MRC Clinical Trials Unit

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SAFETY REPORTING

VERSION 9.0

APPROVALS

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UPLOAD TO SOPBOX

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The effective date of this SOP is the day on which it is uploaded to SOPbox and is available to use. This is the date associated with the signature of the SOPbox Administrator.

For the Revision History please see the Version History Summary in SOPbox.

STANDARD OPERATING PROCEDURE TITLE

TABLE OF CONTENTS

The following symbols may be used in this SOP:

 Indicates a link to a related document

 Indicates instructions to document trial-specific processes elsewhere

Throughout this document the MRC Clinical Trials Unit at UCL, will either be referred to as 'MRC CTU at UCL' or 'the unit'. In instances where neither read well in the sentence, 'the CTU' may be used.

1 BACKGROUND AND RATIONALE

It is essential that all Adverse Events (AEs) which occur during a study are appropriately recorded and reported in order to ensure the continuing safety of study participants.

This SOP covers how to comply with the current European legislation and Good Clinical Practice in the recording and processing of Serious Adverse Events in trials where the MRC CTU is responsible for safety management.

1.1 DEFINITIONS

TERM	DEFINITION
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Reference Safety Information (RSI) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any 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 ▪ Is another important medical condition***

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation.

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or 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; for example, a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug dependency.

2 PURPOSE

This SOP describes the steps in the process for recording, managing and reporting Serious Adverse Events for Clinical Trials of Investigational Medicinal Products (CTIMPs), where MRC CTU at UCL are responsible for any aspect of safety management. For non-CTIMPs, the SOP will serve as guidance on elements which need to be considered, however, they may not all apply.

A trial-specific Safety Management Plan (SMP) will document the safety management procedures for both IMP and non-CTIMP trials.

The nature and extent of safety management processes employed in a trial will be dependent on the nature of the trial and the level of risk involved. This is assessed at a high level at the trial design stage and aspects of the protocol are designed accordingly. Risks are subsequently assessed in more detail via a formal risk assessment during which issues regarding safety will be identified.

Please refer to MRC_CTU_SOP_059_Risk Assessment

Following identification of risks, each trial will complete a Pharmacovigilance Checklist (PV checklist) in which each aspect of safety management will be considered and responsibilities will be assigned.

This SOP should be used as the basis for the trial-specific procedures covering the handling of Serious Adverse Events. The timelines and the requirements for reporting in non-EU countries may differ and will be documented in the trial safety management plan.

Where another party has some responsibility for safety reporting (e.g. a pharmaceutical company has responsibility for reporting to the Competent Authorities (CAs)) the roles should be clearly delegated in the trial agreement/contract and in any documented trial delegation of responsibilities.

This SOP covers the systems in place in the MRC CTU at UCL to record Serious Adverse Events once the trial is open to recruitment. The trial Safety Management Plan based on this SOP should be in place before recruitment starts and will be reviewed by the appropriate Trial Management Group (TMG) members and by the CTU Quality Management Advisory Group (QMAG)

All trials will also have an ongoing review of safety, based on factors such as; new data from other trials or from industry or when a significant amendment is being made to the trial; this should be done as a minimum as part of the process of preparing annual safety reports and should be described in the Safety Management Plan (SMP).

3 RESPONSIBILITY AND ROLES

The following table lists the roles relevant to this SOP and a brief description of their responsibilities.

This SOP will be circulated for Read and Understand to all appropriate roles identified in the training matrix.

ROLE	RESPONSIBILITIES
Sponsor	• Overall responsibility for safety management
Chief Investigator (CI)	• Maintains oversight of safety management processes and documentation, including information in the protocol • Review of accumulating safety information (may be delegated to a clinical reviewer) • Input into, review and sign off of periodic safety reports
Trial Manager (TM) /Data Manager (DM)	• Production and maintenance of SMP, PV checklist and other safety management tools • Coordination of the production of periodic safety reports • Processing of safety data and onward reporting to Competent Authorities and Ethics Committees when required • Ensuring appropriate training for sites on safety management processes is in place.
Clinical Project Manager (CPM) /Project Lead (PL)	• Review and sign off of SMP and PV checklist • Ensuring appropriate staffing resource is in place to cover all safety management tasks • Review and sign off of periodic safety reports
Clinical Reviewer	• Review of incoming Serious Adverse Events (SAEs) • Review of SMP and PV checklist • Review and/or production of periodic safety reports
Statistician	• Inputs into preparation of safety data for review by IDMC and any other applicable oversight committee • Inputs into production of the periodic safety reports
Independent Data Monitoring Committee (IDMC)	• Review of accumulating safety data (both internal and external to the trial) • Advise the Trial Steering Committee (TSC) of any safety concerns

