Portsmouth Hospitals NHS
NHS Trust

Standard Operating Procedure (SOP) for Investigators

Recording, Assessing & Reporting Adverse Events in Clinical Research

For Completion by SOP Author	
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You must therefore verify that the version number and date are the most recent, by cross-checking with the Trust research website before proceeding with implementation.

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Portsmouth Hospitals NHS Trust is committed to ensuring that, as far as is reasonably practicable, the way we provide services to the public and the way we treat our staff reflects their individual needs and does not discriminate against individuals or groups on any grounds. This SOP has been assessed accordingly

1. INTRODUCTION

Portsmouth Hospitals NHS Trust is a research and innovation-based organisation, acting as both host and Sponsor to high quality research activity. This document has been produced to ensure the Trust meets UK clinical trial regulatory requirements [(1)]*;* as well as National Research Ethics Service (NRES) reporting procedures [(2)], and standards of good practice for the management and reporting of Adverse Events during clinical research studies [(3)(4)]

Adverse Events and clinical incidents which occur during any research study should be recorded and monitored because they can indicate when things are going wrong; for example when the safety profile of an investigational product has changed, or when a study protocol or procedure may be causing harm. It is therefore important that we know when an event or incident is serious, unexpected, occurring at an unexpected frequency or an escalation of events; and when an event may be caused by a research intervention, investigation, procedure, or due to the study design. This information will help us to make decisions and take action where necessary to mitigate any risk to our research participants and our patients.

The Medicines for Human Use (Clinical Trials) Regulations 2004 in conjunction with the Amendment Regulations [(1)] (collectively referred to hereafter as "the Regulations") stipulates the reporting requirements for Clinical Trials of Investigational Medicinal Products (CTIMPS) and these are incorporated into this procedure. A serious breach of these regulations may constitute a breach in criminal law.

2. PURPOSE

The purpose of the document is to provide the Standard Operating Procedure (SOP) for investigators, when recording, assessing and reporting adverse events during clinical research at Portsmouth Hospitals NHS Trust, or for which Portsmouth Hospitals is responsible.

This SOP should be read in conjunction with the Trust's clinical research safety monitoring policy, (PHT/RDPOLICY/002) [(5)] and the Trust's Policy for the Management of Adverse Incidents and Near Misses [(6)]

3. SCOPE

This Standard Operating Procedure applies to:

- All clinical research activity conducted at Portsmouth Hospitals NHS Trust
- All clinical research activity for which PHT is responsible as Sponsor (including external sites),
- All clinical research for which the Trust has been delegated Pharmacovigilance monitoring responsibilities

Who should follow this SOP

All investigators and staff participating in research for which Portsmouth Hospitals are responsible, and those responsible persons outlined in *Section 5*.

The Trust recognises that some external sponsors, networks, funders and employers may require the use of their own SOPs for the good governance of research. In such cases it is the responsibility of

the Portsmouth Hospitals Trust user (including those individuals contracted to work on behalf of the Trust), to ensure that the external SOP does not conflict the SOP outlined below.

In the event of an infection outbreak, flu pandemic or major incident, the Trust recognises that it may not be possible to adhere to all aspects of this document. In such circumstances, staff should take advice from their manager and all possible action must be taken to maintain ongoing patient and staff safety

4. DEFINITIONS

Adverse Events (AE) can be any unfavourable and unintended sign (including abnormal lab results), symptom or disease temporally associated with a clinical research protocol [7]. **In CTIMPS**, The Regulations define an adverse event to be 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

Comment: An adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease in any subject in a clinical trial (including those in an untreated control group), whether or not considered related to the intervention investigational medicinal product

Adverse Incident (AI) is defined as an event or omission, which caused physical or psychological injury to a patient, visitor or staff member or any event of circumstances arising during NHS care that could have or did lead to unintended or unexpected harm, loss or damage.

Comment: An AI might be for example, a lack of essential or life saving equipment available in a research setting during an interventional clinical study

Adverse Reaction (AR) is any untoward and unintended response in a subject to an investigational medicinal product, which is related to any dose administered to that subject. Note: Any adverse event judged by either the reporting investigator or the sponsor as having reasonable causal relationship to an IMP qualifies as an AR as there is evidence or argument to suggest a causal relationship. All adverse reactions are adverse events**.**

Clinical Trial of an IMP (CTIMP) means any investigation in human subjects, other than a non-interventional trial, intended:

- To discover or verify the clinical, pharmacological or other pharmaco-dynamic effects of one or more medicinal products
- To identify any adverse reactions to one or more such products, or
- To study absorption, distribution, metabolism and excretion of one or more such products, with the objective of ascertaining the safety or efficacy of those products.

