South Eastern Health and Social Care Trust

Standard Operating Procedure (SOP) Research and Development Office

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Version No.	Date	Author	Reason for Change
1.0	Sept 2007	Katrina Hughes	N/A
2.0	Dec 2007	Katrina Hughes	add annual reporting requirements and other expedited reports
2.1	May 2009	Katrina Hughes	Addition of reference to adverse event reporting for tissue samples Addition of information surrounding definition of SAE
3.0	May 2011	Alison Murphy	Title revised, included guidance on study planning, eSUSAR reporting requirements, recording and reporting a pregnancy and expanded guidance in other sections. Additional appendices added.

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1. Introduction

There are different reporting requirements for NHS/HSC research involving clinical trials and medicines (where legal requirements for reporting have been introduced) and non-clinical trials.

The European Clinical Trials Directive 2001/20/EC transposed into UK Regulations by 'The Medicines for Human Use (Clinical Trials) Regulations 2004' (SI2004/1031) and subsequent amendments, set out the legal requirements for adverse event recording, management and reporting in clinical trials. The pharmacovigilance strategy in the EU Clinical Trials Directive is designed to ensure:

- The prompt reporting of serious adverse events (SAE's) and the ongoing review of safety in CTIMPs
- The identification of AEs where an association with a study drug is suspected
- The effective dissemination of information on SUSARs across the EU and the research community

Adverse event reporting for clinical and non-clinical trials should be undertaken in accordance with the Trust Policy on reporting and managing adverse events and it is the researcher's responsibility to familiarise themselves with Trust incident policies. Adverse events and near misses should be reported, as appropriate, to the Clinical Risk Department using the Accident/Incident form reporting system. However, researchers are also responsible for ensuring that legal requirements relating to the use of a medicinal product or a medical device are fulfilled.

2. Objective

The objective of the Standard Operating Procedure (SOP) is to set out the procedure to be followed when reporting an adverse or serious adverse event. Adherence to the guidance included in this SOP and any associated notes should ensure compliance with the protocol and legislative requirements.

3. Scope

All clinical trials involving medicinal products requiring registration with the MHRA and all other research projects, sponsored by South Eastern Health & Social Care Trust. All staff with responsibility for recording or reporting adverse events.

Research studies sponsored by an external organisation are exempt from this SOP, but researchers must follow sponsor or study specific SOPs.

4. Study Planning

All protocols should list known side effects and adverse reactions contained within the manufacturer's product information. This should be written in agreement with the relevant drug company where applicable. Rare/very rare events may or may not be included depending on individual study requirements.

A detailed explanation of SAE reporting procedures should also be included in the protocol

A generic SAE reporting Form is available in Appendix 1. This form can be amended to create a study specific form.

4.1 Which AE to record

The Chief Investigator (CI) can decide how to record and report adverse events, whether expected or not. Adverse events are usually described on case report forms (CRFs), unless they are classified as serious, in which case they should be reported on a specific SAE Form (see appendix 1). It should be clearly stated in the study protocol and the trial specific SOP (if applicable) what will be recorded and how the reporting is to be managed.

It may be decided that all, or only some, non-serious AEs are to be recorded. Whatever option is chosen, it must be consistent with the purpose of the trial and any toxicity and efficacy end points.

4.2 Which SAE to Report

The management and reporting arrangements for SAEs should be clear for all trials. Agreements at the beginning of the trial should be made for such SAEs that can be defined as disease-related and therefore not subject to expedited reporting. The procedures for managing and reporting SAEs must be clearly defined in the protocol.

It is recommended that an Independent Data Monitoring Committee (IDMC) is appointed in order to review safety data regularly throughout the trial and when necessary, recommend to the sponsor whether to continue, modify or terminate the trial. Again this procedure must be defined in the protocol.

As with all recording and reporting, subject confidentiality and adherence to the Data Protection Act (1998) must be maintained on all reports.

4.3 When to start and stop recording AE/Rs

All AE/Rs (non-serious, serious, expected, unexpected) need to be recorded from the point of consent of a subject into a trial and not from the first dose of the administered IMP. This will also include placebo run-in periods (if applicable). Serious adverse events for which the onset occurs during the pre-randomisation period should be reportable if they are a result of a protocol specified intervention or can cause the participant not to be allocated to randomisation treatment.

All AEs and SAEs should be recorded within the established off therapy follow-up period for safety described in the protocol, normally through to 3 months after study compound has finished. This time period needs to be defined in the protocol.

5. Adverse Event (AE) / Adverse Reaction (AR)

5.1 Definition

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered an investigational medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse reaction is any untoward and unintended responses to an investigational medical product related to the investigational medicinal product.

5.2 Reporting Adverse Events

Adverse events that are not considered to be serious should be recorded on the relevant case report forms and reported in the medical notes of the patient in accordance with Good Clinical Practice guidelines. This will include adverse events concerning tissue samples that come under the remit of the Human Tissue Act (SOP 28)

Adverse events must be monitored and followed throughout the study period. For instance, in studies involving investigative medicinal products, the study period runs from enrolment and commencement of study compound through to 3 months after study compound has finished.

Should an adverse event be upgraded to a serious adverse event then the procedure for dealing with a serious adverse event should be followed.

