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Safety Reporting in Clinical Trials of Investigational Medicinal Products (CTIMPs)
Standard Operating Procedure

Introduction and Aim

The reporting of safety events is one of the most important aspects of clinical trial management. The Medicines for Human Use (Clinical Trials) Regulations (2004) and subsequent Amendment Regulations apply to the conduct of Clinical Trials involving Investigational Medicinal Products (CTIMPs) and specify safety reporting requirements. To breach these requirements constitutes a breach in criminal law. In accordance with the UK Policy Framework for Health and Social Care Research, and the Clinical Trials Regulations, all organisations who sponsor clinical research must have systems in place to record and report research related adverse events, and provide regular safety updates to the relevant authorities.

This procedure aims to provide clear information and signposting, for individuals and research teams, in safety recording and reporting, including managing adverse events which arise during the course of a UHB Sponsored or Hosted CTIMPs to ensure appropriate safety data is reported accordingly and to ensure patient safety.

Objectives

- To provide guidance and signposting by which safety events arising in CTIMPs are assessed, recorded and reported according to the requirements of the UK Policy Framework for Health and Social Care Research and the Clinical Trials Regulations.

- To ensure that all members of the research team with responsibility for pharmacovigilance or safety reporting are aware of their responsibilities in reporting any research-related adverse events to the appropriate bodies, and are directed to the appropriate reference documents in order to comply with their responsibilities.

Scope

This procedure applies to all individuals undertaking or involved in UHB Sponsored or Hosted CTIMPs, including both commercially Sponsored or non-commercially Sponsored CTIMPs, within the UHB where the individual has any responsibility for safety recording and reporting, including adverse events. This includes those individuals:

- holding substantive or honorary contracts/titles with the UHB;
- holding ‘letters of access’ to UHB;
- undertaking clinical research involving UHB patients or staff;
- undertaking clinical research on UHB premises

For guidance on safety reporting in research studies other than CTIMPS (non-CTIMPs) please refer to the Information Sheet Adverse Event and Serious Adverse Event reporting requirements for non CTIMPs (ISR-RG-003).

Equality Health Impact Assessment	An Equality Impact Assessment has been completed on the Research Governance Policy (UHB 099) under which this SOP sits. The Equality Impact Assessment completed for the policy found there to be a no impact.
Documents to read alongside this Procedure	Medicines for Human Use (Clinical Trials) Regulations 2004 and associated Amendments. UK policy framework for health and social care research 2017 Research Governance Policy (UHB 099) Research Audit SOP (UHB 236) Applying for Cardiff and Vale University Health Board Sponsorship SOP (UHB 453) Managing Breaches Of Good Clinical Practice Or The Study Protocol SOP (UHB 235) Reporting Requirements for Cardiff and Vale Health Board Sponsored Research SOP (UHB 406) SAE/SAR/SUSAR Initial Report Form (FR-RG-014)
Approved by	Research Governance Group

Accountable Executive or Clinical Board Director	Medical Director
Author(s)	Research Governance Manager

Disclaimer

If the review date of this document has passed please ensure that the version you are using is the most up to date either by contacting the document author or the Governance Directorate.

Summary of reviews/amendments

Version Number	Date of Review Approved	Date Published	Summary of Amendments
1	22/01/15	10/04/15	This is a new SOP which replaces *Reporting Research-Related Adverse Events for Cardiff and Vale UHB Sponsored Clinical Trials of Investigational; Medicinal Products (UHB 180)*

			and *Reporting Research-Related Adverse Events in Externally Sponsored Clinical Trials of Investigational; Medicinal Products Hosted by UHB (UHB 181)* and encompasses other Safety Reporting Requirements in Clinical Trials of Investigational; Medicinal Products.
2	24/04/18	03/07/18	Updated to: • includes reference to forthcoming Legislation • remove reference to Cardiff University Clinical Trials procedures • includes clarifications regarding the reporting of incidents in research and potential serious breaches • includes reference to the UK policy framework for health and social care research • includes information in relation to the MHRA safety reporting update December 2017
3	28/04/21	21/06/2021	Reviewed and amended to reflect and signpost to updated information on: Clinical Trials legislation Post Brexit MHRA reporting procedures and systems. Removal of outdated information Clarifications.

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1.0 ABBREVIATIONS AND DEFINITIONS

1.1 Please read **Appendices A** and **B** alongside this document, as technical terms and abbreviations to reflect the language used in the Medicines for Human Use (Clinical Trials) Regulations 2004, and associated amendments (Clinical Trials Regulations) and the supporting EU guidance documents are used throughout.

