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Managing Adverse Events in Clinical Trials of Investigational Medicinal Products (CTIMPs)

SOP Reference:	**SOP/RD/006**	
Version Number	**Version 5.0**	
Date:	**20-April-2015**	
Effective Date:	25-May-2015	
Review by:	25-May-2017	
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Version	Date	Reason for Change
1	01/Oct/2012	Addition of pregnancy notification, DSUR reporting, SOP training record, Expectedness section 4.3, SAE Reporting Form section 4.4, Governance, Audit & Safety Committee, R&D Safety Team. Updated Blinded Trials section with comparator/placebo, SAE reporting procedure with Sponsor notified immediately of SAEs, Multi-centred trials section 4.6 and SAEs Received in R&D Department section 4.7
2	18/Oct/2012	Updated to include SAE reporter following up fax with a telephone call to CIRU reception or a member of the R&D Safety team. Inclusion of telephone reporting of SAE in the event of fax system failure
3	08/Jan/2013	Trial specific SAE reporting forms. Cross referencing to other BSUH SOPs. Addition of appendices – training record and SAE reporting form
4	20th April 2015	CI and PI responsibilities clarified. Governance, Audit and Safety Committee now known as Operational Management Group: Quality & Safety. Option for scanning & emailing SAE Reporting Form in the event that fax machines are unavailable. Other minor updates including updates to the SAE Reporting Form.

1.0 Purpose

This SOP describes the processes for the management of Adverse Events (AEs) in clinical trials of medicinal products (CTIMPs) sponsored by Brighton & Sussex University Hospitals NHS Trust (BSUH). This SOP should be read and understood by all research staff involved in CTIMPs sponsored by BSUH. Evidence of this training should be provided by completion of a Training Record (RD/TR001 Training Record for BSUH SOPs, appendix 1).

2.0 Introduction

The Medicines for Human Use (Clinical Trials) Regulations 2004 and the Department of Health's Research Governance Framework stipulate the requirements for the management of AEs. Each AE must be assessed for causality and expectedness.

AEs are classified into the following 5 different categories; each classification is subject to different reporting requirements.

2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

2.2 Adverse Reaction (AR)

All untoward and unintended responses to an IMP related to any dose administered. This includes medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

All AEs judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship (possible, probable or definite) to the IMP qualify as ARs. The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship.

2.3 Serious Adverse Event/Reaction (SAE/SAR)

Any untoward medical occurrence or effect that at any dose:-

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients' hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

Life threatening in the definition of a 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.

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AEs/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

2.4 Suspected Serious Adverse Reaction (SSAR)

Any AR that is classed as serious **and** which is consistent with the information about the IMP contained in the Summary of Product Characteristics (SmPC) for authorised IMPs or Investigator Brochure (IB) for unauthorised IMPs.

2.5 Unexpected Adverse Reaction (UAR)

An AR that is not serious, where the nature or severity of the event is **not** consistent with the information about the IMP contained in the IB or the SmPC.

2.6 Suspected Unexpected Serious Adverse Reaction (SUSAR)

An AR that is serious, where the nature or severity of the event is **not** consistent with the information about the IMP contained in the SmPC or IB.

All serious adverse events/serious adverse reactions should be reported to the Sponsor immediately. Exceptions to this include those SAEs that the protocol or other document (such as the Investigator Brochure) identifies as not needing immediate reporting. Certain adverse events critical to safety evaluations of the trial may be subject to immediate reporting if specified in the protocol.

3.0 Responsibilities

3.1 Chief Investigator (CI) Responsibilities

The CI is responsible for ensuring the protocol contains a list of known side effects and adverse reactions contained within the manufacture's product information. It may be decided that all, or only some, non-serious AEs are to be recorded. This must be clearly documented in the protocol. The appropriate decision must be made taking into account the purpose of the trial and any toxicity and efficacy endpoints.

The CI is responsible for ensuring that all investigators, the REC and the MHRA are promptly notified of any findings that may impact on subject safety.

The CI has the responsibility of producing and submitting the Development Safety Update Report (DSUR) to the Sponsor, the MHRA and the REC.

3.2 Principal Investigator (PI) Responsibilities

The PI is responsible for ensuring all AEs are reported in accordance with this SOP and the trial protocol.

