Standard Operating Procedure

RESEARCH SAFETY REPORTING

SETTING Trust-wide

AUDIENCE All staff involved in research

ISSUE To inform staff involved in clinical research studies sponsored by University Hospitals Bristol and Weston NHS Foundation Trust (UHBW) or University of Bristol (UoB), of the necessary requirements for the reporting of adverse events

QUERIES Contact R&D department via research@uhbw.nhs.uk

Document History

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3.5	Minor change to errors in addresses
4.0	Change from annual reporting to Development Safety Update Reporting
4.0	Change from annual reporting to Development Safety Update Reporting
5.0	Changes to out-of-date website links and clarification on responsibilities of research team.
6.0	Clarification of process of reporting and updates to website links.
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V8.0	Update to template in line with new R&D SOP template, update to SAE forms, addition to appendices of processes, minor clarification of reporting process and clarification of expectation of DSMBs
V9.0	Additional information about Reference Safety Information, revising order of SOP, updates, and clarifications
V9.1	Removal of template appendices into standalone templates and minor revision to wording.
V9.2	Removal of unnecessary wording and minor updates and clarifications.
V10	Major amendment to update reporting requirements for follow ups of ongoing SAEs and other minor amendments and clarifications as part of biennial review.
V11.0	Major amendment to update reporting requirements in line with regulatory changes taking effect from 1 January 2021 after end of the EU transition period.
V11.1	Departmental name change from Research & Innovation to Research & Development. Other minor amendments to further clarify processes.
V12.0	Major amendment to include safety reporting in Clinical Investigation of a Medical Device (CIMD) trials, clarification on agreed process if using alternative SAE trial database, possible acceptable variation to process for low risk trials, clarification on process for blinded trials, updates around urgent safety measures and updates on SUSAR reporting requirements as well as minor updates and clarifications as part of biennial review.
V12.1	Correction of typo on review date.
V13.0	Major update to include required amendments in line with the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, such as updating ‘subject’ to ‘participant’, timelines for urgent safety measure reporting and other clarifications on what is meant by hospitalisation.

Acknowledgements:

1. Ms Tanya Symons; T Symons Associates Ltd. North Bristol NHS Trust

1. Introduction

In accordance with the UK policy Framework for Health & Social Care Research, UHBW must have systems in place to record, investigate and report adverse incidents arising from any research undertaken within the Trust.

Furthermore, the Medicines for Human Use (Clinical Trials) Regulations 2004 (and subsequent amendments, including the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025), which apply to all clinical trials involving investigational medicinal products (CTIMPs), and the Medical Devices Regulations 2002; specify the reporting requirements for research related adverse events. To breach these requirements constitutes a breach in criminal law. The requirements have been incorporated within this policy.

In the same way that adverse incidents, including clinical, non-clinical and near misses can involve patients, staff and visitors during routine care, adverse incidents can also occur during research related activities. It is important that adverse incidents occurring in the context of research are treated in the same way as non-research related adverse incidents – i.e. they should be reported in accordance with Trust policy (see Adverse Incident Reporting Policy and Guidelines located on UHBW intranet). NB: an adverse incident may also be an adverse event and should be reported through both routes.

2. Purpose

The purpose of this SOP is to provide instruction and guidance of the safety reporting requirements for staff working on research studies sponsored by UHBW and UoB to ensure compliance with all applicable regulations.

3. Scope

In Scope: Recording and reporting all types of Adverse Events, including Adverse Reactions, Serious Adverse Events, Serious Adverse Reactions and Suspected Unexpected Serious Adverse Reactions will be managed in line with the reporting policy of the sponsor of the research study. Where UHBW is the sponsor, where UoB is the sponsor, where no sponsor policy exists, or where the minimum reporting requirements laid out within the UHBW Research Safety Reporting SOP are not met for hosted studies, this SOP must be followed as a minimum.

Out of scope: Adverse incidents which should be reported in accordance with UHBW Adverse Incident and Near Miss Reporting SOP.

4. Responsibilities

It is the responsibility of the sponsor, Chief Investigator (CI) and delegated individuals to ensure that the dignity, rights, safety and well-being of research participants are given priority at all times and appropriate action is taken to ensure their safety.