Note – in the UK, The Competent Authority is The Medicines and Healthcare products Regulatory Agency (MHRA). For the purpose of this SOP, the acronym MHRA will be used. However, for International, multicentre trials, this would also mean the relevant Competent Authority in each country, as defined in the trial protocol.

2.0 ROLES AND RESPONSIBILITIES

2.1 GENERAL

The key points relating to safety reporting and responsibilities are included in Part 5 of The Medicines for Human Use (Clinical Trials) Regulations 2004: SI 2004/1031 (Clinical Trials Regulations) and in

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')

The Clinical Trials Regulations were due to be replaced by the delayed EU Clinical Trials Regulation 536/2014. However, this EU Regulation has not come into force and following Brexit, The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations amend the Medicines for Human Use (Clinical Trials) Regulations 2004 to enable the MHRA to operate as a regulator outside the EU.

All reference to The Clinical Trials Regulations in this document should be taken to mean The Medicines for Human Use (Clinical Trials) Regulations 2004 and associated amendments.

The MHRA has published new guidance for clinical trials, for organisations to follow. Some of the roles in safety reporting may be delegated between the Sponsor, Chief Investigator (CI), Principal Investigator (PI), Co-Investigator, Clinical Trials Unit (CTU), Safety Monitoring Committee (SMC) and other members of the research team. These delegated responsibilities should be documented in the Clinical Trial Agreement(s) and the Study Delegation Log (SDL). They should be managed in line with the reporting requirements of the Sponsor of the Clinical Trial.

All appropriate documentation, including the Investigator Brochure (IB), simplified IMP Dossier (IMPD) or Summary of Product Characteristics (SmPC) should be used as a reference by the CI/PI, any Trial Steering Committee (TSC), Data Monitoring Committee (DMC) and/or Sponsor's representative when reviewing Adverse Events (AEs) in order to assess the expectedness and causality of any given event.

2.2 SAFETY REPORTING AND PRE-TRIAL PLANNING

Before initiating a clinical trial, the Sponsor should give careful consideration to the following points:

- The specific requirements for recording and notifying adverse events in the trial;
- Which events should be recorded and where; and

- Which events should be notified to the Sponsor/REC/MHRA and the timelines for notification

In order to make these decisions, the Sponsor should carry out an assessment of the risk associated with the clinical trial.

Risk to clinical trials subjects will vary, dependant on what is already known about the IMP and the risks of the extra interventions undertaken.

The CI should initiate early discussions regarding any potential Cardiff and Vale UHB Sponsored CTIMPs, which should subsequently be submitted for sponsor review in order to assess the risk. Please refer to Standard Operating Procedure, UHB 453 Applying for Cardiff and Vale University Health Board Sponsorship

There will be involvement of a Clinical Trials Unit (CTU) in the management of Cardiff and Vale UHB Sponsored CTIMPs. Delegation of any safety reporting activities will be discussed and agreed during the risk assessment process and will be clearly laid out in relevant agreements before the trial begins.

Investigators should always ensure they are aware where and how the most up to date Reference Safety Information (RSI) can be accessed.
Clinical trial protocols may list the known side effects and safety events contained within the RSI, but should also direct the investigator to the RSI.

The guidance for the reference safety information (RSI) for clinical trials has been updated to include UK specific clarifications. The update, and further information can be found at
https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-yourauthorisation-report-safety-issues#reference-safety-information--updatedguidance

Investigators should familiarise themselves with this guidance and refer to MHRA website as required, to ensure they are aware of the most recent information.

Rare events may or may not be included in the protocol, depending on individual trial requirements. Similarly non-serious events may be regarded as ‘notable’ by the Sponsor and require recording and reporting. Any anomalies such as these should be included in the protocol, along with a mechanism for recording and reporting.

A detailed explanation of safety reporting procedures should be included in the protocol and all members of the research team trained on the procedures. Code/blind breaking procedures should be discussed beforehand and agreed with pharmacy or the relevant department at each participating site.

For clinical trials, including large national or international multi-centre trials, it is recommended that a DMC is appointed to review safety data regularly throughout the trial and, when necessary, recommend to the Sponsor whether to continue, modify or terminate the trial, or sections of the trial.

The protocol must clearly define the duration of AE recording.

There have recently been some changes in MHRA reporting procedures and it is important that anyone responsible for safety reporting familiarises themselves with the latest information on The MHRA Safety Reporting web pages, and information for submitting safety reports to the REC can be found via the HRA safety reporting web pages.

2.3 SPONSOR RESPONSIBILITIES

The Sponsor has defined legal responsibilities in relation to pharmacovigilance in clinical trials. Before a project begins, the Sponsor should ensure that, there are arrangements in place to allocate responsibilities for the management, monitoring and reporting of adverse events as well as reviewing significant developments, particularly those which put the safety of participants at risk.