6. Serious Adverse Event (SAE) / Serious Adverse Reaction (SAR)

6.1 Definition

This is an adverse event or adverse reaction that

- Results in death.
  Death may occur as a result of the basic disease process. Nevertheless, all deaths occurring within 30 days of the last administration of the study agent must be treated as an SAE and reported as such. All deaths which may be considered as related to the trial agent, regardless of the interval, must be treated as a SAE and reported as such.

- Is life-threatening
  It places the subject, in the view of the investigator, at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have caused death); or

- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay), even if the hospitalisation is a precautionary measure for continued observation. Therefore, participants do not need to be hospitalised overnight to meet the hospitalisation

criteria. Hospitalisation (including hospitalisation for an elective procedure) for a pre-existing condition (prior to study entry) which has not worsened does not constitute a serious experience; or

- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions)

- Consists of a congenital anomaly or birth defect (in offspring of subjects or their partners) taking the IMP regardless of time of diagnosis; Or

- Other Important Medical Event,
  (these can include events that do not meet the standard criteria for seriousness but based on appropriate medical judgement are considered serious as they may jeopardise the participant and may require medical or surgical intervention to prevent the above outcomes from occurring. They also include:

    - Overdoses (accidental or intentional)
    - Pregnancy (of subject or partner)
    - An alarming adverse experience
    - Non-serious adverse events and/or laboratory abnormalities which are listed in the trial protocol as critical to safety evaluations and requiring reporting

6.2 Reporting Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

If the AE/AR is assessed as serious, the PI must report the event to the CI immediately or within 24 hours of being made aware of the event (other than those SAEs identified in the protocol as not requiring immediate reporting). The initial report can be made verbally but must be promptly followed with a detailed written report. The PI must record the event with their assessment of seriousness, (along with causality, expectedness and severity) on a trial SAE form, provided by the CI (see appendix 1). The PI should ensure that follow up information is provided when available.

Serious Adverse events should be documented in the patient's medical notes. This should include times, dates, nature of event, actions, plan of action and should include legible signatures.

Serious adverse events and near misses should also be reported through local Trust procedures, as appropriate.

6.2.1 Trust Sponsored CTIMPs

The CI must send all SAE/SAR reports to the Trust Research Office as soon as possible after becoming aware of the event.

There is no requirement to routinely report SAE/SARs to the REC, other than through the Annual Safety Report (ASR).

6.2.2 Trust sponsored Other Research

There is no requirement to routinely report SAE/SARs to the Trust Research Office, other than through the Annual Progress Report.

The CI must report all SAE/SAR to the Research Ethics Committee that gave a favourable opinion of the study (the 'main REC') where in the opinion of the chief investigator 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 related and unexpected SAEs should be submitted within 15 days of the chief investigator becoming aware of the event, using the form in appendix 2. The form should be completed in typescript and signed by the chief investigator.

7.0 Suspected Serious Adverse Reaction (SSAR)

7.1 Definition

This is an adverse reaction that is classed in nature as serious and which **is consistent** with the information about the medicinal product in question set out in the,

- Summary of Product Characteristics (SmPC) in the case of a licensed product being used within its licensed dosage and indication

- Investigator's Brochure (IB) in the case of any other investigational medicinal product or a licensed product being used outside its licensed dosage and indication

7.2 Reporting Suspected Serious Adverse Reaction (SSAR)

If the AR is assessed as serious, the PI must report the event to the CI immediately or within 24 hours of being made aware of the event (other than those SARs identified in the protocol as not requiring immediate reporting). The initial report can be made verbally but must be promptly followed with a detailed written report. The PI must record the event with their assessment of seriousness, (along with causality, expectedness and severity) on a trial SAE/AR form, provided by the CI (see appendix 1). The PI should ensure that follow up information is provided when available.

SSARs should be documented in the patient's medical notes. This should include times, dates, nature of event, actions, plan of action and should include legible signatures.

Serious adverse events and near misses should also be reported through local Trust procedures, as appropriate.

The CI should include all SSARs in the Annual Safety Report (ASR).

7.2.1 Trust Sponsored CTIMPs

The CI must send all SSAR reports to the Trust Research Office as soon as possible after becoming aware of the event.

There is no requirement to routinely report SSARs to the REC, other than through the Annual Safety Report (ASR).

8.0 Suspected Unexpected Serious Adverse Reaction (SUSAR)

8.1 Definition

This is an adverse reaction that is classed in nature as serious and which **is not consistent** with the information about the medicinal product in question set out in the Summary of Product Characteristics (SmPC) or Investigator's Brochure (IB)

An event that is assessed as being

- Serious
- Possibly, probably or definitely related to the administration of the IMP and is
- Unexpected

Is defined as a SUSAR.

8.2 Reporting Suspected Unexpected Serious Adverse Reaction (SUSAR)

The CI should contact the Research Office immediately the decision is taken that an SAR is a SUSAR, using the dedicated email address **(see section 14.0).** The Research Manager/Associate Medical Director (Research) and CI will undertake a further assessment to determine whether it is a fatal or life-threatening SUSAR, or a non-fatal or life-threatening SUSAR.

For fatal or life-threatening SUSARs (7 day reporting), the Research Office in collaboration with the CI will submit the SUSAR report as soon as possible but, within seven days of the becoming aware of the event.

