to discuss the issue with a medical assessor.
3. The CI liaises with the R&D Coordinator to notify the MHRA and the REC of the measures taken and the reason for the measures by submitting a substantial amendment within the following timelines:
    a. Immediately and in any event no later than 3 days from the date the measures are taken.
    b. As soon as possible for any period during which a disease is pandemic and is a serious risk to human health or potentially a serious risk to human health.
4. The substantial amendment should include a covering letter detailing the measures taken, the reason for them and the medical assessor contacted, a Notification of Amendment Form, and supporting documentation.
5. The substantial amendment should be sent to the Clinical Trials Unit as PDF documents on disk to: Information Processing Unit, Area 6, Medicines & Healthcare products Regulatory Agency, 151 Buckingham Palace Road, Victoria, London. SW1W 9SZ.
6. Where the Research Department is closed for a period of time greater than 3 days (for example Christmas and Easter), the CI will be responsible for contacting the MHRA immediately to discuss the Urgent Safety Measure with a medical assessor, completing the substantial amendment form and forwarding this to the REC and MHRA within 3 days as per points 3a and 3b above, copying the R&D Coordinator into all correspondence.
7. 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 as PDF documents on disk to Information Processing Unit, Area 6, Medicines & Healthcare products Regulatory Agency, 151 Buckingham Palace Road, Victoria, London. SW1W 9SZ.

8. 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 and the MHRA has not raised grounds for non-acceptance of the recommencement within 35 days of them receiving a valid submission.

Examples of Urgent Safety issues[2] might include:

1. Single case reports of a Serious Adverse Reaction with an unexpected outcome (e.g. death)
2. An increase in the frequency of a Serious Adverse Reaction which is judged to be clinically important
3. A new event relating to the use or development of the IMP that is likely to affect the safety of the study participants, e.g.:
    a. An SAE that could be associated with the trial procedures which could lead to a modification of the conduct of the trial
    b. A lack of efficacy of an IMP used for the treatment of a life-threatening disease
    c. A major safety finding from a completed clinical trial using the same IMP

6. Pregnancy in STH Sponsored CTIMPs

The study protocol must include information regarding how to deal with pregnancy of a participant or their partner 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 inclusion criteria should list the use of 2 methods of contraception (used by either participant or partner if participant is male) in order for a participant to be consented. 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.

If the IMP used holds a risk of causing a negative outcome on pregnancy and a research participant (or their partner- where relevant) becomes pregnant during the study, this should be notified by the Investigator to the Sponsor using the STH template pregnancy reporting form within 24 hours of notification of incident. The pregnancy must be followed up until resolution, again submitting an updated pregnancy reporting form unless pregnancy is noted within the protocol as being an event that does not require reporting, for example in the case of studies where pregnancy is the primary outcome of the study.

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 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

[2] Advice on examples of Urgent Safety issues taken from Cambridge University Hospitals NHS Foundation Trust Research and Development Department guidance

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 may be produced.

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 suspected serious adverse reactions 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 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
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

7. The R&D Coordinator submits the DSUR as a pdf file on a disk and sends this to: Information Processing Unit, Area 6, Medicines & Healthcare products Regulatory Agency, 151 Buckingham Palace Road, Victoria, London, SW1W 9SZ.
    a. The disk should be labelled with the EudraCT number, sponsor name (STH NHS Foundation Trust) and the date of the report.
    b. A cover letter should be included (in hard copy and as a pdf on the disk). A template letter is available
8. The R&D Coordinator sends a hard copy of the report to the REC who provided the original favourable opinion, along with the completed CT safety report form that is found on the NRES website: http://www.nres.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-ctimps/submitting-safety-reports-to-the-rec/
9. 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
10. The R&D Coordinator enters the date that the report was sent the MHRA and REC into RMS
11. The R&D Coordinator ensures that a hard copy of the report is filed in the R&D Master File
12. 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 6 months), 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.

Wherever possible, during the set up 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.