The Sponsor is responsible for:

- Ensuring the most up-to-date version of the reference safety information (RSI) is available at all participating sites

- Keeping detailed records of all adverse events relating to a clinical trial. The Sponsor may be required to submit these records to the MHRA and/or Research Ethics Committee (REC) on request

- Notifying the REC, MHRA, and other investigators of findings that may affect the health and safety of subjects, within timelines defined in the Clinical Trials Regulations and/or in the protocol

- Reporting suspected unexpected serious adverse reactions (SUSARs) to MHRA and REC within timelines defined in the Clinical Trials Regulations and/or in the protocol

- Performing an assessment with respect to seriousness, causality and expectedness on Serious Adverse Events (SAEs) reported by the CI

- Breaking treatment codes in accordance with agreed procedures, where required, before submitting expedited reports to the relevant bodies, even if the Investigator has not broken the code

- Performing ongoing safety evaluations of any Investigational Medicinal Products (IMPs)

Annual Reports

- Submitting the annual safety report for each trial or Investigational Medicinal Product (IMP), in the form of a Developmental Safety Update Report (DSUR) to the MHRA and REC taking into account all new available safety information received during the reporting period

- Submitting the Annual Progress report to the REC and to all Principal Investigators at participating sites within given timelines

End of Trial Reports

- Notifying The MHRA and Main REC of the conclusion or early termination of a trial

- Submitting the End of Trial Report (also known as Clinical Study Report) to the MHRA and REC within given timelines

2.4 INVESTIGATOR (CI AND PI) RESPONSIBILITIES

The CI and PI must ensure that the research team gives priority at all times to the dignity, rights, safety and wellbeing of participants, including carrying out required care, following a safety event, and making judgement on the patient's ongoing participation in the trial.

Adverse Events

Regulation 32 of the Clinical Trials Regulations (SI 2004/1031) sets out the following responsibilities for the notification of adverse events to Sponsors by the CI/PI:

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

**There is no legal definition of "immediate", but 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') specifies it should not exceed 24 hours following knowledge of the event.*

- The CI/PI is responsible for the clinical assessment and reporting any safety events. For multi-centre projects, the PI or local investigator is usually required to inform the CI or overall Trial Manager of all safety events that occur at his/her site, following the guidelines and timescales set out in the Clinical Trials Regulations and/or as agreed in the protocol.

This includes the provision of any supplementary information requested by the CI, Sponsor and R&D offices.

- The CI must ensure the AE log is reviewed regularly. This can be performed by the CI alone or reviewed collectively at trial meetings. These reviews should be documented, with a copy of this documentation filed in the Trial Master File (TMF).

Annual and End of Trial Reporting

- It is common for the Sponsor to delegate the routine safety and progress reporting and the end of trial reports to the CI. Where this is not delegated, the CI's input into these reports will be of utmost importance. The CI should comply with any requests from the Sponsor.
- The PI must ensure that all relevant events are reported to the CI or Sponsor so they may be included in the reports.

2.5 RESPONSIBILITIES OF OTHER MEMBERS OF THE RESEARCH TEAM.

- Tasks relating to the management of safety events are commonly delegated to other members of the research team. These must be recorded on the SDL.

- The clinical assessment and classification of any safety event should be undertaken by the CI/PI. However, this may be formally delegated to another medically qualified member of the research team, as per the SDL. If initial reports are not completed by an investigator (e.g. if they are completed by the study research nurse) the follow up reports should contain evidence that the assessment decisions were made by a medically qualified doctor. In these circumstances, the SAE form should be reviewed and countersigned by the CI/PI, as per SDL, as soon as possible, afterwards, or in accordance with the protocol.

2.6 RESPONSIBILITIES OF ORGANISATIONS PROVIDING CARE

Organisations providing care to participants or providing access to participants, their organs, tissue or data, remain liable for the quality of care. They are also required to report any safety events through their internal systems as appropriate. (see Section 5 for AEs and incident reporting in C&V).

3.0 ADVERSE EVENT RECORDING AND REPORTING PROCEDURE AND TIMELINES

1. RECORD	2. ASSESS	3. REPORT

Step 1: Record

The CI/PI or delegated member of the research team must review all documentation, including Case Report Forms (CRFs) and source documents (hospital notes, laboratory and diagnostic reports) relevant to the safety event.

The trial protocol should be consulted to see whether the safety event is disease-related (and thus expected). Unless the protocol states otherwise, all safety events including non-serious AEs should be recorded, consistent with the purpose of the trial and any toxicity and efficacy endpoints.