For UHBW or UoB sponsored studies the responsibility of safety reporting (including urgent safety measures) is delegated to the CI and Principal Investigator(s) (PI(s). The CI is responsible for reporting urgent safety measures to regulatory bodies and to participating sites and for reviewing safety reports where applicable, The PI(s) are responsible for implementing urgent safety measures at sites and reporting safety reports to the sponsor within the necessary timelines and in accordance with applicable SOPs.

The R&D department at UHBW as sponsor representative is responsible for maintaining oversight of safety reporting and ensuring any Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to regulatory authorities within the required timeframes.

5. Abbreviations and Definitions

Abbreviations	
AE	Adverse Event
AI	Adverse Incident
AR	Adverse Reaction
CI	Chief Investigator
CIMD	Clinical Investigation of a Medical Device
CTA	Clinical Trials Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EU	European Union
HRA	Health Research Authority
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
nIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
REC	Research Ethics Committee
R&D	Research and Development
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UHBW	University Hospitals Bristol and Weston NHS Foundation Trust
UoB	University of Bristol

Definitions	
Adverse event	Any untoward medical occurrence in a participant to whom a medicinal product/medical device/intervention has been administered, including occurrences which are not necessarily caused by or related to that product/device/intervention. *An adverse event can therefore be any unfavourable and unintended sign (including abnormal lab results), symptom or disease temporally associated with the use of the medicinal product/medical device/intervention, whether or not considered to be related to the medicinal product/medical device/intervention.* Not all adverse events are adverse reactions, but all adverse reactions are adverse events.
Adverse reaction	Any untoward and unintended response in a participant to an investigational medicinal product (IMP)/medical device/intervention which is related to, any IMP dose administered /use of the medical device/ or the intervention to that participant. *Any adverse event judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product/medical device/intervention qualifies as an AR; i.e. there is evidence or argument to suggest a causal relationship. All adverse reactions are adverse events.*
Unexpected adverse reaction	An adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product/medical device/intervention in question set out in the Reference Safety Information, which may be: (a) the summary of product characteristics – SmPC (for a product with a marketing authorisation) (applicable to CTIMPs only), (b) the investigator's brochure – IB (for any other investigational medicinal product) (applicable to CTIMPs only (c) or other document containing equivalent information e.g. the study protocol/ clinical investigation plan. *When the outcome of the adverse reaction is not consistent with the reference safety information this adverse reaction should be considered as unexpected. All unexpected adverse reactions are adverse events.*
Serious adverse event, serious adverse reaction or unexpected serious adverse reaction	An *adverse event*, *adverse reaction* or *unexpected adverse reaction* is defined as **serious** if it: (a) results in death, (b) is life-threatening*, (c) requires hospitalisation** or prolongation of existing hospitalisation, (d) results in persistent or significant disability or incapacity, or (e) consists of a congenital anomaly or birth defect. **Life threatening in the definition of an SAE or SAR refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Medical judgement should be exercised in deciding whether an AE/AR is serious.* ***"Hospitalisation" means that the participant has been admitted to the hospital for inpatient care, for example to an inpatient ward or to an emergency department for observation and/or treatment (usually involving at least an overnight stay), that would not have been appropriate in the physician's office or outpatient setting. The protocol should clarify what is considered as hospitalisation in the context of the*

	trial setting since this may vary depending on the overall risk assessment for the trial. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is generally not considered an SAE. *SAE/SARs (also referred to as 'important medical events') that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent any of the outcomes listed in the definition above, should also be considered serious.*
Suspected serious adverse reaction (SSAR),	Any ***serious adverse reaction*** that is suspected (possibly or probably or definitely) to be related to the investigational medicinal product/medical device/intervention.
Suspected unexpected serious adverse reaction (SUSAR)	For CTIMPs a SSAR which is also "unexpected", meaning that its nature and severity are not consistent with the information about the medicinal product in question set out in the agreed Reference Safety Information examples of which are: (a) in the case of a product with a marketing authorisation, in the summary of product characteristics for that product (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question or other document containing equivalent information, e.g. the study protocol.
Reference Safety Information	Means information relating to expected serious adverse reactions associated with an investigational medicinal product/medical device/intervention, which is used to determine the adverse reactions that are to be treated as suspected unexpected serious adverse reactions in relation to that investigational medicinal product.
Investigational Medicinal Product	A pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be 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 a) used or assembled (formulated or packaged) in a way different from the approved form or b) being used for an unapproved indication according to the SmPC, or c) when used to gain further information about an approved form.
Non-Investigational Medicinal Product	A medicinal product used or to be used in a clinical trial, as described in the protocol, but not as an investigational medicinal product.
Medical Device	A Medical Device is defined, in the Medical Devices Regulations, as: an instrument, apparatus, appliance, material or other article, whether used alone or in combination, together with any software necessary for its proper application, which: a. is intended by the manufacturer to be used for human beings for the purpose of: i. diagnosis, prevention, monitoring, treatment or alleviation of disease, ii. diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap, iii. investigation, replacement or modification of the anatomy or of a physiological process, or iv. control of conception; and: b. does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, even if it is assisted in its function by such means.

