Standard Operating Procedure

RESEARCH SAFETY REPORTING

SETTING Trust wide/Research & Innovation

FOR STAFF All staff involved in research

Standard Operating Procedure (SOP)

Research Safety Reporting Standard Operating Procedure		
Approved by:	Diana Benton	Deputy Director of Research & Innovation
Updated by:	Jess Bisset	Research Operations Manager

	Date	**Version**	**Reason for change**	**Author/Responsible person**
Original policy	September 2005			Research and Development Manager (Governance and Quality)
Review	September 2008			
Review	August 2011	3.4		
Update	February 2012	3.5	Minor change to errors in addresses	Research Operations Manager
Review & Update	February 2012	4.0	Change from annual reporting to Development Safety Update Reporting	Research Operations Manager
Approved	February 2012	4.0	Change from annual reporting to Development Safety Update Reporting	Deputy Director of Research and Innovation
Review & Update	March 2013	5.0	Changes to out of date website links and clarification on responsibilities of research team.	Acting Research Operations Manager.
Review & Update	April 2014	6.0	Clarification of process of reporting and updates to website links.	Research Operations Manager
Review & Update	February 2015	7.0	Clarification of process of reporting, updates to website links and minor changes to reporting templates	Research Operations Manager

Review date	Version number	Version Date	Effective Date	Reason for change	Author/Responsible person	Authorised by
September 2015	V8.0	12/10/2015	03/11/2015	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	Jess Bisset – Research Operations Manager	Diana Benton
November 2016	V9.0	06/01/2017	14/02/2017	Additional information about Reference Safety Information, revising order of SOP, updates and clarifications	Jess Bisset	Diana Benton
July 2017	V9.1	14/07/17	17/07/2017	Removal of template appendices into standalone templates and minor revision to wording.	Jess Bisset	Elinor Griffiths

Acknowledgements:

1. Ms Tanya Symons; T Symons Associates Ltd. 154 Tivoli Crescent North, Brighton, East Sussex.
2. North Bristol NHS Trust

RESEARCH SAFETY REPORTING

1 Background, guidance and legislation

1.1 In 2001 the Government published the Research Governance Framework for Health and Social Care. Enquiries into adverse incidents relating to research have criticised the lack of clarity in relation to responsibilities and accountabilities for research in health and social care. This is of particular importance, given the very wide range of individuals and organisations that can be involved in research. The Framework pays particular attention to clarifying responsibilities and accountabilities with the aim of forestalling research related adverse incidents. In accordance with the Research Governance Framework for Health and Social Care UH Bristol must have systems in place to record, investigate and report adverse incidents arising from any research undertaken within the Trust.

1.2 The Medicines for Human Use (Clinical Trials) Regulations 2004 came into force on the 1st May 2004. These regulations including any amendments apply to all clinical trials involving investigational medicinal products (CTIMPs) and 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.

1.3 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 UHBristol intranet). NB, an adverse incident may also be an adverse event and should be reported through both routes.

1.4 All Trusts have a responsibility to report adverse incidents relating to research to the National Patient Safety Agency.

1.5 For CTIMPs, updated guidance (Development Safety Update Report (DSUR) – ICH E2F) was published in September 2010 in the EU and was implemented in September 2011. DSUR should be provided at yearly intervals from the date of the original exemption, for trials ongoing on 1 May 2004, or the date of the first CTA approval for trials starting after 1 May 2004. For trials with marketed products the date is the first marketing authorisation granted in the EU. The purpose of the DSUR is to introduce a common standard for periodic reporting on drugs under development among the ICH regions, highlighting new safety issues and giving a current safety profile of an IMP.

2 Scope

2.1 In scope:

Recording and reporting 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 UH Bristol is the sponsor, where no sponsor policy exists, or where the minimum reporting requirements laid out within the UH Bristol Research Safety Reporting SOP are not met, this SOP must be followed as a minimum.

2.2 Out of scope:

Adverse incidents which will be reported in accordance with UH Bristol Adverse Incident Reporting Policy and Guidelines (see section 1.3).