The safety event should be recorded in subjects' medical notes, worksheets and/or a CRF as stipulated in the protocol. All available information should be recorded for analysis at a later stage and for inclusion in any reports.

Step 2: Assess

Adverse events should undergo three main assessments to enable classification

- **Assessment of Seriousness**
- **Assessment of Causality**
- **Assessment of Expectedness**

The Adverse Event Assessment Guide **(Appendix C)** provides guidance on safety event assessment and classification.

The assessment should be undertaken by the CI/PI or medically qualified delegate. This should be outlined in the protocol and recorded on the SDL.

For multi-sites trials a CI cannot downgrade a PI's assessment of an event but the CI/ Sponsor may upgrade an event if it is judged necessary.

In blinded trials involving a placebo and active drug, the factors in **Appendix C** should be evaluated on the basis that the subject was on the active drug.

In blinded trials involving two active drugs, the person responsible for assessment may be able to state that if the subject were on drug 'A', the event would be causal and/or unexpected, but if on drug 'B' it would be expected.

Where the event is believed to be a SUSAR, then the trial may need to be unblinded depending on the circumstances (see Section 4.0 below).

Step 3: Report

Reports should be sent to the relevant bodies depending on the nature of the safety event. These are as follows:

	Sponsor (or Delegate)	CI	MHRA	REC
AE/AR	✓			
SAE/SAR	✓	✓		
SSAR	✓	✓		
SUSAR	✓	✓	✓	✓

Adverse Events (AEs) & Adverse Reactions (ARs)

Where an AE/AR is identified in the protocol as critical to the evaluation of the safety of the trial, then they must be reported to the Sponsor.

For all other AE/ARs, except where the protocol states otherwise, these should be recorded in detail in the subject's medical notes or other source data, and on a case record form or equivalent, as per Sponsor requirements.

Serious Adverse Events (SAEs) & Serious Adverse Reactions (SARs)

Reports of SAEs/SARs must be notified, to the relevant bodies (as per table above) within **24 hours** from the point a safety event has been assessed as an SAE/SAR (other than those identified in the protocol as not requiring immediate reporting).

An initial report may be made orally but must be followed up as soon as is practically possible with a written report on the SAE/SAR report form, or as stipulated in the protocol, including an assessment of seriousness. Information not available at the time (such as test results) must be forwarded once available.

Suspected Unexpected Serious Adverse Reactions (SUSARs)
SUSARs must be reported to the Sponsor immediately, using the Sponsor's report form or as stipulated in the protocol.

All SUSARs must be reported to the MHRA by the Sponsor or delegate, via the relevant MHRA reporting system, in an unblinded state. Following Brexit, there have been some changes in reporting systems. Sponsors and Contract Research Organisations (CROs) must register to either the Individual Case Safety Reports (ICSR) Submissions or the MHRA Gateway to enable configuration of their systems in order to submit SUSARs to the MHRA. Latest information on reporting SUSARs using the new operating systems and instructions for registering has been published at MHRA Guidance on submitting clinical trial safety reports.
This information may be subject to updates, so it is important to refer to the latest information on the Managing your Authorisation section of the Managing Your Authorisation pages of the MHRA website to ascertain the appropriate system for individual trials.

The trial protocol should contain instructions on unblinding, and these instructions should be followed.

The main REC (which granted approval for the trial to proceed) should also be sent an unblinded report using the format set out on the safety reporting pages of the HRA website.
The Sponsor or delegate is required to ensure that the investigators responsible for the conduct of a trial are informed of any SUSARs that occur. No timelines are specified in the regulations for reporting to investigators; however, this should be done in a timely manner to ensure investigators are kept fully informed of all safety information.

Fatal or Life-threatening SUSARs
The Sponsor or delegate must inform the relevant bodies as soon as possible but no later than **7 calendar days** after the Sponsor first has knowledge of a reaction which requires expedited reporting. Any further information should be forwarded to these bodies within an additional **8 calendar days**.

Non-fatal or Non life-threatening SUSARs
The Sponsor or delegate must inform the relevant bodies as soon as possible but no later than **15 calendar days** after they first have knowledge of a reaction which requires expedited reporting. Follow up information should be sent within 15 days of the Sponsor having knowledge of the information. If significant new information on an already reported case is received by the Sponsor, the clock starts again at day zero, i.e. the date of receipt of new information. This information should be reported as a follow-up report within 15 days (or 7 days for fatal/life threatening events.).