For non-fatal or life-threatening SUSARs (15 day reporting), the Research Office in collaboration with the CI will submit the SUSAR as soon as possible but within fifteen days of becoming aware of the event.

All SUSAR reports are to be reported electronically through the MHRAs e SUSAR website (www.esusar.mhra.gov.uk). The CI will provide the required information for the eSUSAR Report, see appendix 3, to enable the Research Office to submit the eSUSAR report.

The eSUSAR website will provide a pdf output to report to the Research Ethics Committee. However, there is a standard covering form for sending reports to RECs in the UK, see appendix 4.

Where incomplete information is available at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be provided as follow up reports as it becomes available.

The CI will retain a copy of the expedited report and associated documentation in the TMF. SUSARs should be documented in the patient's medical notes. This should include times, dates, nature of event, actions, plan of action and should include legible signatures.

8.3 Reporting to PIs involved in Study

All PIs within the trial concerned must also be informed of the SUSAR, although this does not have to be within the 7/15 day deadline. The CI should send all PIs a summary of SUSARs approximately every 3 months. This timeframe may vary between trials depending on the rates of recruitment and/or SUSARs.

If the CI is informed of SUSARs from other trials by a pharmaceutical company, the CI should inform PIs as above.

9.0 Evaluating Adverse Events

The following documents need to be at hand when assessing any AE in the trial, especially since they contain the required information for the expectedness of the AE and timelines for reporting to the sponsor.

- Protocol
- Summary of Product Characteristics (for marketed products only)
- Investigator's Brochure (if applicable)
- IMP Dossier (if applicable)
- Trial specific procedure for unblinding (in the case of a SUSAR in a blinded trial)

Each AE must be evaluated for seriousness, causality, severity and expectedness. The responsibility for this evaluation can be shared between the CI and PIs. It may be most appropriate for the treating PI at each local site to evaluate each event, before reporting it to the CI. It should be stated in the clinical trial protocol and trial specific SOP (if applicable) who will take responsibility for the assessment and reporting of such events to the Sponsor and CI simultaneously. This SOP assumes that responsibility of initial assessment and reporting to the CI lies with the PI. The CI cannot downgrade the PI's assessment.

9.1 Seriousness

Seriousness should be assessed as per the definition of a SAE in section 6.0

9.2 Causality

The relationship between the drug and the occurrence of each adverse event will be assessed and categorised (as detailed below). The CI/PI will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors etc. will also be considered. The CI/PI will also consult the IB or SmPC.

- **Not Related:** Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.

- **Unlikely:** Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause which can by itself explain the occurrence of the event.

- ***Possibly related:** Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause.

- ***Probably related:** Temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and the event is more likely explained by the product than any other cause.

- ***Definitely related:** temporal relationship of the onset, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

** Where an event is assessed as possibly, probably or definitely related, the event is an AR.*

9.3 Severity

The assessment of severity will be based on the CI/PIs clinical judgement using the following definitions:

- **MILD:** An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- **MODERATE:** An event that is sufficiently discomforting to interfere with normal everyday activities.
- **SEVERE:** An event that prevents normal everyday activities.

Note: severity is often used to describe the intensity of a specific event. This is not the same as 'seriousness', which is based on patient/event outcome or action criteria.

9.4 Expectedness

This will be determined according to the reference documents as defined in the study protocol (e.g. Investigator Brochure or Summary of Product Characteristics).

- Expected reactions are previously identified and described in protocol and/or reference documents.

- Unexpected reactions are not previously described in the protocol or reference documents.

Note: ARs must also be considered as unexpected if they add significant information on the specificity or severity of an expected AR.

10. Other Safety Issues Considered to be Serious in Clinical Trials

Other safety issues where they might materially alter the current benefit-risk assessment of an IMP or that would be sufficient to consider changes in the IMP administration or in the overall conduct of the trial also need to be considered serious, for example,

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important
- Post-study SUSARs that occur after the patient has completed clinical trial and are reported by the investigator to the sponsor,
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as
- An SAE which 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 from a newly completed animal study (such as carcinogenicity)
- Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same investigational medicinal products in another country by the same sponsor.
- Recommendations of the Data Monitoring Committee (DMC), if any, where relevant for the safety of the subjects.

11.0 Recording and Reporting a Pregnancy

All pregnancies in clinical trial subjects need to be recorded and reported to the sponsor as soon as the investigator is aware of the event. See appendix 5 for Pregnancy Reporting Form.

Pregnancy data provides vital data to the overall knowledge concerning the IMP. Any pregnancy that occurs in a female trial subject during a clinical trial should be

followed to termination or to term. Under special circumstances, it may be necessary to monitor the development of the newborn for an appropriate period post delivery. There may be special situations when it will be necessary to monitor the pregnancy of a woman whose male partner is the trial subject. All trial protocols should describe in detail the process for monitoring and managing pregnancy occurrences in a trial.

12.0 Annual Safety Reports (ASR)

Annual Safety Reports are required to be produced by the CI and submitted to the MHRA and the REC that granted the favourable opinion, 12 months after the date of the granting of a CTA Certificate and annually thereafter.