Non-CTIMP SUSAR	An ***SAE*** that occurs in a non-CTIMP trial and is: • "Related" – that is, possibly, probably or definitely 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.
Urgent Safety Measures (USMs)	The sponsor and investigator may take appropriate USMs to protect a research participant from an immediate hazard to their health and safety. This measure can be taken before seeking approval from the competent authorities (MHRA in the UK) and ethics committees of all member states concerned (http://www.ct-toolkit.ac.uk/routemap/urgent-safety-measures)

6. Procedure

6.1 Assessment of Adverse Events

All adverse events should be assessed as follows:

6.1.1 Intensity assessment

- The assessment of intensity is based on 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.
- *Comment: 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.*

6.1.2 Seriousness

- The adverse event should be assessed by the investigator for seriousness (please see definitions section for further information on when an event is considered serious).

6.1.3 Causality

6.1.3.1 Reference Safety Information

- Prior to the trial commencing the CI should determine what will be used as the Reference Safety Information (RSI) to determine causality of any adverse events. For CTIMPs, the RSI should be submitted to the MHRA as part of the Clinical Trial Authorisation (CTA) application and may be found:
    - in the case of a product with a marketing authorisation, in the summary of product characteristics – (SmPC) for that product.
    - in the case of any other investigational medicinal product, in the investigator's brochure – IB relating to the trial in question.

    - Any other agreed document as approved by the MHRA (e.g. Protocol).
- It must be clear which section of the SmPC or IB is the RSI for the trial.
- An RSI is required for the active IMP and for any comparator IMPs. For further information, see the MHRA blog on RSIs which is referenced at the end of this SOP.
- The CI, Sponsor and all other PIs should be provided with the approved RSI prior to the trial commencing. If the CI and/or sponsor is informed of any updates to the document being used as the RSI (for example, if the SmPC is updated by the manufacturer), the sponsor and the CI must agree whether this should replace the existing RSI. If it is agreed to replace the existing RSI, a modification request should be submitted to the MHRA and only once approved should the updated RSI be used, except in the case of Urgent Safety Measures, in which case the process described in 6.4 will be followed.
- A robust process must be in place for checking for any applicable updates to the SmPC if it is being used as the RSI. Where changes are required, the process described above should be followed to implement accordingly. UHBW as sponsor delegates this responsibility to the CI and trial management team.
- It is a legislative requirement that the IB is reviewed by the sponsor annually and the review is appropriately documented. This may be delegated to the CI. For non-commercial trials the IB is often prepared and updated by the IMP provider (Marketing Authorisation Holder). In such cases the non-commercial sponsor should have a written agreement in place with the company, confirming that the updated approved IB will be sent to the sponsor immediately.
- Any updates to the RSI section of the IB should be reviewed by the CI to assess whether the updated IB should replace the existing RSI. The review should be appropriately documented, even if it is decided that an update to the RSI for the trial is not required.

  The RSI used to assess causality and expectedness must be the one which was MHRA approved at the time of onset of the event.

- The relationship between the IMP/device/procedure and the occurrence of each adverse event should be assessed and categorised as below. The investigator should use the agreed RSI in conjunction with their clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors etc. should be considered.
    - **Not related:** Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.
    - **Unlikely:** Temporal relationship of the onset of the event, relative to administration of the product, or is likely to have another cause which can by itself explain the occurrence of the event.
    - ***Possibly related:** Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause.
    - ***Probably related:** Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and the event is more likely explained by the product than any other cause.
    - ***Definitely related:** Temporal relationship of the onset 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.