SUSARs Associated with Non IMP/IMP Interactions
A Non Investigational Medicinal Product (NIMP) is a medicinal product which is not classed as an IMP in a trial, but may be taken by subjects during the trial. Examples include concomitant or rescue/escape medication used for preventive, diagnostic or therapeutic reasons and/or medication given to ensure that adequate medical care is provided for the subject during a trial. See EU Guidance on Investigational Medicinal Products (IMPs) and Non Investigational Products (NIMPs) SUSARs that result from a possible interaction between an IMP and a NIMP, (i.e. the reaction cannot clearly be attributed to the NIMP alone) should also be reported as above.

Minimum Reporting Requirements for SUSARs
Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits set out in the Clinical Trials Regulations, when the following minimum criteria are met:

- A suspected investigational medicinal product;
- An identifiable subject (e.g. trial number);
- An adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship;
- An identifiable reporting source;

And, when available and applicable:

- A EudraCT number (or, in the case of non-European community trials, the Sponsor's trial protocol code number); and
- A unique case identification (i.e. Sponsor's/CTUs case identification number)
- Treatment assignment after unblinding and validation (or not) of the suspected causes.

The Sponsor is responsible for ensuring that all relevant follow-up information is requested and submitted to MHRA and REC as appropriate.

For multi-site EU trials, Sponsors should ensure the latest guidance on the MHRA website is followed, to ensure appropriate safety reporting.

Serious Adverse Events in CTIMP's hosted at Cardiff and Vale UHB

It is the responsibility of the PI/CI to act in the best interest of the participant at all times and to evaluate the participants' ongoing inclusion in the trial taking any adverse events into consideration.

It is also the responsibility of the PI/CI to inform the R&D Office of any concerns he/she may have regarding safety events concerning a participant, or the ongoing safety profile of the trial. The R&D office may require periodic information on SAE/SARs which will usually be requested by email, from the PI/delegate. Instructions on the types of information required and the method of submitting this information will be provided in the information request.

4.0 SAFETY REPORTING AND BLINDED TRIALS

Where possible, the blind should be maintained for all participants prior to final analysis and, in the case of double-blinded trials, for all those involved with the trial on a daily basis and involved in data analysis at the end of the trial.
Individual trials, where one or more IMPs are blinded should have a section in the protocol which describes the circumstances in which unblinding is necessary and also the procedure for unblinding. This may also be detailed in a trial specific unblinding procedure, which should be referred to in the protocol. The PI may take advice on individual circumstances, from the CI, CTU or Sponsor or the relevant pharmacy department.

C&V Sponsored CTIMPs which require the trial to be blind should have a robust unblinding procedure written into the protocol, or trial specific unblinding procedure, before the trial is approved. The CI should discuss the unblinding requirements and details with the pharmacy department to ensure a robust system is agreed and detailed in the protocol.
In the event of an SAE/SAR, for which an assessment of causality or expectedness is proving difficult, the blind may be broken for the specific patient to confirm whether the occurrence is linked to the trial drug(s).

The person responsible for unblinding should provide the information upon request, and in accordance with the protocol. Depending on the severity of any occurrence,

the Sponsor or delegate should be consulted before unblinding. The breaking of the code should be recorded and justified on the CRF and any other documentation, as required in the protocol.

The following three possibilities should be considered when unblinding has occurred.

1) If the product administered to the subject is the **test IMP**, the case should be reported as a SUSAR.

2) If the product administered to the subject is a marketed **comparator IMP** the event should be reassessed for expectedness according to the SmPC and the protocol. If the event is unexpected, the SUSAR should be reported and otherwise it is an expected SSAR and is not reportable on an expedited basis.

3) If the product administered to the subject is the **placebo** then this will not usually satisfy the criteria for a SAR and therefore will not require expedited reporting. However, it is the Sponsor's responsibility to report any cases which they suspect might be SUSARs to the relevant bodies, at their discretion.

5.0 ADVERSE EVENT AND INCIDENT REPORTING

Host organisations may have different requirements for internal recording of SAEs and incidents. PIs should ensure they are acting in accordance with these requirements. In C&V UHB, SAEs, as defined in the protocol do not require reporting via the Datix system.
Other research related breaches, ie prescribing or drug administration errors, major drug storage temperature deviations etc should be reported to the Sponsor, as soon as possible after the breach has been identified.
Events which are considered as a potential serious breach of GCP or of the protocol should be reported to the C&V UHB R&D Office in accordance with the C&V SOP Managing Breaches of Good Clinical Practice or the Study Protocol (UHB 235). The R&D Office will liaise with the research team regarding corrective actions and preventative measures.