3 Abbreviations and definitions

3.1 Abbreviations

AE	Adverse Event
AI	Adverse Incident
AR	Adverse Reaction
CI	Chief Investigator
CTIMP	Clinical trial of an Investigational Medicinal Product
EU	European Union
HRA	Health Research Authority
IMP	Investigational Medicinal Product
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
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
UHBristol	University Hospitals Bristol NHS Foundation Trust
UoB	University of Bristol

3.2 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: (a) the summary of product characteristics (for a product with a marketing authorisation), (b) the investigator's brochure (for any other investigational medicinal product). *This applies to the medicinal product/medical device/intervention in question* *When the outcome of the adverse reaction is not consistent with the applicable product 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 SAE/SAR is serious in other situations. Important 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.
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)**	Where 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)

4 Assessment of Adverse Events

4.1 Intensity

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.*

4.2 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).

4.3 Causality

4.3.1 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. This RSI will be submitted to the MHRA as part of the CTA application and may be

(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) Any other agreed document as approved by the MHRA

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.

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***.

4.3.2 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

NB The protocol must identify the RSI used.

5 Investigator Responsibilities

5.1 All Adverse Events

5.1.1 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.

5.1.2 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 the Gaining and Maintaining Authorisations SOP.

5.1.3 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 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.

5.1.4 The Investigator is responsible for ensuring that all ***adverse incidents***, whether or not related to research, are reported in accordance with the University Hospital Bristol's Serious Incident Policy and associated policies.

5.1.5 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).

5.1.6 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. A template for recording adverse events is provided as a standalone template on the R&I website.

5.1.7 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 may increase, resulting in the event becoming unexpected, which may change the reporting requirements.

5.1.8 ***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.

5.1.9 The Chief Investigator will review all adverse events/reactions reported to identify any trends which may require urgent action.

5.1.10 The Chief Investigator will keep the Sponsor and the main REC informed of any significant findings and recommendations by an independent Data Monitoring Committee or equivalent body where one has been established for the trial.

5.1.11 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.

5.2 Serious Adverse Events

5.2.1 **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/investigator 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 UH Bristol is the sponsor or where no form has been provided, the investigator will use the UH Bristol Research Related 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 will include as much information as is available at the time.

5.2.2 In addition to 5.2.1 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 5.2.1 and 5.2.2 is where the protocol or other relevant RSI (e.g. investigator brochure) identifies the event as not requiring immediate reporting.

5.2.3 After the initial report the investigator is required actively to follow up the subject. The investigator (or delegated person) must provide information missing from the initial report within five working days of the initial report to the bodies specified in section 5.2.1 and 5.2.2.

5.2.4 Investigators (or delegated persons) will provide follow-up information, each time new information is available, using the UH Bristol Research Related SAE/SUSAR Follow-up Report form available on the R&I website, form provided by the sponsor or other agreed form, until the ***SAE*** has resolved or a decision for no further follow up has been taken.

5.2.5 For all studies the Chief Investigator must inform all Principal Investigators of relevant information about ***SAEs*** that could adversely affect the safety of subjects.

5.2.6 The Chief Investigator will review *all* serious adverse events/reactions reported to identify any trends which may require urgent action.

5.2.7 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.

5.2.8 For IMP studies, on request of the MHRA the Chief Investigator will submit detailed records of all ***adverse events*** that have been reported.

5.3 Urgent Safety Measures

5.3.1 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 UHBristol is sponsor, the CI/PI 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 website. All communication between the MHRA, the CI/PI and the R&I office should be documented and placed in the ISF and TMF.

5.4 Data Safety Monitoring Boards

5.4.1 During trial set up it will be assessed by Sponsor and Chief Investigator 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 UH Bristol 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 process of how actions must be addressed in an efficient manner documented
- A member of the board or research team is delegated responsibility for maintaining the DSMB paperwork and acting as a liaison point between the DSMB, Sponsor and CI

- For blinded trials review unblinded data in order to maintain oversight of safety
- 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 UH Bristol are Sponsor the requirements of a DSMB will be discussed during the Study Set Up and Management Plan (SUMP) and the expectation and processes documented in an agreed charter.

