Standard Operating Procedure

RESEARCH SAFETY REPORTING

SETTING Trustwide

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&I department : Ext 29873 or research@uhbw.nhs.uk

Document History

SOP number	SOP 009	**SOP Version**	11.0
Effective Date	22/NOV/2021	**Review Date**	22/NOV/2023

Review date	Version number	Version date	Effective date	Author/ Reviewer	Authorised by
This information is not available for previous versions (prior to version 8.0)					
September 2015	V8.0	12/OCT/2015	03/NOV/2015	Jess Bisset	Diana Benton
November 2016	V9.0	06/JAN/2017	14/FEB/2017	Jess Bisset	Diana Benton
July 2017	V9.1	14/JUL/17	17/JUL/2017	Jess Bisset	Elinor Griffiths
22/DEC/2017	V9.2	22/DEC/2017	12/MAR/2018	Jess Bisset	Diana Benton
September 2020	V10.0	12/OCT/2020	16/NOV/2020	Sarah Bishop Sandra Mulligan Katharine Wale	Jess Bisset
January 2021	V11.0	13/JAN/2021	22/NOV/2021	Katharine Wale	Diana Benton

Version Number	Reason for change
This information is not available for previous versions (prior to version 3.5)	
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5.0	Changes to out of date website links and clarification on responsibilities of research team.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.
7.0	Clarification of process of reporting, updates to website links and minor changes to reporting templates
V8.0	Update to template in line with new R&I 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.

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 the Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019 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 will 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 Chief Investigator and Principal Investigator(s). The Chief Investigator is responsible for reporting urgent safety measures to regulatory bodies and to participating sites and for reviewing safety reports where applicable, The Principal Investigator(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&I 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
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
PI	Principal Investigator
REC	Research Ethics Committee
R&I	Research and Innovation
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 subject to whom a medicinal product/medical device/intervention has been administered, including occurrences which are not necessarily caused by or related to that product. *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 subject to an investigational medicinal product/medical device/intervention which is related to any dose administered to that subject *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; 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 set out in the Reference Safety Information, which may be: (a) the summary of product characteristics (for a product with a marketing authorisation), (b) the investigator's brochure (for any other investigational medicinal product). (c) or other document containing equivalent information e.g. the study protocol *This applies to the medicinal product/medical device/intervention in question* *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 subject 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. SAE/SARs 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 or the other 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 an 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 (c) or other document containing equivalent information.
Reference Safety Information	The information used for assessing whether an adverse reaction is expected.
Investigational Medicinal Product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial including a medicinal product which has a marketing authorisation but is, for the purposes of the trial being used or assembled (formulated or packaged) in a way different from the approved form or being used for an unapproved indication or when used to gain further information about an approved use.
Non-IMP SUSAR	An ***SAE*** that occurs in a non-IMP 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 action 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 will need to be assessed as follows:

6.1.1 Intensity assessment

- The assessment of intensity will be 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 will 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 Chief Investigator will determine what will be used as the Reference Safety Information (RSI) to determine causality of any adverse events. For CTIMPs, the RSI will be submitted to the MHRA as part of the CTA application and may be found:
    - in the case of a product with a marketing authorisation, in the summary of product characteristics for that product
    - in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
    - Any other agreed document as approved by the MHRA (e.g. Protocol)

- 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 Principal investigators will 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 summary of product characteristics is updated by the manufacturer), the sponsor and CI must agree whether this should replace the existing RSI. If it is agreed, an amendment will be submitted to the MHRA and only once approved will the updated RSI be used, except in the case of Urgent Safety Measures, in which case the process described in 5.3.1 will be followed.

- A robust process must be in place for checking for any applicable updates to the Summary of Product Characteristics (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.

  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 drug/device/procedure and the occurrence of each adverse event will be assessed and categorised as below. The investigator will 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. will 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, 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 related, probably related, 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:** Reaction previously identified and described in the RSI and/or protocol
    - **Unexpected:** 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 or severity of an expected adverse reaction
- The protocol must identify the RSI used.
- SARs due to lack of efficacy or due to disease progression should <u>not</u> be considered as expected events unless 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 subjects are given priority at all times and must take appropriate action to ensure the safety of all staff and patients in the study. The Investigator will 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 patients (see 5.1.1), the Investigator must ensure appropriate regulatory permissions are obtained for the amendment in line with *GD_001 Gaining and Maintaining Authorisations.*
- If the amendment is due to implementation of urgent safety measures, the amendment will be implemented immediately and then submitted for necessary approvals. Initial notification of the urgent safety measure should be by telephone to R&I on 0117 342 0233 and to REC and MHRA (details of the applicable phone numbers can be found on both the HRA and MHRA website). Notice in writing to REC, R&I and MHRA should be sent within three days.