5.1 CLINICAL TRIAL NAMED CONTACT

Persons other than the applicant named in the clinical trial application form, who call or email the MHRA CTU helpline, reports to be from the sponsor/applicants company and knows the EudraCT number and security word/phrase (previously provided to MHRA by the named applicant) for a trial may obtain information on that trial.

For ongoing studies, the applicant named in section C.1 of the CTA application form should notify the MHRA of their chosen security word/phrase by emailing

clintrialhelpline@mhra.gov.uk with 'Clinical Trials named contact' as the subject line and listing the EudraCT number(s) in the body of the email.

For new applications, the applicant named in section C.1 of the application form is requested to include the security word/phrase in the cover letter for the submission.

6.0 URGENT SAFETY MEASURES (USMs).

The Sponsor, delegate or Investigator may take appropriate and immediate USMs in order to protect participants against any immediate hazard to their health or safety. Approval is not required before taking these measures.

The Sponsor or delegate should call the MHRA's Clinical Trials Unit on 020 3080 6456 to discuss the issue and measures taken with a medical assessor, ideally within 24 hours but no later than 3 days from the date the measures are taken. The main REC should also be notified within this timeframe.

Information you will be asked for on the call with MHRA:

1. EudraCT number of;
   a. The trials for which USM action has been taken,
   b. Other ongoing trials with the same Investigational Medicinal Product(s) (IMP(s))
   c. Trials run by a different Sponsor affected by the USM action
2. The affected IMP(s) - commercial or developmental names
3. Nature of the safety concern and whether it has been reported as a SUSAR
4. Which USMs have been taken and when
5. The number of UK subjects who are currently receiving the IMP, the number of subjects who received it and the number affected by the USM
6. Contact details in case of further questions

Where this information is not available during the initial call it should be provided as soon as possible.

You must then provide the MHRA written notification of the measures taken and discussed with the medical assessor, within 3 days from the date the measures were taken, by email to clintrialhelpline@mhra.gov.uk.

Where applicable, oversight committees (such as the Data Monitoring Committee) should review information relating to urgent safety measures and report any recommendations to all relevant parties.

If the Principal Investigator (and not the sponsor) has instigated the USM, the sponsor should be notified immediately so that they can assess and report the USM within the timelines required.

Details of any USMs taken should be recorded in the patient medical notes and trial documentation.

Where a USM requires a substantial amendment to the protocol or other documentation, a substantial amendment should be submitted after the safety measures have been implemented, to the MHRA, REC and R&D Offices via the mechanism laid out on the appropriate websites.

The substantial amendment covering the changes made as part of the USM is anticipated within approximately two weeks of notification of the MHRA. Any potential reason for delay to submission of the substantial amendment should be discussed and agreed with the MHRA at the time of initial notification or through a follow up call if necessary. Submission of the substantial amendment should not be delayed by additional changes outside of those taken and required as an urgent safety measure. Unrelated and unacceptable changes may result in rejection.

At the time of publishing this SOP, these substantial amendments must be submitted using MHRA Submissions via the Human Medicines Tile. Please select 'Clinical Trial' as the Regulatory Activity and 'CT - Amendment' from the Regulatory sub activity dropdown list. However, those responsible should check the MHRA websites for any updates to this submission system.

7.0 PREGNANCY OF RESEARCH PARTICIPANTS

Many CTIMPs have an exclusion criteria of pregnancy or refusal to take measures to avoid pregnancy, and information should be given to potential trial subjects before they give informed consent. However, information regarding pregnancy data provides vital information to the overall knowledge concerning the IMP and is therefore reportable to the Sponsor but not reportable to the regulatory agencies as expedited reports and will be incorporated into the DSUR.

Where pregnancy is not a desired outcome of the trial, the protocol should contain detailed information regarding pregnancy in any of the trial subjects and/or partners, as appropriate.

With consent, the investigator should collect pregnancy information for those who become pregnant while participating in a CTIMP or during a stage where the foetus could have been exposed to the investigational medicinal product (e.g. if the active substance or one of its metabolites have a long half life).

Depending on any known effects of the IMP on spermogenesis, it may be necessary to monitor the pregnancy of a woman whose male partner is the trial subject.

The pregnancy should be recorded in the medical notes and trial documentation as per protocol and Sponsor requirements.

Where pregnancy is an exclusion criterion, the participant would usually be withdrawn from the trial.

The pregnancy should be followed to termination or to term. In some circumstances, it may be necessary to monitor the development of the newborn for an appropriate period post-delivery.

It will be necessary to take informed consent in order to follow up the pregnancy. The trial subjects should be aware of this before they enter the trial, and if consent for pregnancy follow up is not incorporated in the original PIS/ICF, separate informed consent should be gained.