5.5 Development Safety Update reports

5.5.1 For CTIMPs, 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, a DSUR must be compiled and submitted. Preparation and submission of the DSUR will be the responsibility of the Chief Investigator, supported and co-ordinated by the sponsor if required. Submission should be made electronically to the MHRA through the Common European Submission Platform (CESP). The Research Operations Manager in R&I will provide members of the research teams delivering UH Bristol Sponsored CTIMPs user access to CESP where appropriate.

And via email to:

- Research Ethics Committee that granted approval.

Appendix 2 provides guidance for DSUR completion and UH Bristol standalone template – DSUR can be found on the R&I website. If the UHBristol template is not used, the DSUR report should still be submitted to the Research Projects Manager for review before submission to the MHRA.

5.5.2 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 Annual Progress Reports

6.1 Annual progress reports should be submitted thereafter until the end of the study

6.2 For all studies (IMP and non-IMP studies), 1 year following the granting of a favourable ethical opinion and thereafter annually, the Chief Investigator will submit progress reports to the Research Ethics Committee. 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.

6.2.1 For blinded studies where UH Bristol 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.

6.3 End of study declaration and reports

6.3.1 For UH Bristol sponsored studies the CI must inform R&I when the study has ended and they are preparing the end of study declaration. R&I will review the study using the standalone template 'study 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 the Gaining and Maintaining Authorisations SOP

- Once the declaration of end of study has been submitted to both REC & MHRA no amendments can be made to the study.

6.3.2 For blinded studies where UH Bristol 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.

7 Department of Research and Innovation Responsibilities

7.1 Where UH Bristol is the sponsor of a blinded research study in which the ***SAE/SUSAR*** has occurred and where the Investigator and Sponsor have assessed that an unblinded assessment is required, the Research and Innovation Department will follow the unblinding process described within the approved 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 Research and Innovation 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.*

7.2 The Research and Innovation Department will consider whether any actions, in addition to those already taken by the investigator, are required and will discuss these with the investigator.

7.3 The Research and Innovation Department reserves the right to suspend or withdraw sponsorship and NHS permission (or equivalent) 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.

7.4 The Research and Innovation Department will maintain a record of all ***SAEs*** reported to the Department.

7.5 Non-IMP SUSARs

7.5.1 Where UH Bristol is the sponsor of a blinded 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.*** This assessment will be made by either the investigator or the un-blinded assessor. The report will be sent to the research ethics committee that granted approval within 15 days using the applicable form available on the HRA website.

7.6 IMP SUSARs

7.6.1 This section applies only where UH Bristol 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***.

7.6.2 In the event of a SUSAR occurring in a UHBristol or University of Bristol 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. 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 within required timeframes regardless of who carries out the reporting.

7.6.3 The Research and Innovation 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.

7.6.4 The Research and Innovation Department will delegate responsibility to the research team to report any additional relevant information to the bodies described in section 7.6.3 within eight days of the report being made.

7.6.5 The Research and Innovation 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 becoming aware of the event.

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

7.6.6 Initial notifications of ***SUSARs*** may be made by fax, e-mail or telephone. Follow-up reports and all other safety reports should be sent to the REC office by email.

7.6.7 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.

7.7 Development Safety Update, annual progress and end of study reports

7.7.1 Where UH Bristol is sponsor, at the request of the Chief Investigator the Research and Innovation Department will assist the Chief Investigator by co-ordinating the compilation of the Development Safety Update, annual progress and end of study reports. In meeting such requests 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.

8 References

1. **Department of Health Second edition April 2005** Research Governance Framework for Health and Social Care.
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/139565/dh_4122427.pdf
2. The Medicines for Human Use (Clinical Trials) Regulations 2004 Statutory Instrument 2004 No. 1031
http://www.legislation.hmso.gov.uk/si/si2004/20041031.htm#33

3. 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
http://ec.europa.eu/health/files/eudralex/vol-10/21_susar_rev2_2006_04_11_en.pdf

4. DSUR guidance: ICH E2F
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2F/Step4/E2F_Step_4.pdf

9. Dissemination and training in the SOP

9.1 Dissemination of this SOP

9.1.1 New SOPs and new versions of existing SOPs: The Research Operations Manager will be responsible for ensuring authorised SOPs are uploaded to the DMS in line with Trust policy and on the R&I website as described in the SOP “Authorship, review, revision and

approval of research procedural documents produced by Research & Innovation". Internal Trust Staff are expected use the DMS to access latest versions of SOPs and to check the website regularly for updates, as communicated in the Training SOP.