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

6.1.3.2 Expectedness

- The expectedness of an adverse reaction shall be determined according to the RSI and as defined in the study protocol.
    - **Expected:** A reaction previously identified and described in the RSI and/or protocol
    - **Unexpected:** A reaction not previously described in the RSI and/or protocol.
- Adverse reactions must be considered as unexpected if they add significant information on the specificity, severity or frequency of an expected adverse reaction
- The protocol must identify the RSI used to perform the assessment.
- SARs due to lack of efficacy or due to disease progression should not be considered as expected events unless this is explicitly stated in the RSI.

6.2 Investigator Responsibilities

6.2.1 All Adverse Events

- The Investigator must ensure that the dignity, rights, safety and well-being of participants are given priority at all times and must take appropriate action to ensure the safety of all staff and participants in the study. The Investigator should consider what actions, if any, are required and in what timeframe.
- Should the protocol need to be amended as a result of actions that the Investigator has taken to maintain the safety of staff and participants, the Investigator must ensure appropriate regulatory permissions are obtained for the modification in line with *GD_001 Gaining and Maintaining Authorisations.*
- If the modification is due to implementation of urgent safety measures, the modification should be implemented immediately and then submitted for necessary approvals. Initial notification of the urgent safety measure should be by telephone to R&D on 0117 342 0233 and by telephone to the MHRA (details of the applicable phone number can be found on the MHRA website). Notice in writing to REC, R&D and MHRA should then be sent within seven days. The notice should set out the reasons for the urgent safety measures and a plan for further action. Further information can be found in section 6.4.
- The Investigator is responsible for ensuring that all ***adverse incidents*** *in research taking place at UHBW*, whether or not related to the research, are reported in accordance with the UHBW's Serious Incident Policy and associated policies. These policies can be accessed by UHBW staff through the Trust document management system called My StaffApp, via the UHBW Intranet homepage. Incidents occurring at other locations should be reported in accordance with local policies.
- In the event of an ***adverse event/reaction***, the Investigator (or delegated member of research team) must review all documentation (e.g. hospital notes, laboratory and diagnostic reports) relevant to the event. The event and relevant comments must then be recorded in the participant's medical notes (or source data where this is not the medical notes).
- Except where the protocol states otherwise, all ***adverse event/reactions*** should be recorded in detail on a case report form (CRF) or equivalent to allow analysis at a later

stage. On the R&D website, the *TMPL_024 Adverse Events Template* can be used to record adverse events.

- For all ***adverse event/reactions*** the Investigator must make an assessment of intensity, causality, and seriousness as described in 6.1. It is important to record intensity because in some expected events the intensity could become greater than expected, resulting in the event being defined as unexpected, and this may change the reporting requirements. Expectedness will be assessed by a senior member of the UHBW R&D, band 7 and above.
- ***Adverse events*** and/or ***laboratory abnormalities identified in the protocol as critical*** to the evaluations of the safety of the study must be reported to the sponsor in accordance with the reporting requirements documented in the protocol.
- The Chief Investigator should review all adverse events/reactions reported to identify any trends which may require urgent action.
- The Chief Investigator should keep the Sponsor, the main REC and the MHRA informed of any significant findings and recommendations by an independent Data Monitoring Committee or equivalent body where one has been established for the trial.
- At the conclusion of a study, all ***adverse event/reactions*** recorded during the study must be subject to statistical analysis as determined by the protocol and that analysis and subsequent conclusions should be included in the final study report.

6.2.2 Serious Adverse Events

- **Within 24 hours** of a member of the research team becoming aware of a *serious adverse event* the sponsor must be notified. The Investigator may delegate this to appropriate personnel within their research team, and they are required to make an initial report, orally or in writing. Oral reports should be followed up in writing within 24 hours of the initial report. Written reports should be made by completing an SAE/SUSAR report form provided by the sponsor of the research study.

  Where UHBW is the sponsor or where no form has been provided, the investigator should use *TMPL_025 SAE/SUSAR Initial Report form* available on the R&D website, unless there is documented agreement with R&D that a different template form can be used; including the use of a research study database where the sponsor can log in and view SAE reports as soon as they have been inputted. The initial report form should include as much information as is available at the time and be signed by the PI or delegated other. Please refer to *WI_002 Instructions for completion of SAEs* for further details on this process. Please note, any forms that have been submitted to the sponsor with missing information, including causality assessment and expectedness (as applicable) and PI/delegated individual sign off, must be re-submitted and signed ASAP (within at least 72 hours of the initial report).