4 PROCEDURES

4.1 TRAINING

All those involved in safety management processes must be appropriately trained to do so. All training, including safety management training, must be documented in individual training folders. For anyone involved in these processes who are not MRC CTU staff member e.g. external clinical reviewers; documentation of their training should be discussed within the trial team and a copy of their training record covering the points below should be held in the TMF.

4.1.1 CLINICAL REVIEWER

The designated clinical reviewer must have completed the following training:

- Good Clinical Practice
- Read and understand the study protocol
- Read and understand this SOP
- Read and understand MRC_CTU_SOP_085_Clinical Input
- Read and understand MRC_CTU_SOP_086_Reference Safety Information
- Read and understand MRC CTU SOP_092_DSUR Production
- Read and understand the study SMP and PV checklist
- Read and understand appropriate IB and SmpC for trial IMP

The above listed training must be completed and documented before any of the Clinical Reviewer activities are undertaken

4.1.2 MRC CTU AT UCL TRIAL MANAGEMENT TEAM (TMT)

All members of the TMT involved in safety management must have undertaken the following training, this should be documented in individual training folders:

- Good Clinical Practice
- Read and understand the study protocol
- Read and understand all unit SOPs relevant to their role
- Read and understand the study SMP and PV checklist
- Attended the MRC CTU at UCL safety management training course (when available)

With the exception of attendance at the safety management training course, the above listed training must be completed and documented before any of the activities described in Section 3 of this SOP are undertaken.

4.1.3 INVESTIGATORS AND SITE STAFF

All relevant site staff i.e. those involved in safety reporting must be trained on the specific safety management procedures for the trial.

Please refer to MRC_CTU_SOP_006_Site Evaluation and Training

4.2 CLINICAL SITE RESPONSIBILITIES

SAE forms are completed by the Investigator responsible for the patient's care and in trials taking place within the European Union should be reported to the MRC CTU within 24 hours of the

Investigator becoming aware of the event. In trials outside of the European Union, Investigators may report SAEs within one working day of them becoming aware of the event. If the Investigator is not available then the form may be completed by another member of staff on the delegation log, delegated to assess and report SAEs, however this should be signed off by the Investigator as soon as possible.

4.2.1 CAUSALITY

The Investigator gives the reason why the event qualifies as an SAE and assesses the causality. Trials should consider the option of asking Investigators to give a rationale for their assessment of causality as this may assist with consistency of reporting. The Clinical Reviewer may discuss the assessment of causality with the Investigator, but the opinion of the Investigator on this cannot be overruled.

When discussing the causality assessment with the Investigator, the Clinical Reviewer must ensure that no attempt is made to influence that assessment. Therefore, the reviewer may ask for a rationale for or further information on the Investigator assessment, but they should not indicate that they disagree with this assessment.

It should be noted that if at the time of receipt of an SAE, the investigator assessment of causality is missing, the event should be assumed to be possibly related to the IMP(s) and handled accordingly, until data is received to indicate otherwise.

In the case of an SAE, the patient must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. An SAE may result in ongoing sequelae for the patient. Once this is stable and if further information is unlikely to change the interpretation of the event, then the clinical reviewer in discussion with the Investigator may determine the event has stabilised such that no further information is required the outcome of such discussions should be documented in the SAE narrative. . Follow-up may continue after completion of protocol treatment if necessary, e.g. in instances of development of a chronic condition such as diabetes, and this procedure will be documented in the trial safety management plan.