The PI or delegated individual must assess each AE for causality, seriousness and expectedness between the IMP and/or concomitant therapy and the AE (see SOP/RD/010 Delegation of Roles and Responsibilities).

The PI is responsible for ensuring relevant members of their research team are promptly informed of any relevant safety information relating to the trial.

3.3 Sponsor Responsibilities

The Sponsor is responsible for reporting AEs to the Medicines and Healthcare products Regulatory Agency (MHRA) and to the relevant Research Ethics Committee (REC).

The Sponsor has the responsibility of appointing a named Medical Monitor (MM) for each CTIMP as well as a back up MM. The MMs will be independent from the CI's research team but will be trained in the study protocol and Managing AEs in CTIMPs SOP as well as being familiar with the IB or SmPC. This will be documented on the Medical Monitor Declaration Form (RD/F004). The MM will be responsible for reviewing and countersigning all SAEs reported to BSUH from BSUH sponsored trials.

The Sponsor is responsible for ensuring the current reference safety information is provided to all investigators involved in assigning expectedness to adverse events, as well as the medical monitors.

If deemed necessary by the Sponsorship Approval Committee, the Sponsor has the responsibility for appointing members to and convening a Trial Safety Group (TSG) to meet quarterly to review safety reporting for that particular trial.

The Sponsor is responsible for reporting all SAEs reported from BSUH sponsored CTIMPs to the Operational Management Group sub-committee: Quality and Safety.

The Sponsor is responsible for creating and maintaining a database of reported SAEs and tracking their outcome.

The Sponsor is responsible for ensuring there are written SOPs and systems in place to ensure quality standards are met.

The Sponsor is responsible for setting up each sponsored CTIMP on the MHRA electronic reporting site for SUSARs.

4.0 Procedure

AEs should be evaluated for causality, seriousness & expectedness using the following guidelines:

4.1 Causality :- *Table 1*

Causality	Description
Unrelated	No evidence of any causal relationship
Unlikely	Little evidence to suggest a causal relationship (e.g. the event did not occur within a reasonable time after administration of the IMP). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible	Some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatment).
Probable	Evidence to suggest a causal relationship and the influence of other factors is unlikely
Definite	Clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out
Not Assessable	Insufficient or incomplete evidence to make a clinical judgement of the causal relationship

If the AE is recorded as having either a possible, probable or definite relationship to the IMP by the PI, CI, MM or Sponsor then this is an adverse reaction. If the reaction is also recorded as serious and unexpected then this is a SUSAR (Suspected Unexpected Serious Adverse Reaction). The SUSAR should be notified to the MHRA, the REC and the Sponsor immediately.

4.2 Seriousness

The definition of a serious adverse event is given in section 2.3 of this SOP.

Table 2

Type of AE	Action	Timeline
AE/AR	Include in patient notes and on Case Report Form as specified in the protocol	As soon as possible
SAE/SAR	1) The PI must report all SAE/SAR/SSAR/SUSARs to the Sponsor and the CI immediately as specified by the protocol. The event should be recorded on the standard SAE reporting form (RD/F006, appendix 2) 2) The SAE reporting form must be faxed to the BSUH R & D Office for the attention of the R&D Safety team	1) Immediately, at least within 24 hours 2) Immediately, at least within 24 hours
SUSAR	1) The Sponsor must report fatal or life-threatening SUSARs to the MHRA via the eSUSAR system at http://esusar.mhra.gov.uk/ and to the REC by using the REC CTIMP Safety form 2) The Sponsor must report non-fatal or non life-threatening SUSARs to the MHRA via the eSUSAR system at http://esusar.mhra.gov.uk/ and to the REC by using the REC CTIMP Safety form	1) Immediately, no later than 7 calendar days of becoming aware of the event (minimum data only). This should be followed by a full report within an additional 8 calendar days 2) Immediately, no later than15 calendar days of becoming aware of the event. Further relevant information should be given as soon as possible

4.3 Expectedness

Adverse reactions should be considered unexpected if the nature, seriousness, severity or outcome of the event is not consistent with the Reference Safety Information (RSI) for the IMP. The RSI should be determined using the IB for an unauthorised IMP or SmPC for an authorised IMP. The RSI should be clearly identified within the protocol (see SOP/RD/012 Writing a Protocol to GCP Standards). If the RSI changes during the conduct of the clinical trial, for the purpose of SUSAR reporting, the version of the RSI at the time of occurrence of the event applies. The current version of the IB or SmPC used for the RSI for a trial will be checked quarterly by the Sponsor.