- The Investigator completing the initial SAE form should record the verbatim term for any AE/SAE in a participant and make every effort to include the relevant MedDRA preferred term (PT). MedDRA coding should be performed as per the MedDRA 'Best practice guidelines and Points to Consider' document which requires selection of the lowest level term and then review to determine the MedDRA PT which an event codes to. When recording and reporting safety data MedDRA should be used for consistency across the trial and with the RSI.
    - UHBW R&D staff should review all MedDRA PTs provided. Where the MedDRA PT has not been provided, UHBW R&D staff should assign a PT, and if necessary, should contact the Investigator to confirm their agreement on the PT.

- In addition, the following bodies must also be notified in a timely fashion. It is strongly recommended that this be at the same time as notifying the sponsor:
    - The Chief Investigator
    - Any other persons or bodies specified in the protocol (e.g. Data Safety Monitoring Board)
- The only exception to sections 6.2.1 and 6.2.2 is where the protocol or other relevant RSI (e.g. investigator brochure) identifies the event as not requiring immediate reporting.
- If at the time of the initial report the event is ongoing, the investigator is required to actively follow up the participant:
    - For SUSARs the investigator (or delegated person) must provide a follow up report within five days of the initial report to UHBW at research@uhbw.nhs.uk
    - For Non-SUSARs the investigator (or delegated person) must provide a follow up report within ten days of the initial report to UHBW at research@uhbw.nhs.uk
- If at the time of the initial report the event is resolved and the Investigator (or delegated person) obtains relevant additional information, this must be documented on the initial report and re sent to sponsor (and applicable other bodies/personnel/groups as specified in section 6.2.1 and 6.2.2.)
- After the first follow up report, further Follow up Report Forms do not need to be completed within a specified timeframe unless the R&D department informs you that this is a requirement. They should only be submitted if there has been a significant change/update of the SAE including where the event is now resolved or a decision for no further follow up has been taken. Please refer to *WI_002 Instructions for completion of SAEs* available on the R&D website.
- For all studies the CI must inform all PIs of relevant information about ***SAEs*** that could adversely affect the safety of participants.
- The CI should review *all* serious adverse events/reactions reported, to identify any trends which may require urgent action.
- The CI should provide the main REC with copies of all reports and recommendations of any independent Data Safety Monitoring Board established for a trial as applicable.
- For IMP studies, on request of the MHRA the CI must submit detailed records of all ***adverse events*** that have been reported.
- For some UHBW or UoB sponsored research where the IMP/s or intervention/s are considered low risk, it may be agreed within the approved protocol that a slight variation in the process described above is acceptable. Including for example, a description of anticipated events within the patient population which if not causally related to the study drug/intervention, do not require onward reporting to sponsor. However, any variations will be reviewed by a member of the UHBW R&D department or UoB sponsor team and agreed prior to implementation of the process. The agreement will be based on risk ensuring patient safety is at the forefront of any decision making.

6.3 Department of R&D responsibilities

- On receipt of an SAE the Research Governance and Quality Officer (RGQO) or Research Management Facilitators (RMFs) are expected to process the SAE in line with *WI_003 processing of R&D reports* in R&D which includes ensuring all CTIMPs or CIMDs are sent to a senior manager within R&D for review.

- For UHBW and UoB sponsored CTIMPs or CIMDs a team of senior managers (band 7 and above) are responsible for reviewing all received SAE/SUSARs against the correct RSI and the investigators' assessments of causality. The intended purpose of this is a quality check ensuring any requiring onward reporting is identified and reported as required, and any appropriate actions taken rapidly.
- For UHBW sponsored blinded research studies to enable processing of a SUSAR, expectedness is assessed initially using the assumption that the test drug/intervention has been given to the participant. If it is assessed as unexpected as per the RSI for the test drug/intervention, the SUSAR should be unblinded for reporting. The R&D Department should follow the unblinding process described within the study Protocol.
- If, following unblinding, the participant is found to have received a placebo, the event does not require reporting to the licensing authority , unless in the opinion of the investigator or sponsor the event was related to the placebo.
- The R&D Department should consider whether any actions, in addition to those already taken by the Investigator, are required and will discuss these with the Investigator.
- The R&D Department reserves the right to suspend or withdraw sponsorship and capacity & capability confirmation for a study. This may happen, but is not limited to, where public health and safety is considered to be at risk, and/or where the safety and well-being of research participants or staff are considered to be at risk.
- The R&D Department will maintain a record of all ***SAEs*** reported to the Department.