See appendix 6 for a template Annual Safety Report, which should include,

(1) A report on the subjects' safety in the clinical trial

- Concise safety analysis and benefit-risk evaluation describing all new findings related to the safety of the IMP treatments and critical analysis of them with respect to their impact for the subjects
- An analysis of the implications for the population of the clinical trial, analysis of the safety profile of the tested IMP and its implications for subjects' exposure , taking into account all available safety data
- When relevant the following points should be considered;
    - Relation with dose, duration, time course of the treatment
    - Reversibility
    - Evidence of previously unidentified toxicity in the trial subjects
    - Increased frequency of toxicity
    - Overdose and its treatment
    - Interactions or other associated risk factors
    - Any specific safety issues related to special populations
    - Positive and negative experiences during pregnancy or lactation
    - Abuse or misuse of IMP
    - Risks which might be associated with the investigation or diagnostic procedures of the clinical trial
    - Supporting results of non-clinical studies or other experience with the IMP likely to affect subject's safety
    - Detailed rationale on whether necessary to amend the protocol/consent form/patient information leaflet and Investigator Brochure.

(2) A line listing of all suspected SSARs (including all SUSARs) that occurred in the trial

- Trial-specific line listing of all suspected SARs reported during the trial
- Key information but not necessarily all the details usually collected on individual cases
- Should include each subject only once regardless of how many adverse reaction terms are reported for the case
- Different adverse reactions on different occasions should be treated as separate reports tabulated by body system
- One listing for each trial, but separate listings for active comparator or placebo

(3) An aggregate summary tabulation of suspected SARs that occurred in the trial

- Summary tabulations of SAR terms for signs, symptoms and/or diagnoses across all patients to provide an overview for the trial
- These tabulations should contain more terms than subjects
- If the number of cases is very small, a narrative description may be more suitable
- The summary tabulation should specify the number of reports; for each body system; for each ADR term; for each treatment arm (if applicable)
- The unexpected ADR terms should be clearly identified in the tabulation

12.1 Submitting Annual Safety Reports

12.1.1 Submission to MHRA

Annual safety reports should be provided as electronic documents on disk and be sent to:
Information Processing Unit
Area 6
Medicines & Healthcare products Regulatory Agency
151 Buckingham Palace Road
Victoria
London
SW1W 9SZ

12.1.2 Submission to REC

There is a standard covering form for sending reports to RECs in the UK, see appendix 4, which should be used when submitting the ASR to the REC.

12.1.3 Submission to the Trust Research Office

A reminder will be sent by the Research Office to the CI one month prior to the due date of the ASR requesting an electronic copy of the ASR and covering REC form and a paper **SIGNED** copy of the two reports. Confirmation that the reports have been submitted to the REC and MHRA will also be required.

13.0 Development Safety Update Reports (DSUR)

As of 1 September 2011 Development Safety Update Reports (DSUR), will replace the Annual Safety Reports (ASR).

Guidance on the DSUR can be found on the ICH DSUR guidance page
http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/development-safety-update-report.html

14.0 Contact details for CI Reporting SUSARs to the Trust Research Office

A dedicated email account has been set up for the reporting of SUSARS to the Research Office for Trust Sponsored CTIMPs,

Clinical.Trials@South Easterntrust.hscni.net

This email address should **only** be used for the reporting of SUSARs, all other reports should be submitted directly to the Post Approval Team within the Research Office.

15.0 Regulations, Guidelines, references, SOP Links etc

The Medicines for Human Use (Clinical Trials) Regulations 2004
http://www.uk-legislation.hmso.gov.uk/si/si2004/20041031.htm

The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006
http://www.opsi.gov.uk/si/si2006/20061928.htm

Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use. April 2006
http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2006/04_2006/susar_rev2_2006_04_11.pdf

16.0 Appendices

16.1 Serious Adverse Event Form

16.2 NRES Report of Serious Adverse Event (SAE) (For all studies except clinical trials of investigational medicinal products)

16.3 eSUSAR Reporting Form

16.4 NRES Clinical Trials of Investigational Medicinal Products Safety Report to Main Research Ethics Committee

16.5 Pregnancy Reporting Form

16.6 Template Annual Safety Report

Appendix 16.1

Serious Adverse Event Form

Serious Adverse Event Reporting Form

Study title					
CTA/DDX/CTX No		**SEHSCT Research Office Project ID No**		**EudraCT number**	
Type of report	☐ **Initial** ☐ **Follow-up**		Has the Chief or Principal Investigator been informed of this event prior to the completion of this form?	☐ Yes ☐ No	

Patient / Treatment details

Patient initials	☐☐☐		**Patient study number**	☐☐☐☐☐☐☐☐	
Date of birth (DOB)	☐☐ ☐☐☐ ☐☐ d d m m m y y	**Height**	☐☐☐ cm	**Weight**	☐☐☐.☐ kg
Gender	☐ Male ☐ Female		**Was study drug unblinded?**		

IMP(s) patient was receiving at time of SAE (if applicable)	**Dose (mg)**	**Route of administration**	**Date of dose initiated**	**Ongoing?**	**End date (if applicable)**
			☐☐ ☐☐☐ ☐☐ d d m m m y y	☐ Y ☐ N	☐☐ ☐☐☐ ☐☐ d d m m m y y
			☐☐ ☐☐☐ ☐☐ d d m m m y y	☐ Y ☐ N	☐☐ ☐☐☐ ☐☐ d d m m m y y