4.4 SAE Reporting Form

The Sponsor and CI should be notified immediately of all SAEs occurring in research participants of BSUH sponsored trials.

The SAE reporting form (RDF006, appendix 2) should be completed with all available information and faxed as an initial report for the attention of the R&D Safety team on:

01273 664741

Trial specific SAE reporting forms should be used for all BSUH CTIMPs. These should be provided by the Sponsor at the site initiation meeting.

A member of the R&D Safety team must be contacted immediately by the SAE reporter to ensure the SAE Reporting form has been received.

Research teams should have a contact list for the R&D Safety team in the site file, filed in section 16.0.

In the event of failure of the faxing system, the SAE should be reported by telephone and alternatively scanned and emailed to the contacted member of the R&D Safety team.

In the unlikely event that the R&D Safety team can't be contacted, CIRU reception should be telephoned as a back up on 01273 696955 ext 3522.

Confirmation of receipt of fax will be given by a member of the R&D Safety team to the SAE reporter.

Follow up reports should be sent as soon as more information becomes available. A final report should be sent once all the required information has been obtained relating to the event.

Reporting of adverse events will ensure subject confidentiality and adhere to the Data Protection Act 1998 (see SOP/RD/017 Data Management).

A detailed explanation of adverse event reporting should be documented in the trial protocol. All SAEs should be followed up until resolution.

After the end of the trial, only if the investigator becomes aware of SARs should these be reported.

4.5 Blinded Trials

The details of the unblinding process must be included in the trial protocol where applicable. The systems for reporting AEs should, as far as possible, maintain the blinding of individual clinicians and of research team members involved in the day to day running of the trial and those responsible for data analysis and interpretation of study results.

For blinded trials involving a placebo and active drug, seriousness, causality and expectedness should be evaluated as though the patient was on the active drug. All SUSARs should be reported in an unblinded fashion.

Each CTIMP should have a clear procedure for unblinding participants. Research team members should be familiar with this procedure.

SUSARs associated with the comparator product should be reported immediately to the MHRA, the REC and the Sponsor, even if the product is authorised. Events associated with placebo will not usually meet the criteria of a SUSAR, but if a SUSAR is associated with placebo (e.g. a reaction to an excipient) then this should be reported immediately to the MHRA, the REC and the Sponsor.

4.6 Multi-centred Trials Sponsored by BSUH NHS Trust

If the trial is multi-centred, SAEs occurring at the research site must be reported immediately to the Sponsor and the CI as per Table 2.

The CI must inform all PIs involved in the trial of any reported SUSARs or other relevant safety information in a timely manner. Acknowledgement of receipt of these notifications by the PI at each research site should be documented and filed in the investigator site file. The PI is responsible for ensuring other members of their research team are promptly made aware of any relevant safety information relating to the trial.

4.7 SAEs received in the R & D department

Once a Notice of Acceptance letter has been received from the MHRA for a BSUH sponsored CTIMP, the R&D eSUSAR administrator will register the trial on the eSUSAR database.

On receipt of a completed SAE reporting form the R&D Safety team will log this on the BSUH R&D SAE database and allocate a unique number to be recorded on the SAE reporting form.

The R&D Safety team will forward the SAE reporting form along with the current RSI for the trial (saved in the Safety folder on the R&D shared drive), to the MM within 24 hours for immediate review, at least within 5 working days. The MM will perform an independent assessment of severity, causality, expectedness and seriousness, referring to the reference safety information. Once reviewed, the MM will sign and

date each SAE reporting form as evidence of the review and return the completed form to the R&D Safety team. If the MM and back up MM are unavailable, the CI and R&D manager will be consulted to provide advice as to who should be approached as an alternative.

The R&D department will update the BSUH R&D SAE database record on receipt of the MM reviewed SAE reporting form and file within a locked storage room. Notification will be sent to the trial manager to ensure follow up and final reports are received. The trial manager will also notify the CI of the SAE.