6.4 Urgent Safety Measures

- The sponsor and investigator may take appropriate ***Urgent Safety Measures*** (USMs) to protect a research participant from an immediate hazard to their health and safety. This measure can be taken before seeking approval from the licencing authority (MHRA) and ethics committees (http://www.ct-toolkit.ac.uk/routemap/urgent-safety-measures**).**
- The first action is to protect patient safety/health.
- Following that, where UHBW is sponsor, the CI on behalf of the sponsor should discuss the urgent safety measure by telephone with an MHRA medical assessor, ideally within 24 hours from the date the measures are taken.
- After discussing the USM with the MHRA assessor via phone the MHRA must be provided with written notification of the measures taken and discussed with the medical assessor, within 7 days from the date the measures were taken. Details of how to make the written notification can be found on the MHRA website .
- The Research Ethics Committee (REC) must be notified in writing within 7 days from the date the measures are taken. Details of how to notify REC can be found on the HRA website. (All communication between the MHRA, the REC, the CI/PI and the sponsor should be documented and placed in the ISF and TMF.
- Where an USM requires a modification to study documents, this should be submitted as a substantial modification as soon as possible and within approximately 2 weeks of notification to the MHRA. The modification should be marked as being in response to USMs. Details of how to submit a modification can be found on the MHRA and HRA websites.
- The USM-related substantial amendment must not include changes different from those required as an USM.

6.5 Data Safety Monitoring Boards (DSMBs) / Data Monitoring Committees (DMCs)

- During trial set up the Sponsor and the CI must assess whether a Data Safety Monitoring Board (DSMB) is required to provide essential oversight of the trial. The role and responsibility of the DSMB should be described in the Protocol and documented in a charter prior to the start of the study.
- Where a DSMB is put in place for a UHBW sponsored trial the expectation of the board and its functions should include but not be limited to the following:
    - The members should be independent of Sponsor and CI and have the necessary expertise to perform the DSMB duties.
    - The frequency of meetings and methods of communication should be documented in a charter prior to study start.
    - The process for DSMB reporting and the process of how actions must be addressed in an efficient manner must be documented in a charter.
    - A member of the board or research team should have delegated responsibility for maintaining the DSMB paperwork and acting as a liaison point between the DSMB, Sponsor and CI.
    - For blinded trials, DSMB has access to review unblinded data in order to maintain oversight of safety.
    - DSMB is expected to provide recommendations to Sponsor or Trial Steering Committee (if in place) on trial design, protocol amendments, urgent safety measures etc.
- Further information on DSMB can be found in the EMA 'Guidance on data monitoring committees' (EMEA/CHMP/EWP/5872/03). Where UHBW is the Sponsor, the requirements of a DSMB will be discussed as part of the Study Set Up and Management Plan (SUMP) and the expectations and processes will be documented in an agreed charter.

6.6 Development Safety Update Reports

- A DSUR must be compiled and submitted for all CTIMPs. This must be done on the first anniversary of (a) the date of the first Clinical Trials Authorisation (CTA) approval (trials starting after 1 May 2004) (b) the date of the original exemption (trials commenced under an exemption) or (c) the date of the first marketing authorisation granted in the EU (marketed products) and thereafter annually until the regulator has been informed of the closure of the trial.
- If the end-of-trial declaration has been submitted within a reporting period, or within 60 days following the data lock point, the corresponding DSUR is not required.
- The following guidance and DSUR template can be found on the R&D website: *GD_006 Guidance on content of Development Safety Update Reports* and *TMPL_028 Development Safety Update Report Template*
- For UHBW sponsored CTIMPs the DSUR report must be submitted to the Research Projects Manager in UHBW R&D for review before submission to the MHRA.