Date of last treatment given prior to SAE	☐☐ ☐☐☐ ☐☐ d d m m m y y	**Most recent cycle number (if applicable)**	☐	**Was treatment given at full dose prior to event?**	☐ Y ☐ *N	*Specify:

Did reaction abate after study medication stopped?	☐ **Yes** ☐ **No** ☐ **N/A**	**Did reaction reappear after reintroduction of study medication?**	☐ **Yes** ☐ **No** ☐ **N/A**

Serious Adverse Event

COMPLETE THIS PAGE FOR EACH SERIOUS ADVERSE EVENT (photocopy as necessary for each event)

Serious Adverse event Term	**Severity** (Mild, Moderate, Severe)	**Date of onset**	**Ongoing?**	**Date resolved**
		☐☐ ☐☐ ☐☐☐☐ d d m m m y y	☐ Y ☐ N	☐☐ ☐☐ ☐☐☐☐ d d m m m y y

Why was the event serious? *(choose most serious)*	**Where did the event take place?**	**Outcome**
☐ Resulted in death	☐ Home	☐ Resolved
☐ Life-threatening	☐ Hospital Admission date ☐☐ ☐☐ ☐☐☐☐ d d m m m y y Discharge date ☐☐ ☐☐ ☐☐☐☐ d d m m m y y	☐ Resolved with sequelae
☐ Required inpatient or prolonged existing hospitalisation	☐ Out-patient clinic	☐ Unresolved
☐ Resulted in persistent or significant disability/incapacity	☐ Nursing Home	☐ Worsened
☐ Resulted in congenital anomaly/birth defect	☐ Hospice	☐ Fatal
☐ Other Important Medical Event *(specify)* _____	☐ Other *(specify)*_____	☐ Not assessable

Expectedness

☐ Unexpected	☐ Expected	*Is the event listed in the reference document, (study protocol, SmPC or Investigator's Brochure)?*

Causal relationship to event *(Is the event related to the subject's involvement in the study)?*

Trial drug	Definitely	Probably	Possibly	Unlikely	Not related	Not assessable	Name of person making decision
	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	

Action taken						
Trial drug	None	*Dose reduction	*Treatment delayed	*Treatment delayed and reduced	Treatment permanently stopped	Name of person making decision
	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	

**If dose was reduced and/or delayed, please specify length of delay/how much dose was reduced by:*

Treatment given for management of SAE

Treatment	**Total daily dose**	**Units**	**Route of administration**	**Start date** d d m m m y y	**Ongoing?**	**End date** d d m m m y y
				☐☐ ☐☐☐ ☐☐	☐ Y ☐ N	☐☐ ☐☐☐ ☐☐
				☐☐ ☐☐☐ ☐☐	☐ Y ☐ N	☐☐ ☐☐☐ ☐☐
				☐☐ ☐☐☐ ☐☐	☐ Y ☐ N	☐☐ ☐☐☐ ☐☐

Any concomitant medications? ☐ **Y** ☐ **N** *(If yes, please specify below and continue on separate sheet if necessary)*

Treatment	**Total daily dose**	**Units**	**Route of administration**	**Start date** d d m m m y y	**Ongoing?**	**End date** d d m m m y y
				☐☐ ☐☐☐ ☐☐	☐ Y ☐ N	☐☐ ☐☐☐ ☐☐
				☐☐ ☐☐☐ ☐☐	☐ Y ☐ N	☐☐ ☐☐☐ ☐☐
				☐☐ ☐☐☐ ☐☐	☐ Y ☐ N	☐☐ ☐☐☐ ☐☐
				☐☐ ☐☐☐ ☐☐	☐ Y ☐ N	☐☐ ☐☐☐ ☐☐

Any relevant tests / laboratory data? ☐ **Y** ☐ **N** *(If yes, please specify below and continue on separate sheet if necessary or attach print outs)*

Any relevant medical history / concurrent conditions? ☐ **Y** ☐ **N** *(If yes, please specify below and continue on separate sheet if necessary)*
Any other relevant information? ☐ **Y** ☐ **N** *(If yes, please specify below and continue on separate sheet if necessary)*

Event summary description *(Give a concise medical description of the event including all relevant symptoms.* ***Please specify the grade for all related symptoms and complete page overleaf for all that meet the definition of serious****)*
For report of death: (state why the death was expected (eg disease progression, or if earlier than expected, provide explanation)
Describe whom this SAE was discussed with for a judgement of assessment:

Describe why and how you reached the assessment of causality for expectedness and related (ie provide the reasoning for the outcome):

Signature of person making the assessment Authorised health professional		**Print name**		**Date of assessment**	d d m m m y y
Signature of person completing the form if different to person above		**Print name**		**Date of report**	d d m m m y y

For Sponsor's Office use only

Date SAE reported to Research Office	d d m m m y y	Date SAE reviewed	d d m m m y y	Event No			
Office Assessment of Expectedness	Expected ☐	Unexpected ☐	*Is the event listed in the reference document, (study protocol, SmPC or Investigator's Brochure)?*				
Was the event a SUSAR? (ie unexpected and either of the following: Definitely, Probably or Possibly related to the IMP)	☐ *Y ☐ N	Date reported to MHRA d d m m m y y	Date reported to Main REC d d m m m y y	Reported to all other PIs	☐ *Y ☐ N		
	Date reported to GTAC (if applicable) d d m m m y y		Form checked by (signature)	Print name	Date d d m m m y y		
Comments:							

Appendix 16.2

NRES Report of Serious Adverse Event (SAE) (For all studies except clinical trials of investigational medicinal products)

Original Copy of Form can be found at:

http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/#safetynonCTIMPrepotingSAEs

National Patient Safety Agency

National Research Ethics Service

REPORT OF SERIOUS ADVERSE EVENT (SAE)
(For all studies except clinical trials of investigational medicinal products)

The Chief Investigator should report any SAE that is both related to the research procedures and is unexpected. Send the report to the Research Ethics Committee that gave a favourable opinion of the research within 15 days of the CI becoming aware of the event.