If the SAE is a SUSAR, the R&D Safety team will report this to the MHRA and the REC. If the SUSAR is fatal or life threatening the event will be reported as soon as possible but no later than 7 calendar days after the Sponsor has been notified of the SUSAR. Relevant follow up information should be sought and a completed report should be submitted within an additional 8 days.

If the SUSAR is not fatal or life threatening the Sponsor must submit the initial report as soon as possible but no later than 15 calendar days after the Sponsor has been notified of the SUSAR. Relevant follow up information should be submitted as soon as possible.

The Sponsor, CI or MM cannot downgrade reported adverse events/reactions. If there is disagreement with the investigators assessment, both opinions should be documented.

All reported SAEs will be reviewed by the Operational Management Group sub-committee: Quality and Safety, which will meet at least 4 times a year to ensure oversight of safety reporting for BSUH sponsored trials.

4.8 Development Safety Update Report

A Development Safety Update Report (DSUR) must be sent to the MHRA and the REC on an annual basis from the first anniversary of the Clinical Trial Authorisation (CTA). The report should be sent to the Sponsor for review prior to submission to the MHRA and the REC. The report must be submitted within 60 days after the CTA anniversary. The report should be in the format specified in the DSUR template (RD/T005). If the CI does not have access to any information (e.g. manufacturing issues, or non-clinical data) this must be indicated in each section.

DSURs should be provided as electronic documents on disk to the MHRA and be sent to:
Information Processing Unit
Area 6, Medicines & Healthcare products Regulatory Agency
151 Buckingham Palace Rd, Victoria, London, SW1W 9SZ

DSURs should also be sent to the REC accompanied by the standard REC Safety Report Form (CTIMPs).

For multi-centred trials, the CI is responsible for the distribution of the DSUR to all participating research sites.

In the event of more than one BSUH sponsored trial involving the same investigational medicinal product (IMP), the Sponsor will liaise with the CI's involved to produce only one DSUR for all trials concerned using the same IMP.

4.9 Pregnancy

Pregnancy, although not considered an SAE, should be reported to the Sponsor immediately as soon as the PI becomes aware of the event using the Pregnancy Notification and Follow Up Form (RD/F005). This applies to pregnancies where the trial participant is female and the foetus may have been exposed to the IMP through maternal exposure or where the trial participant is male and by transmission via semen may have exposed the foetus to the IMP through paternal exposure.

The pregnancy should be followed up by the investigator and the Sponsor until the outcome of the pregnancy. Any events (e.g. congenital anomaly or birth defect) that meet the definition of an SAE must be reported to the Sponsor immediately.

If there is a risk of congenital abnormality or birth defects, plans for pregnancy monitoring should be detailed in the protocol and outlined in the patient information sheet (PIS) as per HRA guidance. A separate trial pregnancy PIS and consent form for pregnancy follow up should be in place in the event of a trial participant or trial participant's partner becoming pregnant during a clinical trial.

5.0 Training

This is a 'read and understand' SOP. To evidence that you have read and understood this SOP, please complete the training record (appendix 1).

Please note that the R&D department discourages the retention of hard copies of SOPs and can only guarantee that the most up-to-date version is on the Trust website.

6.0 Cross Referenced SOPs

SOP/RD/010 Delegation of Roles and Responsibilities

SOP/RD/012 Writing a Protocol to GCP Standards

SOP/RD/017 Data Management

7.0 References

National Research Ethics Service guidance on safety reporting
http://www.nres.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-ctimps/

MHRA guidance on Clinical trials for medicines: Safety reporting – SUSARs and ASRs
http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARsandASRs/index.htm#4

Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use
http://ec.europa.eu/health/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf

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

Appendix 1

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Training Record

SOP Reference/Title: _____

This training record should be completed by the employee once the SOP has been read and understood.