DSUR submission process:

- For CTIMPs not submitted via combined review:
    - Submission to MHRA through MHRA submissions portal

- Email to REC that granted approval alongside CTIMP Safety Report cover sheet found on the HRA website

- For CTIMPs submitted via combined review:
    - single submission through IRAS. This covers both MHRA and REC so no separate REC email required.
- For CTIMPs not submitted via combined review, More information can be found on the HRA website.
- Preparation and submission of the DSUR is the responsibility of the Chief Investigator, supported and co-ordinated by the sponsor if required. The Research Operations Manager in R&D should provide members of the research teams delivering UHBW Sponsored CTIMPs user access to its account on the MHRA Submissions portal, where appropriate.
- No annual safety reports are required for non CTIMPs

6.7 Annual Progress Reports

On 1 August 2024 HRA removed the requirement to submit annual progress reports for studies that have received a final opinion from any Research Ethics Committee (REC) in the UK. However, any studies that have Confidential Advisory Group (CAG) approval are required to submit an annual report for continuation of CAG approval. Further information can be found on the HRA website.

6.8 End of study declaration and reports

- For UHBW sponsored studies, the CI must inform R&D when the study has ended and that they are preparing the end of study declaration. For CTIMPs, R&D should review the study using *TMPL_016 Sponsor close out checklist* to determine whether they are satisfied as sponsor that the study has ended and what close down procedures need to be actioned. Further information on reporting requirements can be found in GD_*001 Gaining and Maintaining Authorisations*
- Once the declaration of end of study has been submitted to REC & MHRA (if applicable) no modifications can be made to the study.
- For blinded studies where UHBW is sponsor, in compiling these reports, at the request of the CI, the Research and Development Department will provide any additional information required relating to the Sponsor's assessment of SAEs. The Research and Development Department should take all reasonable precautions to ensure that no information that could unblind and therefore compromise the study is provided directly to the Chief Investigator unless the Chief Investigator is already unblinded.

6.9 Non-CTIMP trial SUSARs

- Where UHBW is the sponsor of a non-CTIMPs study, the R&D department delegates responsibility to the research team to report all SAEs that are assessed as **non-CTIMP trial SUSARs to the REC.** This assessment should be made by either the Investigator or the un-blinded assessor (for blinded trials). The report should be sent to the REC that granted approval within 15 days of the CI becoming aware of the event using the applicable form available on the HRA website. The R&D department should receive a copy of the email sent to REC to evidence that they have been notified of the non-IMP SUSAR..
- Where UoB is the sponsor, they should also be notified.

6.10 IMP SUSARs for UHBW & UoB sponsored studies

- This section applies only where UHBW or UoB is the sponsor of the research study using an IMP in which the SAE has occurred and where the investigator and/or sponsor has assessed the SAE to be a *SUSAR*.
- SUSARs relating to placebos and comparators, as well as active IMPs, must be reported to the MHRA and ethics.

6.10.1 Non-Investigational Medical Product (nIMP) SUSARs

- nIMPs are those products that are used in accordance with the protocol, but which fall outside of the IMP definition. nIMPs can include challenge agents used to induce a physiological effect, rescue medication used for preventative action, or concomitant medications that are required by the protocol or background therapy.
- SUSARS related to nIMPs, where there is a possibility of an interaction between a nIMP and an IMP must be reported as SUSARs.
- If a SUSAR occurs, and it might be linked to either a nIMP or an IMP but cannot be attributed to only one of them, the SUSAR must be reported.

6.10.2 Reporting SUSARs to the MHRA

- In the event of a SUSAR occurring in a UHBW sponsored CTIMP, a member of the R&D senior management team or delegated individual within the operations team should report the SUSAR to the MHRA using ICSR Submissions, using the login details restricted to R&D staff. The instructions given within ICSR Submissions should be followed. The R&D department should ensure that any SUSARs are reported to the MHRA within required timeframes regardless of who carries out the reporting.
- In the event of a SUSAR occurring in a UoB-sponsored CTIMP, the applicable UoB sponsor representative should be contacted immediately and a decision made as to who would be most appropriate to make the submission to the MHRA. If it is delegated to UHBW R&D the process above should be followed and UoB should be kept informed throughout the process.
- The R&D department should ensure any follow up information is reported to the MHRA within the applicable timeframes.
- Where there is documented agreement (eg in the division of responsibilities appended to the collaboration agreement), reporting of SUSARs to the MHRA may be delegated to the clinical trials unit running the study.