1. Details of Chief Investigator

Name:	
Address:	
Telephone:	
Email:	
Fax:	

2. Details of study

Full title of study:	
Name of main REC:	
Main REC reference number:	
Research sponsor:	
Sponsor's reference for this report: (if applicable)	

3. Type of event
Please categorise this event, ticking all appropriate options:

Death ☐	Life threatening ☐	Hospitalisation or prolongation of existing hospitalization ☐
Persistent or significant disability or incapacity ☐	Congenital anomaly or birth defect ☐	Other ☐

4. Circumstances of event

Date of SAE:	
Location:	
Describe the circumstances of the event: *(Attach copy of detailed report if necessary)*	
What is your assessment of the implications, if any, for the safety of study participants and how will these be addressed?	

5. Declaration

Signature of Chief Investigator:	
Print name:	
Date of submission:	

6. Acknowledgement of receipt by main REC (please insert name):

The [ ] Research Ethics Committee acknowledges receipt of the above.

Signed:	
Name:	
Position on REC:	
Date:	

Signed original to be sent back to Chief Investigator (or other person submitting report) Copy to be kept for information by main REC.

Appendix 16.3

eSUSAR Reporting Form

MHRA eSUSAR Reporting Form

Patient Information

Initials						
Sex				Male / Female / Unknown		
Age at time of Reaction				Years or Months or Days		
Subject ID Number						
Weight		kg		stones		pounds
Height		cm		feet		inches
Disease History (MedDRA term)						
Start Date dd/mm/yyyy						
End Date dd/mm/yyyy						
Continuing				Yes / No / Unknown		
Please enter details of any non-study medication that the patient has taken outside of the last 3 months. Any medication taken within the last 3 months should be entered as Concomitant in Step 4 - IMP Details						
Drug History (MHRA Drug dictionary)						
Start Date dd/mm/yyyy						
End Date dd/mm/yyyy						

Reaction Details

Please enter details of the reactions suffered by the patient		
Country of origin (Country SUSAR occurred in)		
Reaction (MedDRA term)		
Reaction Outcome		Recovered
		Recovering
		Not Recovered
		Recovered with sequelae
		Fatal
		Unknown
Start Date dd/mm/yyyy		
End Date dd/mm/yyyy		
Narrative (Please provide a narrative of the reactions, together with any other information relevant to the SUSAR report, in no more than 20,000 characters)		

Seriousness		Death
		Life threatening
		Hospitalisation
		Disabling
		Congenital anomali
		Other
Please enter details of any medical tests undertaken on the patient that are relevant to the SUSAR report.		
Test (MedDRA term)		
Result		
Unit		
Test Date dd/mm/yyyy		

IMP Details

Please enter details of all study medication the patient has taken in the last 3 months. Note regarding Drug Name entry: A dictionary of drug terms and codes is associated with the eSUSAR reporting form. This is regularly updated with new terms that have been submitted to the MHRA in CTA applications. The term entered into the Drug Name field will be matched against the drug dictionary in real time. When no match is found, the user will be prompted to check and re-enter the term. When no match is found for a second time, the user will be permitted to continue and submit the report with an unmatched name.			
Drug Name			
Drug Characterisation (Select Suspect if the drug is the suspected cause of the SUSAR)		Suspect/Concomitant	
If the patient is taking 200mg four times a day, this should be entered as '800' for the drug dose, 'mg' as the drug dosage unit, '1' as the drug dosage interval, and 'day' as the drug dosage interval unit.			
Drug Dosage		Unit	
Drug Dosage Interval		Unit	
Form			
Route of Administration			
Indication (MedDRA term)			
Start Date dd/mm/yyyy			
End Date dd/mm/yyyy			
Action Taken		Drug withdrawn / Dose reduced / Dose increased / Dose not changed / Unknown / Not applicable	

Appendix 16.4

NRES Clinical Trials of Investigational Medicinal Products Safety Report to Main Research Ethics Committee

Original Copy of Form can be found at:

http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-ctimps/submitting-safety-reports-to-the-rec/

National Patient Safety Agency

National Research Ethics Service

CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS

SAFETY REPORT TO MAIN RESEARCH ETHICS COMMITTEE

Please indicate which type(s) of safety report you wish to notify with this cover sheet (tick all that apply). Use a separate sheet for notifications relating to different trials. Please only send this to the main REC. For further guidance see: *http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/safetyreports/safety-reports-for-ctimps/*

1. **Expedited report(s) of SUSAR in the UK** ☐
   Notify only Suspected Unexpected Serious Adverse Reactions occurring in the concerned trial at a UK site.