The notice should set out the reasons for the urgent safety measures and plan for further action.

- The Investigator is responsible for ensuring that all ***adverse incidents*** *in research taking place at UHBW Bristol*, 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 (DMS) via Connect homepage. Incidents occurring at other sites 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 subject'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 record form or equivalent to allow analysis at a later stage. On the R&I website, *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, expectedness and seriousness as described in section 4. 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.
- ***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 will review all adverse events/reactions reported to identify any trends which may require urgent action.
- The Chief Investigator will 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 the study all ***adverse event/reactions*** recorded during a study must be subject to statistical analysis as determined by the protocol and that analysis and subsequent conclusions 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 will make an initial report, orally or in writing. Oral reports will be followed up in writing within 24 hours of the initial report. Written reports will 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 will use *TMPL_025 SAE/SUSAR Initial Report form* available on the R&I website unless there is documented agreement from R&I that a different template form can be used. 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).
- In addition to 6.2.1 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 subject:
    - For SUSARs the investigator (or delegated person) must provide a follow up report within five days of the initial report to UHBW
    - For Non- SUSARs the investigator (or delegated person) must provide a follow up report within ten days of the initial report to UHBW

- 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.)

- If the event is on-going and is a SUSAR then within five days of UHBW becoming aware of the event the site must complete the Follow up Report Form and send to UHBW at research@uhbw.nhs.uk

  If the event is ongoing and is a non-SUSAR then within 10 days of UHBW becoming aware of the event the site must complete the Follow up Report Form and send to UHBW at research@uhbw.nhs.uk

- After the first follow up report, further Follow up Report Forms do not need to be completed within a specified timeframe unless the R&I 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&I website.
- For all studies the Chief Investigator must inform all Principal Investigators of relevant information about ***SAEs*** that could adversely affect the safety of subjects.
- The Chief Investigator will review *all* serious adverse events/reactions reported to identify any trends which may require urgent action.
- The Chief Investigator will 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 Chief Investigator will submit detailed records of all ***adverse events*** that have been reported.

6.3 Department of R&I responsibilities

- For UHBW sponsored blinded research studies in which the ***SAE/SUSAR*** has occurred and where the Investigator and Sponsor have assessed that an unblinded assessment is required, the R&I Department will follow the unblinding process described within the study Protocol to make an unblinded assessment of intensity, causality, expectedness and seriousness using the criteria described in section 6. In making this assessment the R&I Department will consult the independent Data Safety Monitoring Board (DSMB) for the study or, where a DSMB does not exist, a suitably medically qualified person. This unblinded assessor may be an investigator on the same study if unblinding him/her will not affect the conduct of the study in which the SAE has occurred; this will not be the person who made the initial assessment. *NB A second assessment by the sponsor is not required where the investigator making the initial assessment is unblinded or where it is deemed unnecessary to make an unblinded assessment e.g, the event was expected.*

- The R&I Department will consider whether any actions, in addition to those already taken by the investigator, are required and will discuss these with the investigator.
- The R&I Department reserve 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, where the safety and well-being of research subjects or staff are considered to be at risk.
- The R&I 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 competent authorities (MHRA in the UK) and ethics committees of all member states concerned (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 as soon as it has been put in place with an MHRA safety scientist in the first instance.
- A protocol amendment must be submitted within the following three days to the MHRA, and ethics committee; details are located on the MHRA & HRA websites. All communication between the MHRA, the REC, the CI/PI and the sponsor should be documented and placed in the ISF and TMF.

6.5 Data Safety Monitoring Boards

- During trial set up the Sponsor and Chief Investigator will assess whether a Data Safety Monitoring Board (DSMB) is required to provide essential oversight of the trial. The role and responsibility of the DSMB will be described in the Protocol and documented charter prior to study start.
- Where a DSMB is put in place for a UHBW sponsored trial the expectation of the board and its functions will include but not be limited to the following:
    - The members should be independent of Sponsor and CI
    - The process for frequency of meeting and methods of communication should be documented in a charter prior to study start
    - How reports from the board will be generated and the process of how actions must be addressed in an efficient manner must be documented
    - 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, to review unblinded data in order to maintain oversight of safety
    - 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 Sponsor the requirements of a DSMB will be discussed as part of the Study Set Up and Management Plan (SUMP) and the expectation and processes 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.