Investigational Medicinal Product (IMP) (CTIMPS Only) is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial including a medicinal product which has a marketing authorisation but is, for the purposes of the trial, being used or assembled (formulated or packaged) in a way different from the approved form or being used for an unapproved indication or when used to gain further information about an approved use.

Non-Investigational Medicinal Products (NIMP) applies to **CTIMPs ONLY.** NIMPS are medicinal products that are not the object of an investigation (i.e. other than the tested product, placebo or active comparator), which may be supplied to subjects participating in a clinical research study and used in accordance with the protocol. This might be, for example, medicinal products such as support/rescue medication given for preventative, diagnostic or therapeutic reasons and/or to ensure that adequate medical care is provided for the subject. These medicinal products do not fall within the definition of investigational medicinal products (IMPs) and are called non-investigational medicinal products (NIMPs) [8]

Non-CTIMP SUSAR* is defined as any Serious Adverse Event judged to be:

- Related to the administration of any intervention or any study procedure of interest to the study i.e. having a reasonable causal relationship to that procedure or intervention
- Unexpected, i.e. not listed in the protocol (or product information) as an expected occurrence for those specified procedures/intervention, and
- Unrelated to the administration of an IMP i.e., having no reasonable causal relationship to an IMP

**For Medical Device Trials this may be classified as an Unanticipated Serious Adverse Device Effect (USADE).*

Pharmacovigilence (drug safety) is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.

Serious Adverse Event (SAE): an adverse event, adverse reaction or unexpected adverse reaction that:

- results in death
- is life-threatening*****
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- Other - any other safety concern

Comment: Medical judgment should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important adverse events/reactions 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.

*****Life-threatening in the definition of a serious adverse event or serious adverse reaction 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.

SAE ALERT Notice: is a sticker to be inserted in the health record where SAE reporting is required by the Sponsor.

Suspected Serious Adverse Reaction (SSAR) is any Serious Adverse Reaction that is suspected(*possibly* or *probably*) to be related to an Investigational Medicinal Product

Suspected Unexpected Serious Adverse Reaction (SUSAR) is a Suspected Unexpected Serious Adverse Reaction.

Comment: All adverse events that are suspected to be related to an investigational medicinal product and are both unexpected and serious are considered to be SUSARs.

Source Documents are original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subjects files, and records kept at the pharmacy, at the laboratory and at medico-technical departments involved in the clinical research [4]

Unexpected Adverse Reaction is an adverse reaction the nature and severity of which is not consistent with the information about the IMP/product or procedure in question as set out:

- In the case of an IMP with a marketing authorisation, in the Summary of Product Characteristics (SPC) for that product
- In the case of other IMPs, in the investigator's brochure (IB) relating to the trial in question.
- In the case of non-CTIMP interventions or procedures, in the protocol or other reference documents

Comment: Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented adverse reactions constitute unexpected events

4.1. DEFINING STUDIES OF ADDITIONAL SAFETY RISK

- The Trust considers the following studies to be of a safety risk that is additional to normal patient care or routine practice, and therefore require detailed safety reporting procedures to be set out in the protocol or supporting documents:

  (a) All Clinical Trials of IMP (CTIMPs)*

  (b) All interventional studies of a novel procedure or device without/used outside of its CE mark, (including regulated Device trials*)

  (c) All studies, where the protocol procedures are considered to be of an additional safety risk to participants, compared with routine clinical practice. **For PHT sponsored studies** this will be judged by independent peer review or by the Research Governance Group. **For PHT hosted studies** this will be judged by the clinical team at site study set-up and captured during the site risk assessment.

- **In addition** the Trust will ensure safety reporting procedures are in place and followed for any study with specified safety objectives (this includes observational studies).

  **Means there is also a regulatory requirement to report SAEs*

5. RESPONSIBLE PERSONS

All Health Care Professionals are responsible for:

1. Reporting any Serious Adverse Event to the local research study team, when an SAE Alert Notice is inserted in the health record.