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
    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 NRES website: http://www.nres.nhs.uk/applications/after-ethical-review/endofstudy/ 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 (electronically on a disk to Information Processing Unit, Area 6, MHRA, 151 Buckingham Palace Road, Victoria, London, SW1W 9SZ) and the REC who provided the original favourable opinion (hard copy by post)
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 MHRA and the REC 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 R&D Coordinator ensures that a copy of the final study report is filed in the R&D Master File and provides a copy to the CI for inclusion in the Investigator Site File prior to archiving of the study documents. A copy is also saved on the Research Department departmental drive or Alfresco system as applicable

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. 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.

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.

The RSI for any IMPs involved in a clinical trial should stay consistent for a full reporting period (the period between DSUR submissions). This is because changing this information may result in certain Adverse Reactions no longer being reported as SUSARs, where they were previously and this leads to inconsistencies.

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

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. On the anniversary of the MHRA CTA, the annual DSUR is prepared by the CI with assistance from the R&D Coordinator where required. At this time, the R&D Coordinator reviews the EMC website for any SmPC updates.
4. If the SmPC has been updated in the reporting period, details of this are included in the DSUR.
5. If the RSI section of the SmPC has been updated (section 4.8 of an SmPC acts as the RSI), this requires submission to the MHRA as a substantial amendment on a separate disk in conjunction with the DSUR submission.
6. If any other changes have been made to the SmPC that fulfil the definition of substantial as per the European Guidance: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:082:0001:0019:en:PDF this requires submission to the MHRA as a substantial amendment on a separate disk in conjunction with the DSUR submission.

7. 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.
    a. In this case, 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.
8. Any substantial amendment to the SmPC must be accompanied by a new risk:benefit assessment statement and an updated protocol where required (an updated protocol would also require REC approval).
9. 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.
10. Where a non-substantial amendment is made to the SmPC, this does not need to be submitted to the MHRA as an amendment but a copy is included with the subsequent DSUR.
11. If the CI or Sponsor becomes aware of any new safety information, this must be fed back to the MAH.

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.
4. 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).
5. At this time, the R&D Coordinator either liaises with the CI to update the IB, or contacts the commercial MAH to identify if any updates have been made to the IB that is in use.
6. If the RSI section of the IB is updated (and has been assessed by the MHRA where controlled by a commercial MAH), this requires submission to the MHRA as a substantial amendment on a separate disk in conjunction with the DSUR submission.
7. 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.
8. 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.
    a. In this case, 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.
9. Any substantial amendment to the IB must be accompanied by a new risk:benefit assessment statement and an updated protocol where required (an updated protocol would also require REC approval).
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 benefit/risk 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. Where a non substantial amendment is made to the IB, this does not need to be submitted to the MHRA as an amendment but a copy is included with the subsequent DSUR.
14. 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.

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

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
2. If the third party organisation is not registered with the UKCRC, 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 recevied 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 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 NRES SAE Form. The form should be completed in typescript and signed by the CI as requested on the NRES guidance pages http://www.nres.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research

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 multi centre 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.