Employee Name	
Employee Job Title	

SOP Ref	Version/Date	Date SOP understood	Employee Signature
SOP/RD_____	Version: _____ Date:_____		

RD/TR/001 Training Record for BSUH SOPs, version 1.0, 27-Sep-2012

Appendix 2
Serious Adverse Event (SAE) Reporting Form

EudraCT number: **IRAS number:**
Trial Acronym:

Please fax to 01273 664741 immediately

FAO: R&D Safety Team

Patient Initials: ☐☐☐

Patient Study No: ☐☐☐☐☐☐☐☐

Date of Birth: ☐☐/☐☐☐/☐☐☐☐
D D M M M Y Y Y Y

Date of SAE awareness: ☐☐/☐☐☐/☐☐☐☐
D D M M M Y Y Y Y

Treating Clinician: _____

Hospital: _____

Type of Report
☐ 1= First, 2 = Interim, 3 = Final

Trial Arm
☐ 1 = 2 =

Sex
☐ 1 = Male, 2 = Female

Date of last trial treatment given prior to SAE
☐☐/☐☐☐/☐☐☐☐
D D M M M Y Y Y Y

Was the trial treatment given at full protocol dose prior to event?
☐ 0 = No, specify: _____
1 = Yes

Why was the event serious? (choose most serious)	**Where did the SAE take place?**
☐ Resulted in death	☐ Hospital
☐ Life-threatening	☐ Outpatient clinic
☐ Required inpatient hospitalisation or prolongation of existing hospitalisation	☐ Home
☐ Resulted in persistent or significant disability/incapacity	☐ Nursing home
☐ Resulted in congenital anomaly/birth defect	☐ Hospice

☐ Other medically important event ☐ Other, specify: _____

SAE Term:

Briefly describe SAE (include relevant symptoms, body site, and relevant lab tests, treatments received) continue on a separate sheet if necessary

Details of SAE

Duration of SAE (dd mmm yy)	**SAE Status**	**Expectedness (in relation to the reference safety information for the IMP)**
Date of Onset: ☐☐/☐☐☐/☐☐ Date Resolved ☐☐/☐☐☐/☐☐ Or tick box if ongoing ☐	☐ Resolved ☐ Resolved with sequelae, specify sequelae:_____ ☐ Persisting ☐ Worsened ☐ Fatal ☐ Not accessible	☐ Expected ☐ Unexpected

Trial Treatment						
Trial drugs patient was receiving when SAE started	**Total daily dose**	**Start date of most recent cycle** (dd-mmm-yy)	**Currently ongoing?** 0 = no 1 = yes	**End date** (dd-mmm-yy)	**Causal relationship to event** 1=Definitely 2=Probably 3= Possibly 4=Unlikely 5=Not related 6=Not accessible	**Action Taken** 0=None 1=Dose reduction 2=Treatment delayed 3=Treatment delayed and reduced 4=Treatment permanently stopped

Other Treatments at Time of Event (include concomitant medication, radiotherapy, surgery, palliative care, continue on a separate sheet if necessary or attach copy of Concomitant Medication CRF page)					
Treatment Give generic name of drugs/treatment given in last 30 days	**Total daily dose**	**Start date** (dd-mmm-yy)	**Currently ongoing?** 0 = no 1 = yes	**End date** (dd-mmm-yy)	**Action Taken** 0=None 1=Dose reduction 2=Treatment delayed 3=Treatment delayed and reduced 4=Treatment permanently stopped

Other relevant information to facilitate assessment (Include medical history, drug or alcohol abuse, family history, findings from special investigations)
In view of the patient's clinical history, was this event expected?
☐ 0 = No ☐ 1 = Yes

SAE Reporter

Research Role: _____ **Contact Tel Number:** _____

Signature: _____ **Print name:** _____

Date of Report : ☐☐/☐☐☐/☐☐ (d d m m m y y)

If the Reporter is not the PI:

PI Signature: _____ **PI Print name:** _____

Date: ☐☐/☐☐☐/☐☐ (d d m m m y y)

OFFICE USE ONLY

Was SAE drug related?	Yes ☐ No ☐	Event No	☐☐☐☐
Was event unexpected?	Yes ☐ No ☐	**Comments:**	
Was the event a SUSAR?	Yes ☐ No ☐		
Date sent to MHRA	☐ D D M M M Y Y		
Date entered on database	☐ D D M M M Y Y	**Checked by Medical Monitor: (signature)**	
Form checked by R&D Safety Team (signature)		**Print name:**	
Print Name			
Date	☐ D D M M M Y Y	**Date**	☐ D D M M M Y Y