Investigators (and delegated persons) are responsible for:

All studies

1. Reporting all safety concerns, hazards and clinical incidents to the Trust in accordance with the procedures outlined in *Section 6* of this SOP

CTIMPS & Studies of Additional Safety Risk Only

Regulation 32 of the Clinical Trials Regulations (SI 2004/1031) sets out the following responsibilities (2-4) for the notification of adverse events to sponsors during CTIMP studies, and the Trust has agreed that the duties also apply to studies of additional safety risk

2. An investigator shall notify the sponsor of any SAE that occurs in a subject at a trial site immediately* *(unless covered by point 3 below)*. This immediate report may be made either orally or in writing as long as a detailed written report follows the immediate report.

3. The sponsor may specify in the protocol certain SAEs that an investigator does not have to notify immediately. The protocol should state how and when these events should be notified.

4. Other AEs identified in the protocol as critical to evaluation of the safety of the trial (i.e. notable events) should be notified to the sponsor in accordance with the requirements, including the time periods for notification, specified in the protocol.

In addition, investigators shall:

5. Report all SUSARS/ Non-CTIMP SUSARS or safety observations to the PHT Research Office, in accordance with the procedures outlined in *Section 6* of this SOP

6. Where SAES/SUSARS/Non-CTIMP SUSARS are required to be reported ensure the inclusion of an SAE Alert Notice in <u>all versions</u> of the Health Record for the SAE reporting period

7. Follow up of any adverse event until its conclusion.

8. Check for any adverse events at each contact with the research participants by specific questioning and examination.

9. Regularly review PAS to check whether additional/multiple hospital notes have been created for their research participants during the study, which may contain evidence of adverse event occurrence

Chief Investigators (CI's) of PHT Sponsored studies are additionally responsible for the following:
CTIMPS & Studies of Additional Safety Risk Only

- Ensuring that study personnel are suitably trained for the purposes of AE recording, assessment and reporting
- Supporting the Research Office in the assessment of all SAEs, SSARS, SUSARS and Non-CTIMP SUSARS
- Notifying participating sites of any SUSARs or Non-CTIMP SUSARS, which occur during the study; as well as any information which might adversely affect the safety of their patients.
- Ensuring that all Adverse Events and Reactions, which were recorded during the research study are subject to a statistical analysis; and that any subsequent conclusions are included in the study's final report, copied to the Research Office.
- Ensuring the timely submission of annual progress reports to the Research Office, REC and MHRA as appropriate.
- Ensuring the timely submission of annual Developmental Safety Update Reports (DSUR) for all Trust Sponsored CTIMPS
- Notifying the Research Office, (and the MHRA and REC as applicable), of any significant findings and recommendations made by an Independent Data Safety Monitoring Committee (DSMC), if not directly notified by the DSMC

The Research Department is responsible for:

- Ensuring that departmental mailboxes and fax machines designated to receive SAE reports are checked daily
- The timely recording and assessment of SAE forms reported to the Research Office.
- Activating the appropriate tracking procedure for the assessment and management of SAES, SSARs, SUSARs and Non-CTIMP SUSARS, including ensuring the timely expedited reporting of events to the MHRA and the REC as appropriate.
- Maintaining a database of all reported SAES/SSARs, SUSARs and Non-CTIMP SUSARS for central monitoring, providing safety reports to the Research Governance Group.
- Forming a study-specific DSMC where appropriate; coordinating transfer of safety data to the DSMC and convening meetings, for studies where PHT is the Sponsor.
- The review of all protocols at study set up to ensure appropriate safety reporting processes are in place prior to NHS Permissions.
- Suspending or withdrawing approval for a study if appropriate. This may happen (but is not limited to), where public health and safety is considered to be at risk or where the safety and well being of research subjects or staff are considered to be at risk.
- Providing SAE Alert templates to research staff who are involved in studies with SAE reporting requirements.
- Providing safety reports to the Research Governance Group.

6 PROCESS

Following an Adverse Event, Investigators should:

DOCUMENT

- Document the event in the participant's medical record if relevant to their clinical care

ASSESS SERIOUSNESS

- Assess event for Seriousness *(see Section 6.3)*

SERIOUS (SAE)

NOT SERIOUS (AE)

- Check study requirements for recording Adverse Events

If AE recording is required:

- Assess for causality and intensity
- Record assessment.
- If no form available from the Sponsor, PHT AE Form 1, AE Assessment Form may be used

RECORD & ASSESS

- Record SAE (consult protocol for specified method of recording)
- Assess for causality and intensity and clinical incident*; record assessment

REPORT TO SPONSOR?