4.3 MRC CTU AT UCL RESPONSIBILITIES

4.3.1 RECEIPT OF SAES

SAEs are received at the MRC CTU at UCL in a designated electronic mailbox or directly via the study database, for each study. It is the responsibility of the TM or other TMT delegate to ensure that a procedure is in place whereby mailboxes/databases are checked regularly and SAEs are delivered personally to the appropriate TM/DM.

Each trial team will have documented backup procedures in place for safety reporting for when members of the TMT are not available.

The TM/DM will check that the SAE form has been sufficiently completed and query any missing information with the site by telephone or email if necessary. Refer to section 4.5.4 below for the list of minimum criteria that are required for onward reporting of events.

The TM/DM then forwards the SAE form for clinical review within the appropriate timelines (see below). Electronic transfer of SAEs for clinical review must be done via a secure data transfer method.

If the Clinical Reviewer is an MRC CTU staff member than they should be directed to access the SAE form from its saved network location. The procedure to notify the Clinical Reviewer that there is a saved SAE pending review should be documented in the SMP.

Refer to MRC_CTU_SOP_058_Management of Participant Personal Data

Receipt of the SAE form must be logged outside of the main database and its progress tracked on an SAE tracking log with an SAE event number (or other unique identifiers). The date of receipt of the SAE must be logged on this tracker. The initial date of receipt should be considered as 'day 0' when assessing onward reporting time frames even if data that is pertinent to classifying the event is not available at that point.

An SAE tracking log will be prepared for each trial by the TM and DM.

The information from the SAE should be entered into the study database in accordance with the timelines documented in the safety management plan. This should be done as soon as possible and updated with further information on SAE and its outcome as it is received.

4.3.2 IMMEDIATE REVIEW

The review procedure, documented in the PV checklist, should specify which of the following types of events should be sent for immediate review i.e. ideally within 1 working day, by the Clinical Reviewer(s), these may for example include:

- SARs (i.e. All SAEs that are possibly, probably or definitely related to trial therapy); or
- SAEs that have been described as fatal or life-threatening regardless of relatedness or expectedness; or
- Any SAE which, although it might not have been reported as a SUSAR, the TMT are concerned about. Examples of such events that may be of particular concern in a trial should be documented in the SMP

4.3.3 DEFERRED REVIEW

All other SAE reports are sent for clinical review at a frequency determined by factors such as the number and type of SAEs and the risk of the trial, this should be documented in the PV checklist and Safety Management Plan. Follow-up SAE forms received for each event with significant additional information are also sent for review until the event has been resolved (or resolved with sequelae) or stabilised.

4.3.4 DESCRIPTION OF EVENT

During the review process, either immediate or deferred, every effort should be made to ensure that the site provides a clear and accurate event term describing ultimately the diagnosis of the event rather than a symptom. This clarity on the event term should be sought in real time as far as possible in order to ensure that the event can be appropriately classified and reported as needed.

4.3.5 EXPECTEDNESS

In most trials, the expectedness of the event in relation to the patient's trial therapy will be assessed by the Clinical Reviewer, although in some cases the initial assessment of this may be delegated to the Investigator. The Clinical Reviewer on behalf of the Sponsor retains the overall responsibility for the expectedness assessment and cannot be overruled by the Investigator.

The expectedness of the event, in a CTIMP is assessed against the approved Reference Safety Information (RSI) for that product. For further information refer to section 4.4 of this SOP
An event may also be considered unexpected if the severity, duration or frequency of the undesirable effect is worse than specified in the SmPC or the IB.

4.3.6 POST REVIEW

After SAEs have been clinically reviewed any SUSARs identified/confirmed should be reported to the appropriate RECs and CAs.

Any queries or further information required should be discussed with the site; the event may be re-reviewed if significant additional information is received.

4.3.7 FOLLOW UP OF SAES

The TM should review the status of any ongoing SAEs on a regular basis to ensure all SAEs are followed up until resolution. The frequency of this review of the status of ongoing SAEs should be documented in the Safety Management Plan.

4.4 REFERENCE SAFETY INFORMATION (RSI)

The reference safety information in a trial is the documented known safety information about the IMPs in the trial. This information is described in a section of either the SmPC or IB and is approved by the CAs for use as a reference against which the expectedness of adverse reactions can be assessed.