2. **6-monthly safety report** ☐
   Include a global list of all SUSARs related to the investigational medicinal product (IMP) and occurring in the reporting period.

3. **Annual safety report** ☐
   Include a global list of all SSARs (Suspected Serious Adverse Reactions) related to the IMP and occurring in the reporting period.

4. **Other** ☐
   For example, report of Data Monitoring Committee or other safety review.

Full title of study:	
EudraCT number:	
Research sponsor:	
Name of Chief Investigator:	
Name of main REC:	
Main REC reference number:	

Contact details for person making this notification

Name:	
Address:	
Telephone:	

Fax:	
Email:	
Date of this notification:	
Signature:	

List of enclosed documents
Please list each report submitted with this notification (insert extra rows in table as required).

1. Expedited SUSARs (UK only)

Sponsor's report no./reference	Trial site	Date SUSAR first reported to sponsor	**Is this a 7 or 15 day report?**

2. Other reports

Type of report	Date of report

Acknowledgement of receipt by main REC (please insert name):

The [ ] Research Ethics Committee acknowledges receipt of the above.

Signed:	
Name:	
Position on REC:	
Date:	

Signed original to be sent back only to the sponsor (or other person submitting the report)
Copy to be kept for information by main REC.

Appendix 16.5

Pregnancy Reporting Form

Pregnancy Reporting Form

Study details					
Study title					
CTA/DDX/CTX No		**SEHSCT Research Office Project ID No**		**EudraCT number**	

1) Patient details *(Any information regarding female partners of trial patients should be entered in Other Pregnancy Information section)*					
Patient initials	☐☐☐		**Patient study number**	☐☐☐	
Gender	☐ Male ☐ Female		**Date of Birth**	☐☐ ☐☐☐☐ ☐☐ d d m m m y y	
Type of Report	☐ First ☐ Follow-up		**Height**	☐☐☐ cm	**Weight** ☐☐☐.☐ kg
Has CI been informed?	☐ Yes ☐ No		**Was study unblinded?**	☐ Yes ☐ No	

2) Trial treatment									
Drug Name	**Manufacturer**	**Dose**	**Unit**	**Frequency**	**Is this full dose?**	**Route**	**Start date** d d m m m y y	**Ongoing?**	**End date** d d m m m y y
					☐ Y ☐ N		☐☐ ☐☐☐☐ ☐☐	☐ Y ☐ N	☐☐ ☐☐☐☐ ☐☐
					☐ Y ☐ N		☐☐ ☐☐☐☐ ☐☐	☐ Y ☐ N	☐☐ ☐☐☐☐ ☐☐
					☐ Y ☐ N		☐☐ ☐☐☐☐ ☐☐	☐ Y ☐ N	☐☐ ☐☐☐☐ ☐☐

Most recent cycle number: ☐	**Date last treatment given before pregnancy confirmation:** d ☐☐ m ☐☐ m ☐☐ y ☐☐	**Last treatment given before pregnancy confirmation:** d ☐☐ m ☐☐ m ☐☐ y ☐☐

3) Concomitant medications? ☐ **Y** ☐ **N** *(Only include drugs given within the last 30 days. Continue on separate sheet if necessary)* Continued on a separate sheet: ☐ **Y** ☐ **N**

Drug Name	Manufacturer	Indication	Dose	Units	Frequency	Route	Start date (d d m m m y y)	Ongoing?	End date (d d m m m y y)
							☐☐ ☐☐ ☐☐	☐ Y ☐ N	☐☐ ☐☐ ☐☐
							☐☐ ☐☐ ☐☐	☐ Y ☐ N	☐☐ ☐☐ ☐☐
							☐☐ ☐☐ ☐☐	☐ Y ☐ N	☐☐ ☐☐ ☐☐
							☐☐ ☐☐ ☐☐	☐ Y ☐ N	☐☐ ☐☐ ☐☐

4) Pregnancy Information

Start date of last menses	Date pregnancy confirmed	Method of diagnosis	Anticipated date of childbirth	Mother consented for pregnancy monitoring
☐☐ ☐☐ ☐☐☐ d d m m m y y	☐☐ ☐☐ ☐☐☐ d d m m m y y		☐☐ ☐☐ ☐☐☐ d d m m m y y	☐ Y ☐ N

Pregnancy Outcome

☐ Not known at this date	☐ Still birth	☐ Induced abortion	☐ Spontaneous abortion
☐ Neonatal death	☐ Uneventful (normal/healthy baby)	☐ Birth defects *(provide details in Other Pregnancy Information section below)*	
Date of Above Outcome:	☐☐ ☐☐ ☐☐☐ d d m m m y y		

Date of delivery d d m m m y y	Gestation (weeks)	Mode of Delivery	Gender	Weight (kg)	Antenatal Problems	Postnatal Problems
☐☐ ☐☐ ☐☐☐	☐☐		☐ Male ☐ Female	☐.☐		

Other Pregnancy Information *(concurrent conditions, medical history, complications during birth, birth defects etc)*