CTIMP

Study of ADDITIONAL SAFETY RISK

OTHER STUDY

NB: If Sponsor is PHT report to PHT Research Office

- **YES report *all* Serious Events to the Sponsor Immediately** *(SSARS/ SUSARS/ Non-CTIMP SUSARS/ USADES & NIMP/IMP drug interactions)* **unless explicitly excluded** in the agreed protocol. If excluded from expedited reporting, still record SAE as per protocol instructions

- **No** unless SAE reporting is required by the protocol or the event is a safety concern

PHT Chief Investigators

- Enter AE into line listing or study AE database (to generate periodic reports and statistical analysis).

REPORT TO PHT Research OFFICE?

SUSAR?

Non-CTIMP SUSAR?

Safety Concern?

- **YES** report all local SUSARS to Research Office & any safety concerns

- **YES** report all local NON-CTIMP SUSARS to Research Office & any safety concerns

- **YES** report any clinical incident. Report all safety concerns to Research Officer.

- **PHT Chief Investigators** enter SAE data into lin -listing or study AE database (to generate periodic reports and statistical analysis)

Reporting to PHT Research Office

URGENT SAE REPORT
1st Floor Gloucester House
Queen Alexandra Hospital
Cosham, Hants
PO6 3LY

Tel: 023 9228 6236
Fax: 023 9228 6037

Email: research.office@porthosp.nhs.uk

Reports to PHT Research Office should be made using:

AE Form 2, SAE/SSAR/SUSAR Initial Report Form

CHECK RECEIPT

- If no acknowledgement from the Sponsor within **1 working day** contact them to check receipt.

FOLLOW-UP & REPORT

- Follow up the participants and submit a follow-up report (s) to the Sponsor in accordance with the protocol (if required). This is usually within 5 working days and until the SAE has resolved. Copy to the **PHT Research Office** for all SUSARS and Non-CTIMP SUSARS

- For PHT Sponsored studies, or where no form is available, use AE Form 3 – SAE/SSAR/SUSAR Follow-up Form each time new information becomes available until the SAE is resolved.

Pregnancy

- Pregnancy that occurs in a female CTIMP subject or in a partner of a male CTIMP subject should be notified to the Sponsor and the PHT Research Office, and followed-up. See *Section 6.3.2* for further guidance.

- Pregnancy that occurs in other interventional studies should be reported if required by the Protocol

Outcome is SAE?

*** Clinical Incidents**

- Adverse events and "near misses" that have implications for Trust policy and procedures or are a local safety concern should be reported via the Trust's incident reporting procedures

Outcome is SAE?

- **Report** as SAE/SSAR or **Safety Concern** to Sponsor. Also report to Research Office as above.

6.1 ASSESSING AN ADVERSE EVENT

- Adverse Events should be recorded where required by the research protocol. AE Form 1, AE Assessment Form is provided as a template to record assessments if no provision is made elsewhere, for example in the CRF

- All adverse events should be assessed by the investigator or delegated individual. For CTIMP studies this assessment should be made by a medically qualified individual.

- Although not required to perform rigorous statistical analysis of local adverse events, local investigators should be mindful to observe levels of intensity and expectedness and causality of events, in case the frequency of these events changes. A change in these assessments or a quality change in any clinical event deemed to be of clinical significance by the local investigator must be reported to the Sponsor immediately

Assessment Period

- Events should be identified from the time of a participant's enrolment into a study until the end of their participation, whether an IMP/Intervention has been administered to that subject or not (unless otherwise specified in the protocol).

- Enrolment is usually defined in the protocol as the point in time from which participant-related study procedures commence, including screening. Where Enrolment is not defined by the Sponsor in the protocol, investigators should use this definition

- End of Trial participation is usually defined in the protocol as a minimum period of 30 days. Where End of Trial is not defined by the Sponsor, investigators should use this minimum period

Assessment Criteria *(unless otherwise specified in the Research Protocol)*

- **Intensity**

The assessment of an event's intensity will be based upon the investigator's 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: The term severity is often used to describe the intensity (severity) of a specific event. This is not the same as 'seriousness', which is based on patient/event outcome or action criteria.

- **Causality**

The relationship between an adverse event and the study interventions, IMP or procedures, must be assessed and categorised as below. The assessment will be based upon the investigators clinical judgement to determine the relationship, considering alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors etc.