Any congenital anomalies or birth defects, foetal death or spontaneous abortion or any SAE occurring to the mother or neonate should be recorded and reported as an SAE/SAR/SUSAR, as appropriate.
Guidance on the procedure for recording and reporting pregnancy should be included in the trial protocol.

8.0 PERIODIC PROGRESS AND SAFETY REPORTING

The MHRA and REC require periodic safety and progress reports. Periodic reporting is important to identify any emerging trends in patient safety.

An annual report for each trial must be submitted by the Sponsor to the MHRA and REC taking into account all new available safety information received during the reporting period.

If a CI is conducting more than one trial using the same IMP, one DSUR should be submitted for the IMP rather than submitting individual reports for each trial including that IMP.

This should be in the format of a DSUR and the RSI (IB or SmPC) in place at the start of DSUR reporting period should be appended to the DSUR. When the RSI has been revised during the DSUR reporting period, the current version should also be submitted with the DSUR. The DSUR should include date and version number of the IB or SmPC. For SUSAR reporting, expectedness should be assessed in line with the current approved IB or SmPC.
DSURs should take into account all new available safety information received during the reporting period.

The DSUR should include:

- a cover letter listing all EudraCT numbers of trials covered by the DSUR. Please include an email address for correspondence.
- an analysis of the subjects' safety in the concerned clinical trial(s) with an appraisal of its ongoing risk/benefit
- a line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the trial(s), including all SUSARs from third countries
- an aggregate summary tabulation of SUSARs that occurred in the concerned trial(s)

Full details of what to include in a DSUR can be found in the ICH E2F guidance.

DSURs should be submitted using MHRA Submissions via the Human Medicines Tile. Please select 'Development Safety Update Report' as the Regulatory Activity and 'Original Submission' from the Regulatory sub activity dropdown list. Acknowledgements of receipt for DSUR submissions are generated by MHRA Submissions where a confirmation of submission is emailed to the reporter.

Copies of all UK related safety information supplied to MHRA must also be emailed to the main REC, accompanied by a CTIMPs Safety Report form.

At the end of the DSUR reporting period the Sponsor may assess the new safety information that has been generated and submit any proposed safety changes to the Investigator's Brochure as a substantial amendment. This amendment must be supported by the DSUR and approved before the reference safety information (RSI) is changed.

Short format Development Safety Update Report (DSUR) for clinical trials authorised under the Notification Scheme (Type A trials)
A shortened DSUR may be suitable for individual trials authorised under the Notification Scheme which are not part of a multi-study development programme. This substantially simpler and shorter form may be submitted in lieu of a full DSUR giving a significant time saving.
To assess whether this shortened DSUR is suitable for clinical trials, and information on submitting the shortened report can be found on the MHRA web pages

The DSUR due date is the anniversary of the first international regulatory approval regardless of the approval status in the UK. The DSUR must be submitted within 60 days of the due date.
The data lock point of the DSUR should be the last day of the one-year reporting period.

Further information on routine safety and progress reporting requirements, and the content and submission of DSURs can be found in UHB 046 Reporting Requirements for Cardiff and Vale Health Board Sponsored Research SOP. Documents are available upon request from the C&V R&D Office.

9.0 DISSEMINATION AND TRAINING

The Clinical Board R&D Leads should facilitate implementation by ensuring that all relevant research active personnel within their Boards are aware of the Procedure and the implications for their practice. Education and support should be available from the R&D Office for researchers who are involved in conducting clinical research studies.

10.0 HYPERLINK ADDRESSES

The Medicines for Human Use (Clinical Trials) Regulations 2004: SI 2004/1031
https://www.legislation.gov.uk/uksi/2004/1031/contents/made

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')
https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2011:172:0001:0013:EN:PDF

The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations
https://www.legislation.gov.uk/uksi/2019/744/regulation/13/made

MHRA Clinical Trials guidance for organisations, following BREXIT.
https://www.gov.uk/government/collections/new-guidance-and-information-for-industry-from-the-mhra

Guidance for the reference safety information (RSI) for clinical trials, updated to include UK specific clarifications.
https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#reference-safety-information--updated-guidance

MHRA Safety Reporting web pages
https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues

HRA safety reporting web pages.
https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/

MHRA Guidance on submitting clinical trial safety reports.
https://www.gov.uk/guidance/guidance-on-submitting-clinical-trial-safety-reports#reporting-susars-using-the-new-reporting-routes

MHRA Managing Your Authorisation page of MHRA website
https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#reference-safety-information--updated-guidance

EU Guidance on Investigational Medicinal Products (IMPs) and Non Investigational Products (NIMPs)
https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:082:0001:0019:en:PDF