- The following guidance and DSUR template can be found on the R&I website: *GD_006 Guidance on content of Development Safety Update Reports* and *TMPL_028 Development Safety Update Report Template*
- The DSUR report must be submitted to the Research Projects Manager in UHBW R&I for review before submission to the MHRA. Submission to the MHRA should be made electronically through the MHRA Submissions portal. The DSUR should also be submitted by email to the Research Ethics Committee that granted approval.
- Preparation and submission of the DSUR will be the responsibility of the Chief Investigator, supported and co-ordinated by the sponsor if required. The Research Operations Manager in R&I will provide members of the research teams delivering UHBW Sponsored CTIMPs user access to its account on the MHRA Submissions portal, where appropriate.
- Each submission of a DSUR to the REC must be accompanied by the CTIMP safety report to REC which is available to download from the HRA website.
- Annual safety reports must also be sent to the REC for non CTIMPs. Further information including the required form can be found on the HRA website.

6.7 Annual Progress Reports

- For all studies (IMP and non-IMP studies), annual progress reports should be submitted by the CI to the REC one year following the granting of a favourable ethical opinion and thereafter annually. These reports will include information on the safety of participants and are required in addition to the annual safety report. The form for providing these reports is available on the HRA website.
- For blinded studies where UHBW is sponsor, in compiling these reports, at the request of the CI, the R&I Department will provide any additional information required relating to the Sponsor's assessment of SAEs. The R&I Department will take all reasonable efforts to ensure that no information that could unblind and therefore compromise the study is provided directly to the CI, unless the CI is already unblinded.

6.8 End of study declaration and reports

- For UHBW sponsored studies the CI must inform R&I when the study has ended and that they are preparing the end of study declaration. For CTIMPs R&I will 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 amendments can be made to the study.
- For blinded studies where UHBW is sponsor, in compiling these reports, at the request of the Chief Investigator, the Research and Innovation Department will provide any additional information required relating to the Sponsor's assessment of SAEs. The Research and Innovation Department will take all reasonable efforts 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-IMP SUSARs

- Where UHBW is the sponsor of a non-IMP study, the Research and Innovation Department will delegate responsibility to the research team to report all SAEs that are assessed as

non-IMP SUSARs to the REC. This assessment will be made by either the investigator or the un-blinded assessor (for blinded trials). The report will be sent to the research ethics committee that granted approval within 15 days of the Chief Investigator becoming aware of the event using the applicable form available on the HRA website. The R&I 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 are sponsor they should also be notified.

6.10 IMP SUSARs for UHBW & UoB sponsored studies

- This section applies only where UHBW or the 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 Reporting SUSARs to the MHRA

- In the event of a SUSAR occurring in a UHBW or UoB sponsored CTIMP, a member of the Research & Innovation senior management team or delegated individual within the operations team will make an entry in the European database to report the SUSAR to the MHRA. The procedure is to log into the MHRA eSUSAR system: https://esusar.mhra.gov.uk/ using the login details which are located in the R&I shared J Drive, within the monitoring folders (to which only R&I staff have access). The instructions given within the database will be followed. The R&I department will ensure that any SUSARs are reported to the MHRA within required timeframes regardless of who carries out the reporting.
- The R&I department will ensure any follow up information is reported to the MHRA within the applicable timeframes.

6.10.2 Reporting SUSARs to the REC

- The R&I Department will delegate responsibility to the research team to report all SUSARs that are fatal or life-threatening to:
    - The research ethics committee that granted approval[1] within seven days of becoming aware of the event.
- The R&I Department will delegate responsibility to the research team to report any additional relevant information to the applicable bodies within eight days of the report being made.
- The R&I Department will delegate 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.
- Initial notifications of *SUSARs* may be made by e-mail or telephone. Follow-up reports and all other safety reports should be sent to the REC office by email.
- Each submission of a *SUSAR* report to the REC must be accompanied by the Safety Report form for CTIMPs available on the HRA website.
- 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**.**

6.10.3 Reporting SUSARs to Investigators at all participating sites

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

For UHBW sponsored studies responsibility will be delegated to either the Chief Investigator or co-ordinating trials unit to disseminate SUSAR information to investigators at all participating sites. This responsibility will be documented in the TMPL_ 007 UHBW Sponsor Study Set Up and Management Plan (SUMP) as described in SOP_002 Research Sponsorship at UHBW.

7. Dissemination and training in the SOP

This SOP will be disseminated to applicable research staff (including R&I) and will be available on the R&I website.

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*.

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 • 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&I review of SAEs • TMPL_028 Development Safety Update Report (DSUR) template • WI_002 Instructions for completion of SAE forms • WI_003 UHBristol SAE processing flowcharts within R&I These are available on the R&I 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 & Innovation (R&I) department : Ext 29873 or research@uhbw.nhs.uk