The Investigator should consult the protocol, Investigator Brochure, SmPC and any other product information which has been approved by the MHRA before making a final judgement that the event is one of the following:

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

- Unlikely to be related: Temporal relationship of the onset of the event, relative to administration of the product or procedure, 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 or procedure, 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 administration of the product or procedure, is reasonable and the event is more likely explained by the product/procedure than any other cause.

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

Note: Where an event is assessed as possibly, probably, or definitely related, the event is an adverse reaction.

- **Expectedness**

The expectedness of an adverse event shall be determined according to the reference documents as defined in the study protocol (e.g. investigator brochure or marketing information).

Adverse events should be considered unexpected if they add significant information on the specificity or severity of an event, which is expected.

- Expected: Event is previously identified and described in the protocol and/or reference documents e.g. Investigator Brochure, summary of product characteristics (SPC) for CTIMP studies.

- Unexpected: Event is not previously described in the protocol or reference documents.

- **Seriousness**

An event is considered serious if it meets one or more of the following criteria:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other - any other safety concern

Comment: Medical judgment should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important adverse events/reactions 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.

*****Life-threatening in the definition of a serious adverse event or serious adverse reaction 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.

- **Other Reportable Safety Issues**

Examples of other observable safety issues might include:

- An increase in the rate of occurrence of an expected serious adverse event or reaction
- A qualitative change of an expected serious adverse event or reaction that is judged to be clinically important
- Post-study unexpected, serious and related events/reactions that occur after the patient has completed a study and are reported by the investigator to the sponsor.
- Significant hazards to the subject population such as lack of efficacy of an investigational product 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 temporally halt of a trial for safety reasons and conducted with the same investigational products in another country by the same sponsor
- Recommendations of the Data Monitoring Committee, if any, where relevant for the safety

6.2 REPORTING SERIOUS ADVERSE EVENTS

- Reports should include as much information as is available to the investigator at the time, and make clear the investigator's assessment of intensity, causality and expectedness.

- If the investigator suspects the event to be a SUSAR this should be clearly identified on the report form

- If the investigator does not receive acknowledgement of the SAE report from the Sponsor by the next working day, the Investigator should contact the Sponsor immediately to confirm receipt

- Reports should be made in accordance with the Sponsor's instructions as specified in the study protocol or Sponsor SOP.

- Where there is no SAE reporting form provided by the Sponsor, Trust AE assessment and reporting forms 1-3 may be used.

- The Research Office will acknowledge all reports for Sponsored studies by noon the following working day. Acknowledgement will be sent to the fax machine or email address from which the initial notification was received, unless otherwise specified on the form.

Reporting to PHT Research Office

- Telephone notification may be made in the first instance but must always be followed up in writing

- All written initial notifications should be made on AE Form 2, SAE/SSAR/SUSAR Initial Report Form and submitted to the Trust's Research Office

- Follow up reports should be made using AE Form 3 – SAE/SSAR/SUSAR Follow-up Form

- All written notifications to the Trust Research Office should be marked:

  "Urgent - SAE Report" and made via:

  - Fax: 023 9228 6037
  - Email: research.office@porthosp.nhs.uk
  - Hand: Research Department, First Floor, Gloucester House, Queen Alexandra Hospital, Cosham, Hants. PO6 3LY

NB: The Research Office will acknowledge SAEs for PHT Sponsored studies only, within one working day of receipt.

6.3 REPORTING A PREGNANCY

- If an event is a pregnancy affecting a female CTIMP subject, or a pregnancy is reported in the partner of a male CTIMP subject during the course of a study, the Investigator must ensure follow-up and inform the Sponsor of the outcome of the pregnancy. It may also be necessary to monitor the development of the newborn for an appropriate period post delivery.

- A pregnancy should be initially reported to both the Sponsor and the Trust Research Office

- For **Trust Sponsored studies** investigators should make the report within 7 days of becoming aware of the pregnancy.

- If the pregnancy outcome meets the definition of an SAE/SSAR then the investigator should also follow SAE reporting procedures.