Notice of new or amended procedural documents that have undergone a major amendment will be given via the following routes:

- Inclusion in the R&I e-bulletin (monthly);
- Direct email to Research Leads, Research Unit Managers and Band 7 staff for onward cascade ;
- Direct email to Chief Investigators of CTIMPs sponsored by UHBristol;
- Direct email to the Head of Research Governance at the University of Bristol (as relevant).

9.2 Training in this SOP

9.2.1 All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP.

9.2.2 The training log within the Investigator Site File/Trial Master File should be completed to document that members of staff have read and understood the content of the SOP and its amendments.

10. Appendices and standalone templates:

Appendix 1: UHBristol SAE processing flowcharts within R&I
Appendix 2: Guidance on content of Development Safety Update Reports

Standalone template 1: Adverse Events Template
Standalone template 2: Instructions for completion of SAE forms
Standalone template 3: SAE/SUSAR initial report form
Standalone template 4: SAE/SUSAR follow up report form
Standalone template 5: R&I review of SAEs (UH Bristol/UoB sponsored CTIMPs)
Standalone template 6: Development Safety Update Report (DSUR) template

Please note all standalone templates can be found on the R&I website: http://www.uhbristol.nhs.uk/research-innovation/information-for-researchers/setting-up-and-running-a-clinical-research-study/templates-and-sops/templates/

RELATED DOCUMENTS	002/UHBristol R&I Sponsorship SOP 005/UHBristol R&I Gaining & Maintaining Authorisation SOP
QUERIES	Research Operations Manager or Research Management Facilitators - Research & Innovation Department via 0117 342 0233

Appendix 1 UH Bristol SAE processing flowcharts within R&I

This flow chart is for use by R&I staff as a guidance document for handling SAEs reported to the UH Bristol R&I office for studies where UH Bristol or University of Bristol are acting as Sponsor. SAEs for studies sponsored by other organisations are not required to be sent to R&I. Please refer to the research safety reporting SOP for more information. A current version of the SOP can be found on the R&I website.

SAE picked up by RMF with responsibility for reviewing SAEs that month or when RMF not available the nominated deputy RMF . The rota showing which RMF is allocated to reviewing SAEs and their nominated deputy is stored in the R&I shared J Drive in the safety reporting folder. Please refer to the RMF Team Leader if there are any issues locating the rota.

SAE report received into R&I department either via fax, email or post.

SAE report reviewed for completeness and entered onto SAE spreadsheet located: J:\Research_and_Innovation\Monitoring\Safety Reporting\SAE-SUSAR_Breaches_spreadsheet_v1.3_June 2016.xlsx *note PI signature must be recorded on SAE form or SAE form sent from PI email inbox (PI employer's email account only – no personal accounts) to confirm PI review.

Where SAE form not complete RMF chases research team (all within reporting timelines)

RMF reviews intensity, expectedness, relatedness and seriousness and records this information on SAE spreadsheet identifying any requiring expedited reporting. Monitor/RMF also records whether SAE occurred in CTIMP or non CTIMP trial on spreadsheet.

IF SAE IS UNEXPECTED AND POSSIBLY, PROBABLY OR DEFINITELY RELATED (SUSAR) REQUIRES REPORTING TO REGULATORY AUTHORITIES- Refer to **flowchart A**

IF SAE is (a) expected or (b) unexpected and unlikely/not related to trial intervention, was it in a CTIMP?

YES

For all CTIMPs, provide SAE form and relevant RSI to Senior Manager in R&I for Sponsor review **within 3 days of receipt of SAE**. Attach queries standalone template form provided in for HoR&I to document any queries of SAE to be raised with PI or research team

Sponsor review disagrees or seeks further clarification from 3rd party on causality, relatedness and/or expectedness using standalone template s~~S~~ponsor report form ~~in Appendix 5 of Research Safety SOP~~. ~~Head of R&I~~Senior Manager informs RMF and contacts PI and CI to

Sponsor review in agreement

If SAE resolved SAE report to be filed in study folder (either hard copy if received via fax or electronic if received via email).