6.10.3 Reporting SUSARs to the REC

- The R&D Department delegates responsibility to the research team to report all SUSARs that are fatal or life-threatening to:
    - The REC that granted approval[1] within seven days of becoming aware of the event.
- The R&D Department delegates responsibility to the research team to report any additional relevant information to the applicable bodies within eight days of the report being made.

[1] In the case of the main REC, UHBW is only required to report in an expedited fashion SUSARs occurring in the UK.

- The R&D Department delegates responsibility to the research team to report all *SUSARs* that are not assessed as life threatening or fatal to:
    - The research ethics committee that granted approval[1] within 15 days of the sponsor becoming aware of the event.
- For CTIMPs not submitted via combined review: REC should be emailed with the REC Safety Report Form (CTIMPs), available on the HRA website, and SUSAR report enclosed.
- A single form may be used for the submission of several safety reports relating to the same trial. Reports should not normally cover more than one trial. However, the REC may permit this where two trials are very closely connected, for example a main study and an extension study with the same treatment regime**.**
- For CTIMPs submitted via combined review: There is no requirement to email the REC. The MHRA will liaise with the REC if deemed appropriate.

6.10.4 Reporting SUSARs to Investigators at all participating sites

The Medicines for Human Use (Clinical Trials) Regulations 2004 ('the Clinical Trials Regulations'), as amended by the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, no longer require notification of SUSAR information to investigators at all participating sites.

6.11 Reporting requirements for CIMDs

For UHBW and UoB sponsored CIMDs **all serious adverse events** must be reported to the MHRA (**regardless of expectedness**). Full details on how to report these can be found on the MHRA website including details of any online systems for the forms to be uploaded to. https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device .In addition to this, quarterly summary reports of all serious adverse events require reporting to the MHRA. Again, full details of the requirements of this quarterly report can be found on the MHRA website. UHBW R&D takes responsibility for this onward reporting unless otherwise agreed during study set up and delegated to another to report.

7. Dissemination and training in the SOP

This SOP should be disseminated to applicable research staff (including R&D) and is available on the R&D website.

Plan Elements	**Plan Details**
The Dissemination Lead is:	Research Operations Manager
Is this document: A – replacing the same titled, expired SOP, B – replacing an alternative SOP, C – a new SOP:	A – replacing the same titled, expired SOP
If answer above is B: Alternative documentation this SOP will replace (if applicable):	N/A

This document is to be disseminated to:	All applicable research staff (including R&D)
Method of dissemination:	For major updates to the SOP dissemination will be: 1. To Chief Investigators of UHBW Sponsored CTIMPs 2. Research Unit leads across UHBW 3. Head of Research Governance at UoB (where SOP is applicable) All updates (major and minor to the SOP) will be: 1. Updated on the trust Document Management System 2. Updated on the R&D website 3. Cascaded in R&D communications
Is Training required:	All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP. The personal training log of the individual (and the Investigator Site File/Trial Master File if required) should be completed to document that the content of this SOP has been read and understood as described in *SOP_007 Research Training UHBW*

REFERENCES	• UK Policy Framework for Health & Social Care Research. https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/ • The Medicines for Human Use (Clinical Trials) Regulations 2004 Statutory Instrument 2004 No. 1031. • The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019 • The Medicines for Human Use (Clinical Trials) (Amendments) Regulations 2025 • EMEA Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use. April 2006 • DSUR guidance: ICH E2F • https://mhrainspectorate.blog.gov.uk/2021/02/05/reference-safety-information-rsi-for-clinical-trials-part-iii/

RELATED DOCUMENTS AND PAGES	• GD_006 Guidance on content of Development Safety Update Reports • TMPL_024 Adverse Events Template • TMPL_025 SAE/SUSAR initial report form • TMPL_026 SAE/SUSAR follow up report form • TMPL_027 R&D review of SAEs • TMPL_028 Development Safety Update Report (DSUR) template • WI_002 Instructions for completion of SAE forms • WI_003 Processing of SAE reports in R&D These are available on the R&D section of UHBW's website: http://www.uhbristol.nhs.uk/research-innovation/
AUTHORISING BODY	Approved by Trust Research Group
SAFETY	N/A
QUERIES AND CONTACT	Research & Development (R&D) department via research@uhbw.nhs.uk
AUDIT **REQUIREMENTS**	R&D departmental Quality Management System audits are undertaken annually.