The following text is taken directly from the MRC/DH joint document, Work stream 6: Pharmacovigilence [(12)], and provides greater clarity

"Pregnancies that occur while a subject is on a clinical trial should be notified to the sponsor as specified in the protocol. The local investigator must also ensure that any pregnancy is followed-up until outcome. This follow-up ensures the detection of any congenital anomalies or birth defects that may occur when:

- *Females participating in trials become pregnant; or*
- *The female partners of males participating in trials become pregnant*

Any events (including congenital anomalies/birth defects) that meet the definition of a SAE/R would need to be notified in accordance with the Clinical Trials Regulations (see section 1.2 SAE/R definition and section 4). In addition, if evidence exists to suggest foetal exposure to a particular IMP may cause a longer term safety issue, (for example, learning difficulties caused by exposure to methotrexate), then the follow up period should be defined appropriately and these timeframes and any follow-up requirements, made clear in the protocol.

A congenital anomaly would only need to be expedited to competent authorities and ethics committees if it met the definition of a SUSAR or if the requirement to report specific safety information is specified in the protocol (usually if it was known that the IMP posed a specific risk).

If it was suspected that a pregnancy occurred due to a drug interaction that reduced the efficacy of hormonal contraception (resulted in a healthy pregnancy and baby), this would be a drug interaction of note that should be considered in all future trials. Such information would also be relevant to report in the annual safety report (DSUR) for that trial/IMP."

6.4 ANNUAL REPORTING REQUIREMENTS FOR PHT SPONSORED STUDIES

Annual Developmental Safety Update Reports (DSURS): *CTIMP Studies Only*

- In addition to the expedited reporting required for SUSARS, the Trust is required to submit annual safety reports to the MHRA and the Ethics Committee for any Sponsored CTIMP.
- For PHT Sponsored studies, this reporting responsibility is delegated to the Chief Investigator, with support from Research Office staff.
- DSURs should be provided at yearly intervals, by the Chief Investigator, throughout the study or on request.
- The annual reporting period is from the Development International Birth Date (DIBD) until the data lock point for that year. The report is due 60 days from the data lock point.
    - The Development International Birth Date (DIBD) is the date of the first MHRA CTA approval or, for trials with marketed products, the date of the first marketing authorisation granted in the EU.
    - The data lock point is the last day of the twelfth month from the DIBD.
    - All DSURS must be submitted to the MHRA and REC **no later than** 60 days after the data lock point.
- A calendar template is provided to aid the research team in remembering the DIBD and report due dates
- The aim of the annual safety report 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 annual safety report should take into account all new available safety information received during the reporting period.

The DSUR should include the following information:

- **Part 1:** Analysis of the subjects' safety in the concerned clinical trial(s) with an appraisal of its ongoing risk: benefit
- **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
- **Part 3:** An aggregate summary tabulation of suspected serious adverse reactions that occurred in the concerned trial(s)
- The Research Office holds a template for DSURS and Chief Investigators shall be reminded in advance of their submission due date. Chief Investigators should consult with the Research Facilitators at an early stage for support in the development of their return and must submit their completed reports to the research office a month before the submission date for review and approval. For further details please see

  http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/development-safety-update-report.html or the MHRA website [11]
- The DSUR should be signed by the person submitting the report and should be submitted in PDF to the MHRA and REC. All enclosures should be listed and referenced on the report.

- Evidence of sending and acknowledgement of receipt should always be kept in the TMF in order to evidence submission.

- Reports should be provided as electronic documents on disk and be sent to:

The MHRA:

Information Processing Unit
Area 6
Medicines & Healthcare products Regulatory Agency
151 Buckingham Palace Road
Victoria
London
SW1W 9SZ

The REC

- For the REC submission to the main REC, a standard cover sheet must also be submitted which is available from the National Research Ethics Service (NRES) website: http://www.nres.nhs.uk/

The PHT Research Office

- All submissions must be approved by the Research Department and copied to the Research Office *(details as above)*

Annual Progress Reports: *ALL PHT Sponsored Studies*

- Annual progress reports are required to be submitted to the REC and the Research Pffice for all sponsored studies. This is in addition to the annual safety report for CTIMP studies

- Responsibility for submission of annual progress reports is delegated to the Chief Investigator

- A progress report should be submitted to the REC which gave the favourable opinion (the 'main REC') 12 months after the date on which the favourable opinion was given. Annual progress reports should be submitted thereafter until the end of the study. As above, a calendar template is provided to aid the research team in remembering the DIBD and report due dates

- Reports should be submitted in accordance with guidance at http://www.nres.nhs.uk

- Evidence of receipt should be filed in the TMF in order to evidence submission

7 TRAINING REQUIREMENTS

- All research staff should be trained in this procedure. Evidence of training shall be required for PHT sponsored CTIMP studies and other high risk PHT Sponsored studies. Research staff involved in studies with SAE reporting requirements will be provided with SAE Alert templates by the Research Office at approval.