If sponsor and CI continue to disagree and one review changes SAE to SUSAR- expedited process followed **(refer to flowchart A) –** Both reviews to be submitted to REC & MHRA

NO

For all non-CTIMPs RMF to ensure completeness of report received and relevant information input into spreadsheet. No Head of R&I review required.

If SAE ongoing refer to **flowchart B**

Flowchart A -

IF SAE IS UNEXPECTED AND POSSIBLY, PROBABLY OR DEFINITELY RELATED (SUSAR) REQUIRES REPORTING TO REGULATORY AUTHORITIES

IF SUSAR is **fatal** or **life threatening** SUSAR to be reported to Ethics and MHRA within **7 days.** Any other relevant information must be sent **within 8 days of the report**.
If SUSAR is **non-fatal** or **non-life threating,** SUSAR to be reported to Ethics & MHRA within **15 days**.
The following processes described will occur within the appropriate timeframes depending on whether SUSAR is fatal or life threatening.

SUSAR OCCURRED IN CTIMP

SUSAR OCCURRED IN NON-CTIMP

For all CTIMPs, provide SAE form and relevant RSI to Head of Research & Innovation (or Research Operations manager in absence) for Sponsor review **within 3 days of receipt of SAE**.

RMF reviews SAE report – only provided to Head of R&I for review if issues identified.

Sponsor review disagrees or seeks further clarification from 3rd party on causality, relatedness and/or expectedness using standalone template sSponsor report form ~~in Appendix 5 of Research Safety SOP –~~ informs RMF and Head of R&I contacts PI and CI to discuss.

Sponsor review in agreement with report

Sponsor and CI continue to disagree.

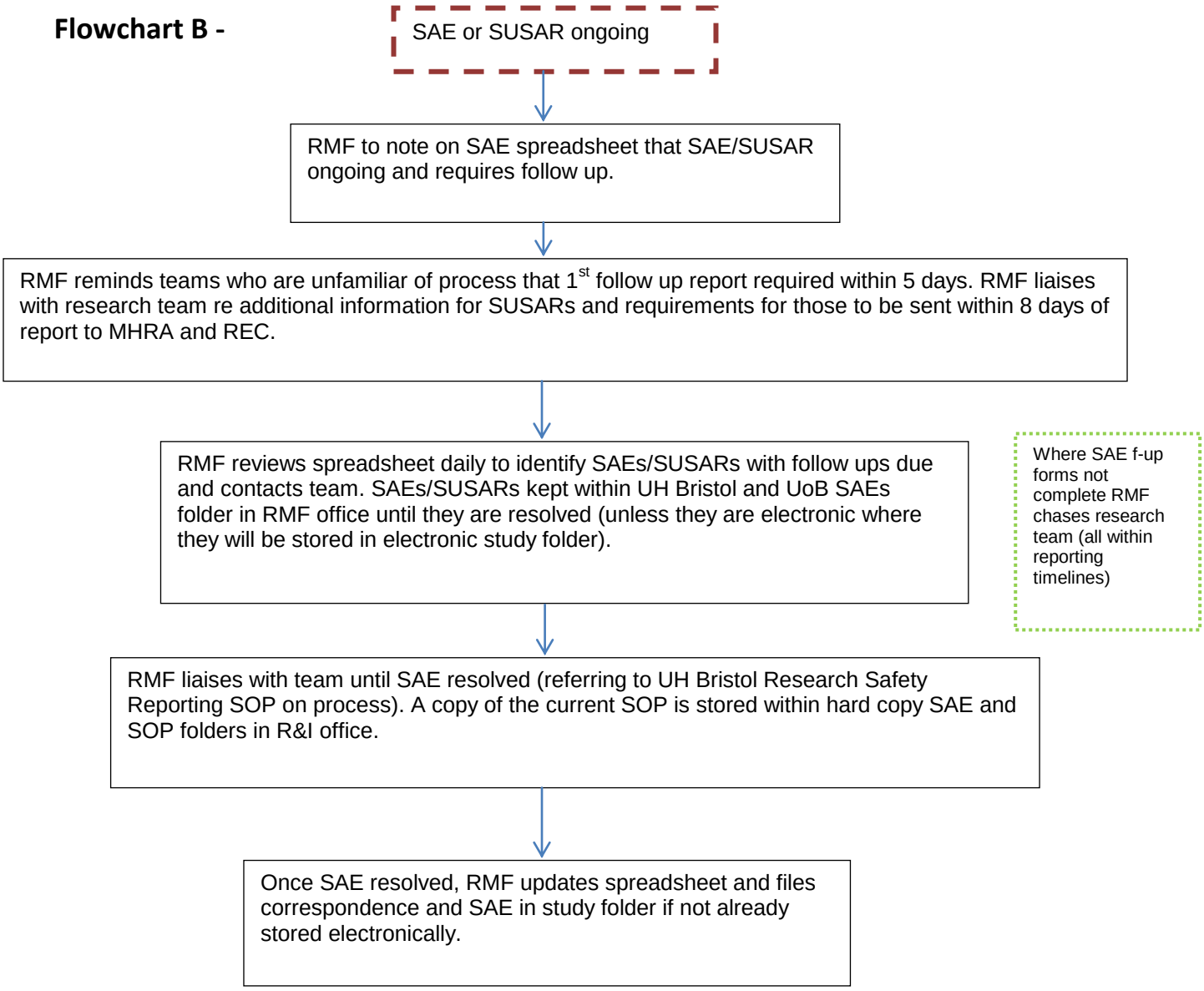
Sponsor and CI come to agreement.