The specific RSI(s) in place for the trial should be documented in the SMP and PV checklist. If Investigators are being asked to assess expectedness then the SMP should describe how the correct approved RSI is provided to Investigators to enable them to do this. The SMP should also describe how the Clinical Reviewer should check and confirm the Investigator assessment and how they can overrule this assessment if necessary.

If the approved reference safety information is updated during the course of the trial, teams must ensure that they have an appropriate mechanism is place to monitor for and review the impact of any updates to the relevant reference safety information for the product(s) used in their trial. The frequency of this review must be documented in the PV checklist and safety management plan and must occur on at least an annual basis.

Refer to MRC_CTU_SOP_086 Reference Safety Information

Changes to the reference safety information are considered as substantial amendments and must be submitted to the relevant RECs and CAs accordingly.

Refer to MRC_CTU_SOP_001_Protocol Development and Amendment

4.5 REPORTING REQUIREMENTS

4.5.1 EXPEDITED REPORTING OF SUSARS BY THE SPONSOR

Once a SUSAR has been identified it must be reported to the CAs and RECs in the countries where the trial is being conducted.

A fatal or life-threatening SUSAR is considered a **7-day SUSAR** - i.e. the event must be reported to the CA and REC as soon as possible but no later than 7 calendar days after the MRC CTU at UCL has first knowledge of the minimum criteria for expedited reporting (see section 4.5.4) i.e. the date of receipt of the event including this minimum information = day 0 for reporting timelines. Relevant follow-up information should be sought as appropriate and should be communicated to the CA and REC within an additional 8 calendar days.

Any other type of SUSAR is considered a **15-day SUSAR** - i.e. the event must be reported to the CAs and RECs as soon as possible but no later than 15 calendar days after the MRC CTU has first knowledge of the minimum criteria for expedited reporting i.e. the date of receipt of the event including this minimum information = day 0 for reporting timelines. Further relevant follow-up information should be given as soon as possible.

4.5.2 REPORTING SUSARS TO COMPETENT AUTHORITIES

Any SUSAR for which the MRC CTU has reporting responsibility in the UK, must be entered by a member of the TMT onto the MHRA eSUSAR database.

The TMT must ensure that the SUSAR is also reported to the CAs in the countries in which the trial is being conducted in accordance with local requirements. For trials taking place in countries in which SUSARs are reported to CAs via the Eudravigilance database (EVWEB) i.e. non-UK countries within the European Economic Area, then the SUSAR must also be added onto this database.(contact the unit safety group for information on this process).

4.5.3 REPORTING SUSARS TO ETHICS COMMITTEES

SUSARs affecting UK patients must be reported via secure email (password protected or Galaxkey) to the main REC within the 7/15 day timelines.

The TMT must ensure that the SUSAR is also reported to RECs in countries in which the trial is being conducted in accordance with local requirements.

4.5.4 MINIMUM CRITERIA FOR INITIAL REPORTING OF SUSARS

Information on the final description and evaluation for a SUSAR report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports are submitted within the time limits as soon as the minimum following criteria are met:

- a suspected reaction to an investigational medicinal product
- an identifiable subject (e.g. trial number)
- an identifiable reporting source (with contact details of both the investigator and the person reporting for the sponsor)

- a unique SAE event number
- the trial Eudract number (or in the case of non-European community trials the sponsor's trial protocol code number)

4.5.5 Other Expedited Reporting to REC/CA

Any finding considered significant and reportable by the IDMC or equivalent body established for the trial should also be evaluated for reporting to the appropriate RECs and CAs.

The European Commission guidance recommends that expedited reports on the following occurrences should also be sent to the CAs according to the same timelines as SUSARs:

- single case reports of an expected serious adverse reaction with an unexpected outcome (e.g. death);
- an increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important;
- post-study SUSARs that occur after the patient has completed a trial;
- a new event, related to the conduct of the trial or the development of the investigational medicinal product (IMP), that is likely to affect the safety of subjects, such as:
    - a serious adverse event 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 (e.g. carcinogenicity) from a newly completed animal study.

Any finding considered significant and reportable by the IDMC or equivalent body established for the trial should also be evaluated for expedited reporting.