MHRA Submissions via the Human Medicines Tile.
https://www.gov.uk/guidance/register-to-make-submissions-to-the-mhra

ICH E2F guidance - DSURs.
https://database.ich.org/sites/default/files/E2F_Guideline.pdf

REC Safety Reporting Form
CTIMPs Safety Report form
https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

Information on shortened DSURs
https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#submit-development-safety-update-reports-dsurs

Appendix A ABBREVIATIONS

AE	Adverse Event
AI	Adverse Incident
AR	Adverse Reaction
CESP	Common European Submission Portal
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trials Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
Clinical Trials Regulations	Medicines for Human Use (Clinical Trials) Regulations
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EU	European Union
EudraCT	European Union Drug Regulation Authorities Clinical Trials.
GCP	Good Clinical Practice
HRA	Health Research Authority
IB	Investigator Brochure
IMP	Investigational Medicinal Product
IMPD	Simplified IMP Dossier
IRF	Incident Record Form
ICSR	Individual Case Safety Reports
MHRA	Medicines and Healthcare products Regulatory Agency
NIMP	Non Investigational Medicinal Product
PI	Principal Investigator
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDL	Study Delegation Log
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TSC	Trial Steering Committee
USM	Urgent Safety Measure

Appendix B

DEFINITIONS

Directive 2001/20/EC, Article 2, lists definitions of terms. The following has been adapted from the Clinical Trials Regulations

Pharmacovigilance
Pharmacovigilance in CTIMPs is the science of collecting, monitoring, researching, assessing and evaluating information on the adverse events of medicines, including placebos, with a view to identifying information about potential new hazards and preventing harm to subjects

Adverse Event (AE)
Any untoward medical occurrence in a patient or clinical trial subject administered an Investigational Medicinal Product (IMP) and which does not necessarily have a causal relationship with this treatment. Therefore an AE can be any unfavourable or unintended sign, symptom including laboratory data, in a subject to whom an IMP has been administered, including occurrences which are not necessarily caused by or related to that product

Adverse Reaction (AR)
All untoward and unintended responses to an IMP related to any dose administered Comment: All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to a medicinal product would qualify as adverse reactions. The expression ‘reasonable causal relationship’ means to convey, in general, that there is evidence or argument to suggest a causal relationship

Serious Adverse Event (SAE) and Serious Adverse Reaction (SAR)

Any AE or AR that at any dose:
- 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

Comment: Medical judgement 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 may 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.

Unexpected Adverse Reaction (UAR)
An adverse reaction, the nature or severity of which is not consistent with the applicable product information (RSI)

Suspected Serious Adverse Reaction (SSAR)
An adverse reaction, the nature or severity of which is not consistent with the applicable product information (RSI)

Suspected Unexpected Serious Adverse Reaction (SUSAR)
An adverse reaction that is classified in nature as both serious and unexpected

Appendix C Adverse Event Assessment Guide

(1) 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.**

***** It is not an SAE if the prolongation of hospitalisation relates to non-medical fitness for discharge

(2) CAUSALITY

The relationship between the drug/device/procedure and the occurrence of each adverse event should be assessed and categorised as below. The Investigator should use clinical judgement to determine the relationship. Alternative causes, such as natural historical events of the underlying diseases, concomitant therapy, other risk factors etc, will also be considered. The Investigator should also consult the SmPC or IB as appropriate. All adverse events judged as having a reasonable suspected causal relationship to the IMP are considered to be adverse reactions. The expression 'reasonable suspected causal relationship' is meant to convey in general that there is reason (e.g. facts, evidence or arguments) to suggest a causal relationship.

NOT RELATED	Temporal relationship of the onset of the AE, relative to the administration of the product, is not reasonable or another cause can explain the occurrence
UNLIKELY	Temporal relationship of the onset of the AE, relative to the administration of the product, is likely to have another cause which can by itself explain the occurrence
POSSIBLY RELATED*	Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause
PROBABLY RELATED*	Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and the event is more likely to be explained by the product than any other cause
DEFINITELY RELATED*	Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive

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

(3) EXPECTEDNESS

Adverse reactions must be considered as unexpected if they add significant information on the specificity or severity of an expected adverse reaction. The expectedness of an adverse reaction shall be determined according to the reference documents as defined in the clinical trial protocol (e.g. IB or SnPC)

EXPECTED	Reaction previously identified and described in protocol and/or reference documents
UNEXPECTED	Reaction not previously described in the protocol of reference documents

NOTE: The protocol must identify the reference documentation used

Appendix D Safety Reporting Flowchart