RMF liaise with research team and request they submit both CI SUSAR review and Sponsor SUSAR review to Ethics for information. RMF/Monitor complete e-SUSAR report with both assessments (CI and Sponsor) and notify research team when complete.

RMF liaises with research team to ensure they submit to Ethics. Monitor/RMF completed e-SUSAR to MHRA and informs research team when complete.

If SUSAR is ongoing refer to **flow chart B**. If resolved, RMF to file all paperwork in appropriate study location (electronic study file if appropriate). SAE spreadsheet information completed.

Flowchart B -


SAE or SUSAR ongoing
RMF to note on SAE spreadsheet that SAE/SUSAR ongoing and requires follow up.
RMF reminds teams who are unfamiliar of process that 1st follow up report required within 5 days. RMF liaises with research team re additional information for SUSARs and requirements for those to be sent within 8 days of report to MHRA and REC.
RMF reviews spreadsheet daily to identify SAEs/SUSARs with follow ups due and contacts team. SAEs/SUSARs kept within UH Bristol and UoB SAEs folder in RMF office until they are resolved (unless they are electronic where they will be stored in electronic study folder).
Where SAE f-up forms not complete RMF chases research team (all within reporting timelines)
RMF liaises with team until SAE resolved (referring to UH Bristol Research Safety Reporting SOP on process). A copy of the current SOP is stored within hard copy SAE and SOP folders in R&I office.
Once SAE resolved, RMF updates spreadsheet and files correspondence and SAE in study folder if not already stored electronically.

Appendix 2 - Guidance on content of Development Safety Update Reports

For Development Safety Update Report (DSUR) standalone template: http://www.uhbristol.nhs.uk/research-innovation/information-for-researchers/setting-up-and-running-a-clinical-research-study/templates-and-sops/templates/

A DSUR is IMP specific. If a Chief Investigator is carrying out more than one trial using the same IMP, one DSUR should be submitted for the IMP. This should occur on the first anniversary of the first regulatory approval in the world, and annually thereafter. For CTIMPS which have more than one IMP, the sponsor and the CI should agree the most appropriate approach to DSUR, and whether a single DSUR should be submitted for each IMP, or whether a combined DSUR should be submitted. Factors which will influence this decision are the dosing regime, form and the method(s) of administration.