In some settings e.g. trials outside of the EU, there are additional expedited reporting requirements to CAs and RECs. These should be documented in the SMP.

Each trial team will have a documented trial SMP in place for the reporting requirements which are applicable to their trial or study; this should also document how the events above could be detected e.g. by review of events at TMG/TMT meetings and from IDMC reports.

4.5.6 Expedited Reporting of SAEs in non-CTIMP Studies

An SAE in a research participant in a non-CTIMP study should be reported to the Research Ethics Committee that gave a favourable opinion of the study (the 'main REC') where in the opinion of the Investigator or Clinical Reviewer 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 Sponsor or delegate becoming aware of the event, using the UK Health Research Authority (HRA) report of serious adverse event form, signed by the Chief Investigator.

4.5.7 UNBLINDING OF TREATMENT ALLOCATION FOR SUSAR REPORTING

In a blinded trial, investigators should be advised to assess AEs on the assumption that the patient is receiving the active product. When a suspected SUSAR is received in a blinded trial the treatment allocation will need to be unblinded as only events in which the patient has received the active product are subject to expedited reporting requirements.

To ensure the TMG are not unblinded, if the patient is on blinded treatment, the TM should pass the completed SAE report to the statistician, deputy, programmer or member of a different trial team, as named in the trial-specific unblinding procedure, for action.

General information in regard to unblinding should be provided to investigators within the protocol.

Refer to MRC_CTU_SOP_028_Blinded Trials

4.5.8 EXEMPTION OF EVENTS FROM EXPEDITED REPORTING

It is acceptable for some events that meet the definition of an SAE to be exempted from the expedited reporting requirements e.g. usually where such events are also reported as trial end-points such as disease progression or death. The decision to exempt events from expedited reported must be documented in the trial protocol.

Refer to MRC CTU Protocol Template

Events that are exempted from expedited reporting that meet the criteria of serious are still SAEs and still form part of the overall safety information for the trial, they must therefore be recorded in other ways e.g. on a follow-up CRF. They must be included in any review by the IDMC and accounted for in any periodic reports such as the Development Safety Update Report (DSUR). The process for capturing and reporting these events should be documented in the SMP.

4.6 SAFETY REPORTS TO INVESTIGATORS

Investigators should be informed of any SUSAR that occurs in the trial. The TMG should determine how frequently and in what format to send SUSAR information to the investigators involved in the trial. For example, summary SUSAR information may be sent to all investigators in real time as each event occurs; alternatively the TMT may produce a summary line-listing of SUSARs that is provided to investigators at specified intervals. This process should be documented in the PV checklist and safety management plan but may change throughout the trial if new safety issues arise.

If a significant safety concern is identified in the trial or from another source e.g. another trial using the same IMP, investigators should be informed as soon as possible.

4.7 PERIODIC REPORTING

4.7.1 ANNUAL SAFETY REPORTS

An annual report on all safety information is sent to all relevant CAs and REC once a year within 60 days of the anniversary of the CTA approval date, unless an alternative reporting date is agreed. In trials that are conducted in more than one country in the EU, the ASR should be submitted to each

member state where the trial is taking place. It should be done on the anniversary of the 1st member state CA approval.

For trials taking places in ICH regions i.e. EU, USA and Japan, ASRs are required to be in the format of a Development Safety Update Report (DSUR). Detailed guidance and a template report on completion of the DSUR are available within SOPbox.

Refer to MRC_CTU_SOP_092 - Development Safety Update Report

ASR formats in non-ICH regions are country specific, trial teams should be aware of the requirements in the region in which their trial is taking place.

4.7.2 PERIODIC SAFETY REPORTS TO ETHICS COMMITTEES

For CTIMPs taking place in the UK, copies of all safety information, including the annual DSUR supplied to MHRA must also be sent to the main REC. For non-CTIMPs there is no requirement for annual safety reports in addition to the information provided through the annual progress report. The periodic safety reporting requirements to ethics committees outside of the UK are country specific and should be documented in the trial specific SMP.