Past Pregnancy History						
Date of delivery d d m m m y y	**Gestation (weeks)**	**Mode of Delivery**	**Gender**	**Weight (kg)**	**Antenatal Problems**	**Postnatal Problems**
☐☐ ☐☐☐ ☐☐	☐☐		☐ Male ☐ Female	☐.☐		
☐☐ ☐☐☐ ☐☐	☐☐		☐ Male ☐ Female	☐.☐		
☐☐ ☐☐☐ ☐☐	☐☐		☐ Male ☐ Female	☐.☐		

Signature PI or other participating clinicians only		**Print name**		**Date of report**	☐☐ ☐☐☐ ☐☐ d d m m m y y

Sponsor Office use only

Date reported to Research Office	d d m m m y y	Date SAE reviewed	d d m m m y y	Event No	d d m m m y y
Was the event a SUSAR? (ie unexpected and either of the following: Definitely, Probably or Possibly related to the IMP)	*Y N	Date reported to MHRA d d m m m y y	Date reported to Main REC d d m m m y y	Reported to all other PIs	*Y N
	Date reported to GTAC (if applicable) d d m m m y y	Form checked by (signature)	Print name	Date d d m m m y y	

Comments:

Appendix 16.6

Template Annual Safety Report

Clinical Trials of Investigational Medicinal Products

Annual Safety Report to MHRA

Report Covering Period xxx to xxx

Full title of trial	
Short title	
IMP(s) under investigation	
Sponsor	
EudraCT number	
MREC that approved the Trial	
Chief Investigator	
CTA number	
Trial start date	
Trial end date	
Target number of subjects for whole trial	

Contact details for person making this notification

Name	
Address	
Telephone	
Fax	
Email	
Date of this notification	

Safety information in reporting period

Number of subjects enrolled during the review period	
How many subjects have been enrolled since the trial started	
Number of SAEs observed	

Part 1. Analysis of the subjects' safety of the clinical trial

1. Are there any new[1] and relevant findings related to the safety of the subjects, including all new findings related to the safety of the investigational medicinal product (IMP) (s) or other treatments used in the trial and any other findings related to the clinical trial procedures? If yes, provide a concise description[2]:	Yes ☐ No ☐
2. Have there been any non-clinical studies or other experiences with this IMP (s) that are likely to affect the subjects' safety? If yes, provide details:	Yes ☐ No ☐
3. Are there any implications for the population of the clinical trial such as new measures to minimise any risks found or any need to amend the protocol, patient information sheet, consent form and investigator's brochure? If yes, provide details:	Yes ☐ No ☐
4. Is there an update of the risk-benefit evaluation for the clinical trial? If yes, provide details:	Yes ☐ No ☐

[1] New findings refers to information not already present in the investigator's brochure or for licensed drugs the summary of product characteristics.

[2] When relevant, the following points should be considered: relation with dose, duration, time course of the treatment; reversibility; evidence of previously unidentified toxicity in the trial subjects; increased frequency of toxicity; overdose and its treatment; interactions or other associated risks factors; any specific safety issues related to special populations, such as the elderly, the children or any other at risk groups; positive and negative experiences during pregnancy or lactation; abuse; risks which might be associated with the investigation or diagnostic procedures of the clinical trial.

Trial Safety Report Line Listing

Subject ID	**Body system** *CTC Version 3* See appendix	**Case Reference Number**	**Country**	**DOB**	**Sex**	**Dose of IMP**	**Dates of Treatment**	**Date of Onset of AE**	**Adverse Reaction**	**Outcome**	**Comments**	**Unblinding Results (where applicable)**

Trial Aggregate Summary Tabulation

Body System / ADR term	**Arm A**	**Arm B**	**Total**

APPENDIX 1
Guidance Notes for Annual Safety Reports Line Listing and Summary Tabulation

Field	Comment
Subject ID	Patient trial number
Body System	Body system is classified according to the Common Toxicity Criteria (Version 3.0) 1. Allergy/Immunology 2. Auditory/Ear 3. Blood/Bone Marrow 4. Cardiac Arrhythmia 5. Cardiac General 6. Coagulation 7. Constitutional Symptoms 8. Death 9. Dermatology/Skin 10. Endocrine 11. Gastrointestinal 12. Growth & Development 13. Hemorrhage/Bleeding 14. Hepatobiliary/Pancreas 15. Infection 16. Lymphatics 17. Metabolic/Laboratory 18. Musculoskeletal/Soft Tissue 19. Neurology 20. Ocular/Visual 21. Pain 22. Pulmonary/Upper respiratory 23. Renal/Genitourinary 24. Secondary Malignancy 25. Sexual/Reproductive Function 26. Surgery/Intra-operative Injury 27.Syndromes 28. Vascular 29. Other
Case Reference Number	This is a number to uniquely identify the SAE event
Country	This refers to the country in which the case occurred
DOB	Date of Birth (dd/mm/yyyy)
Sex	F=female M=male
Dose of IMP	This is given in mg.
Dates of Treatment	Date patient started cycle related to event (dd/mm/yyyy)
Date of onset of AE	Date the symptoms started (dd/mm/yyyy)
Adverse Reaction	Describes the symptoms patient experienced during the manifestation of the event, progression of event, test etc
Outcome	Refers to treatment given (trial or otherwise)
Other Comments	This section is optional, only complete if relevant eg causality disagreement, concomitant medications also suspected
Unbinding Results (where applicable)	Provide details if unblinding took place