Useful guidance on completing the DSUR:

1. **Report on the subjects' safety of a clinical trial** based on the information provided by investigators and the sponsor's own assessments, the sponsor will report all new findings related to the safety of the IMP treatments in the concerned trial. Where UH Bristol is the sponsor, this will be delegated to the relevant research team to report. The concept of new findings refers to information not already present in the investigator's brochure or, for licensed drugs, the summary of product characteristics. When relevant, the following points should be considered:
    a. relation with dose, duration, time course of the treatment
    b. reversibility
    c. evidence of previously unidentified toxicity in the trial subjects
    d. increased frequency of toxicity
    e. overdose and its treatment
    f. interactions or other associated risks factors
    g. any specific safety issues related to special populations, such as the elderly, the children or any other at risk groups.
    h. positive and negative experiences during pregnancy or lactation
    i. abuse
    j. risks which might be associated with the investigation or diagnostic procedures of the clinical trial

    The report should also consider other experiences with the investigational medicinal product that are likely to affect the subjects' safety. It should detail the measures previously or currently proposed to minimise the risks found where appropriate. Finally, a rationale must be given on whether or not it is necessary to amend the protocol, to change or update the consent form, patient information leaflet and the Investigator's Brochure. This report will not replace the request for protocol amendments, which will follow its own specific procedure.

2. **Line-listings**
    The annual report should contain a trial-specific line-listing of all reports of suspected SARs that were reported during this trial. The line listing provides key information but not necessarily all the details usually collected on individual cases. It should include each subject only once regardless of how many adverse reaction terms are reported for the case. If there is more than one reaction, they should all be mentioned but the case should be listed under the most serious adverse reaction (sign, symptom or diagnosis) as judged by the sponsor. It is possible that the same subject may experience different adverse reactions on different occasions. Such experiences should be treated as separate reports. In such circumstances, the same subject might then

be included in a line listing more than once and the line-listings should be cross-referenced when possible. Cases should be tabulated by body system (standard system organ classification scheme). The line listing identifiable by the sponsor listing reference number or date and time of printing should include the information per case as described in 2.1. Usually there should be one listing for each trial, but separate listings might be provided for active comparator or placebo or when appropriate and relevant for other reasons, e.g. in the case that in the same trial for different formulations, indications or routes of administration are studied.

2.1 Content of line listing

The line listing identifiable by the sponsor listing reference number or date and time of printing should include the following information per case:

a. clinical trial identification
b. Study subjects identification number in the trial
c. case reference number (Case-ID-Number) in the sponsor's safety database for medicinal products
d. country in which case occurred
e. age and sex of trial subject
f. daily dose of investigational medicinal product, (and, when relevant, dosage form and route of administration)
g. date of onset of the adverse reaction. If not available, best estimate of time to onset from therapy initiation. For an ADR known to occur after cessation of therapy, estimate of time lag if possible.
h. dates of treatment (if not available, best estimate of treatment duration.)
i. adverse reaction: description of reaction as reported, and when necessary as interpreted by the sponsor, where medically appropriate, signs and symptoms can be grouped into diagnoses. MedDRA should be used.
j. patient's outcome (e.g. resolved, fatal, improved, sequelae, unknown). This field should indicate the consequences of the reaction(s) for the patient, using the worst of the different outcomes for multiple reactions
k. comments, if relevant (e.g. causality assessment if the sponsor disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge/rechallenge results if available)
l. unblinding results in the case of unblinded SUSARs expectedness at the time of the occurrence of the suspected SARs, assessed with the reference document (i.e. Investigator's Brochure/ Summary of Product Characteristics) in force at the beginning of the period covered by the report.

3. Aggregate summary tabulations

In addition to individual cases line listings, summary tabulations of SAR terms for signs, symptoms and/or diagnoses across all patients should usually be presented to provide an overview for each trial. These tabulations ordinarily contain more terms than subjects. When the number of cases is very small, a narrative description would be more suitable.

The aggregate summary tabulation should specify the number of reports:

a) for each body system
b) for each ADR term
c) for each treatment arm, if applicable (IMP, comparator or placebo, blinded treatment)

The unexpected ADR terms should be clearly identified in the tabulation. As an example, the table shown in section 3.1 can be used.

3.1 Example for an Aggregate Summary Tabulation

Number of reports by terms (signs, symptoms and diagnoses) for the trial number ……
*(An * indicates an example of a SUSAR)*

Body system /ADR term	**Verum**	**Placebo**	**Blinded**
CNS			
Hallucinations*	2	2	0
Confusion*	1	1	0
Sub-total	3	3	0
CV			
Sub-total			