- The Research Dept will endeavour to notify staff of SOP developments that may be relevant to them. Updates on SOPs will feature in research bulletins and communications. It is the responsibility of all research active staff to ensure that they read the Issued updates that may be relevant to them.

- When a new SOP is authorised, or when an existing SOP is revised, self directed training must be carried out by all staff to which the SOP is relevant and this training documented in their training record. A study specific SOP training plan will be developed for investigators on high risk PHT Sponsored studies.

- Staff should take time to read and fully understand the SOP and relevant documents, ensuring that they are able to implement the SOP when required. If clarification is needed then the trainee should approach their line manager and the SOP Controller who will arrange additional training. All staff should complete their training prior to the published implementation date.

8 REFERENCES AND ASSOCIATED DOCUMENTATION

(1) The Medicines for Human Use (Clinical Trial) Regulations 2004 and the Medicines for Human Use (Clinical Trial) Amendment Regulations 2006, the Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006, the Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008, and the Medicines for Human Use (Miscellaneous Amendments) Regulations 2009.

(2) National Research Ethics Service *(Last accessed July 2012)* http://www.nres.nhs.uk/applications/after-ethical-review/safetyreports/

(3) Research Governance Framework for Health & Social Care, *Dept. Health*. 2005. *(Last accessed July 2012)* http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962

(4) ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 (R1), Key Requirements Affecting Clinical Trials in Europe, *Canary,* 2010

(5) PHT/RDPOLICY/002: Clinical Research Safety Monitoring Policy

(6) Policy for the Management of Adverse Incidents and Near Misses, *Portsmouth Hospitals NHS Trust.*

(7) MRC http://www.dt-toolkit.ac.uk/glossary.cfm?cit_id=0&startLetter=A

(8) Definition of IMPS and NIMPS. Vol., 10 Clinical Trials, Chapter V. European Commission. *(Last accessed July 2012)* *http://ec.europa.eu/health/files/pharmacos/docs/doc2006/07_2006/def_imp_2006_07_27_en.pdf*

(9) MRC/DH Joint Project Work stream 6: Pharmacovigilence, *Draft Updated July 2012* by T Symons (T Symons Associates Ltd)

(10) http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARsandASRs/index.htm *(Last accessed July 2012)*

(11) 'Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use CT-3 2011

9 VERSION HISTORY LOG

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of Significant Changes
1.0	31/01/2013	N/A
2.0	07/04/2016	Removal of references, addition of 'other' category for SAE, additional information regarding SOP training added and minor typographic changes

10 APPENDICES

10.1 SAE Alert Notice (Template):

SAE ALERT NOTICE

PLEASE REPORT ANY ADVERSE EVENT THAT IS SERIOUS (SAE) TO THE LOCAL STUDY TEAM IMMEDIATELY

An SAE is ANY Untoward Medical Occurrence that either:

- Results in death
- Is Life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other medically significant events

End of SAE reporting date:

10.2 Training Record

Portsmouth Hospitals NHS
NHS Trust

CONFIRMATION OF SOP TRAINING RECORD

A copy of this record may be kept in your personal training file to confirm your training in a specific SOP. The research department or your line manager may request copies to verify your training. If required by a study Sponsor a record may also need to be kept in the Trial Master Files (TMF) or Investigator Site Files (ISF).

SOP Details: To be completed by the SOP Controller	
Title of SOP	For Investigators - Recording, Assessing & Reporting Adverse Events in Clinical Research
Reference Number	PHT/RDSOP/007
Version	v2.0 07 Apr 2016
Issue Date	07 April 2016
Implementation Date	07 April 2016

Personnel Details	
Name	
Job Title & Research Role	
Date of Training	
Nature of Training	Self Directed/Delivered by etc
Records of any meetings to clarify details in SOP	

Signatures
I confirm that I have read and consider myself to be sufficiently trained in the above Standard Operating Procedure with regards to my individual roles and responsibilities Signature of Trainee …… Date …….
I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities Signature of Trainer …… Date …….

Additional Notes & Signatures
Signature of Trainer (where appropriate) I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities Signature of Trainer …… Date ……..