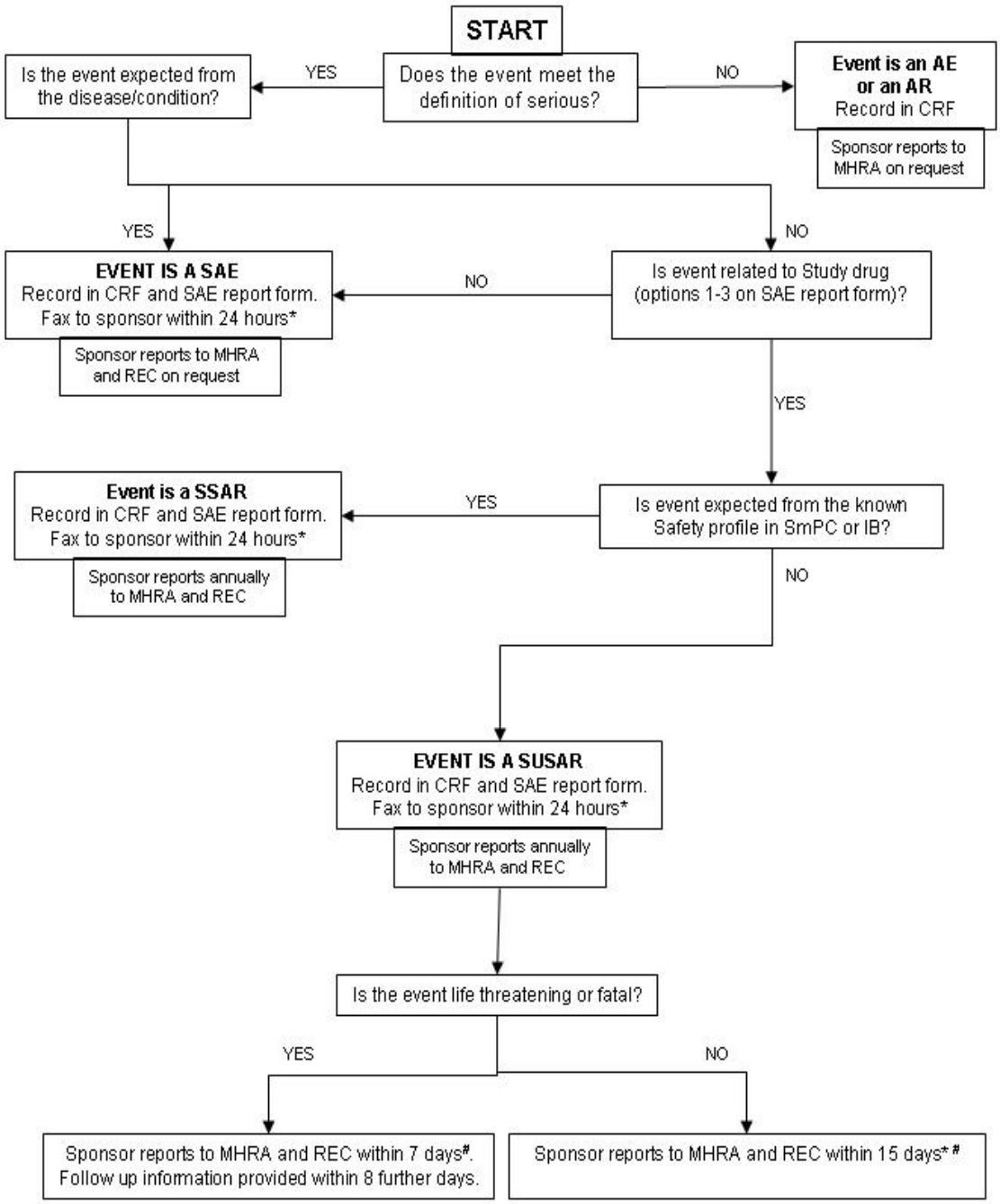
The CI should also inform PIs at other Participating Sites of any "related" and "unexpected" SAEs.

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

SAEs 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 SAE's 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.

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				Total by event
	site 1	Site 2	Site 3	
Event 1 (Medra code)				
Event 2 (Medra code)				
Event 3 (Medra code)				
Total by site				

How to use:
When a new SAE is entered onto RMS, use the MedRA code/event and site/hospital where the event occurs to tally the event in the correct cell of the table.
A trend will be seen where

- one site seems to be reporting significantly more SAEs that other sites (total by site)
- one event seems to be reported more frequently than expected, using information from IB/SmPC /safety information (total by event)

Appendix 3: 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	No	No	AL/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\Data management\Data collection tool\Original generic forms	No	No	AL
4	STH Concomitant Medications CRF page	S:\General\Research Governance\Data management\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\Adverse events	No	No	AL/AP
8	Trend analysis template	S:\General\Research Governance\Pharmacovigilance\Trend Analysis	No	No	AL