4.8 INTERNAL SAFETY REPORTING

4.8.1 TRIAL MANAGEMENT GROUP

A summary of SAEs received should be reviewed at TMG meetings, or more frequently in between meetings if deemed appropriate. The detail of what is to be included in this summary should be documented in the SMP. In addition, the TMG should be informed of any safety concerns or issues with participating sites' reporting of SAEs. When reporting safety information to the TMG, consideration should be given for any need to ensure that some members remain blinded to this data.

4.8.2 INDEPENDENT DATA MONITORING COMMITTEE

The trial-specific IDMC report and the IDMC charter will determine the detail required for their review of AEs, and the requirements may change during the course of the trial.

4.8.3 COLLABORATORS

Depending on the nature of any collaboration safety data may be required to be reported to the collaborators involved in the trial. This will be specified in the contract with the collaborator which will be agreed by the PL and/or CPM and an MRC CTU at UCL Contracts Manager.

4.9 CODING OF EVENTS

SAEs are reported giving the name of the main event which has been classified as an SAE and any associated symptoms. The event terms reported by the investigator must then subsequently classified using a standardised coding system. The coding system required for SUSAR reporting is MedDRA and therefore all SARS must be coded to MedDRA terms as a minimum. Trials may choose to perform additional coding using systems such as CTCAE or DAIDS if deemed appropriate and required for analysis.

Coding should be performed in real-time at the time of clinical review, if required sites will be asked for further information and clarifications in order to determine the appropriate code.

Coding can be performed by any appropriately trained member of the TMT but must be reviewed by a medically qualified person and this responsibility documented in the PV checklist. The coding process i.e. when it will be done, by whom and using what systems should be documented in detail in the safety management plan.

4.10 OTHER SAFETY ISSUES

4.10.1 URGENT SAFETY MEASURES

An urgent safety measure is defined as a change to trial protocol that can be implemented immediately without the usual required approvals in order to ensure the safety of trial participants. E.g. if new information becomes available that an IMP is no longer safe at a particular dose, then all participants should immediately change their dose to a safe level, without waiting for such a change to be approved in a protocol substantial amendment.

Refer to MRC CTU_SOP_062_Urgent Safety Measures for details on how to implement, document and report an urgent safety measure.

4.10.2 PREGNANCY

Pregnancies that occur in female participants whilst taking an IMP should be reported as notable events i.e. within the same timelines as an SAE. The decision about whether to collect information on pregnancies and pregnancy outcome in the partners of male patients exposed to an IMP should be based on risk assessment and documented in the PV checklist. The occurrence of a pregnancy should be followed up until its outcome. If a pregnancy results in a child born with any congenital abnormality then this would require reporting as an SAE.

Refer to MRC CTU_WI_0030_Pregnancy Reporting

5 RELATED DOCUMENTS

For further information on this topic, see also:

MRC_CTU_WI_0029_2.0_eSUSAR WI
MRC_CTU_WI_0030_1.0_Pregnancy Reporting
MRC_CTU_WI_0031_2.0_Safety Management Plan
MRC_CTU_TT_0165_2.0_Pharmacovigilance Checklist
MRC CTU_SOP_062_Urgent Safety Measures
MRC_CTU_SOP_085 Clinical Input
MRC_CTU_SOP_086 Reference Safety Information
MRC_CTU_SOP_092 DSUR Production

6 APPENDICES

6.1 REFERENCES

EU regulations
The EU Clinical Trials Directive (2001/20/EC) 4th April 2001
EU Directive 2005/28/EC (the Good Clinical Practice (GCP) Directive)

Further EU guidance
ENTR/CT3: Guidance notes on the collection, verification and presentation of adverse reaction reports, Revision 2: April 2006
Volume 10 - Communication from the Commission - 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/C 172/01)

September 2010
EMA/CHMP/ICH/309348/2008
Committee for medicinal products for human use (CHMP)
ICH guideline E2F
Note for guidance on development safety update reports
Step 4

UK legislation
The Medicines for Human Use (Clinical Trials) Regulations 2004/1031: 1st May 2004.
The Medicines for Human Use (Clinical Trials) Amendment Regulations (SI 2006/1928): 29 August 2006.

http://www.hra.nhs.uk/news/dictionary/nres/