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**
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Review	September 2008			
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Update	February 2012	3.5	Minor change to errors in addresses	Research Operations Manager
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Review & Update	March 2013	5.0	Changes to out of date website links and clarification on responsibilities of research team.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 authorised by Diana Benton, Deputy Director of Research and Head of Research & Innovation

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

RESEARCH SAFETY REPORTING

Contents

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 research related adverse incidents are treated in the same way as non-research related adverse incidents.

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 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.

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
HR	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

3.2 Definitions

3.2.1 An ***adverse event*** is 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.

Comment: 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.

3.2.2 An ***adverse reaction*** is 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.

Comment: 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.

3.2.3 An ***unexpected adverse reaction*** is an adverse reaction, the nature and severity of which is not consistent with the information set out in:

(a) in the summary of product characteristics (for a product with a marketing authorisation),

(b) in the investigator's brochure (for any other investigational medicinal product).

Comment:

(i) This applies to the medicinal product/medical device/intervention in question

(ii) 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.

3.2.4 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.

Comment: 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.

3.2.5 A ***suspected serious adverse reaction*** (SSAR), is any ***serious adverse reaction*** that is suspected (possibly or probably or definitely) to be related to the investigational medicinal product/medical device/intervention.

3.2.6 A ***suspected unexpected serious adverse reaction*** (SUSAR) is 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:

(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.

3.2.7 Not all adverse events are adverse reactions but all adverse reactions are adverse events.

3.2.8 An ***Investigational Medicinal Product*** is 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.

3.2.9 A ***non-IMP SUSAR*** is 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.

4 Investigator Responsibilities

4.1 All Adverse Events

4.1.1 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.

4.1.2 Action necessitating amendments to the research protocol will require ethical, R&I and MHRA (IMP studies and non-CE marked devices only) approval through the usual routes. Amendments requiring immediate changes to the protocol (e.g. urgent safety measures) will be implemented and then submitted for ethical, R&I and MHRA (IMP studies and non-CE marked devices only) approval. The initial notification should be by telephone. 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.

4.1.3 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.

4.1.4 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).

4.1.5 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 an example in appendix 1.

4.1.6 For all ***adverse event/reactions*** the investigator will make an assessment of intensity, causality, expectedness and seriousness. Detailed guidance on making this assessment is given in section 6. Intensity will not need to be recorded for expected adverse events unless the intensity is such that the event becomes unexpected as a result.

4.1.7 ***Adverse events*** and/or ***laboratory abnormalities identified in the protocol as critical*** to the evaluations of the safety of the study shall be reported to the sponsor in accordance with the reporting requirements documented in the protocol.

4.1.8 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.

4.1.9 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.

4.2 Serious Adverse Events

4.2.1 Within 24 hours of a member of the research team becoming aware of a ***serious adverse event*** the sponsor must be notified. The investigator (or delegated person) 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 reporting 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 (appendix 3). The initial report will include as much information as is available at the time.

4.2.2 In addition to 4.2.1 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 4.2.1 and 4.2.2 is where the protocol or Investigator's Brochure identifies the event as not requiring immediate reporting.

4.2.3 After the initial report the investigator is required actively to follow up the subject. The investigator (or delegated person) will provide information missing from the initial report within five working days of the initial report to the bodies specified in section 4.2.1 and 4.2.2.

4.2.4 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 (appendix 4) or form provided by the sponsor, until the ***SAE*** has resolved or a decision for no further follow up has been taken.

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

4.2.6 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.

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

4.3 Development Safety Update reports

4.3.1 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 (on a disk) to:

- Medicines and Healthcare products Regulatory Agency (MHRA)
  Information Processing Unit, Area 6, MHRA, 151 Buckingham Palace Road, Victoria, London. SW1W 9SZ

  And either electronically on disk or via email to:

- Research Ethics Committee that granted approval.

Appendix 6 and 7 provide guidance and templates for DSU reports.

4.3.2 Each submission of an annual safety report to the REC must be accompanied by the Safety Report form for CTIMPs. This form is available to download from the HRA website.

4.4 Annual progress reports

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

4.4.2 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.

4.4.3 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.

4.5 End of study reports

4.5.1 For non-IMP trials, at the end of the study the Chief Investigator will submit an end of study report to:

- Sponsor (where UH Bristol is the sponsor this will be the Research and Innovation Department).
- Research ethics committee that granted approval.

This report will be submitted on the declaration of end of study form which is available on the HRA website.

4.5.2 For IMP trials, at the end of the study the Chief Investigator will submit an end of study report to:

- Sponsor (where UH Bristol is the sponsor this will be the Research and Innovation Department).

- Medicines and Healthcare products Regulatory Agency (MHRA) using the 'Declaration of the end of a Clinical Trial' form which is available on the MHRA website
- Research ethics committee that granted approval using the 'EudraCT declaration of end of trial form' which is available on the HRA website

4.5.3 For both IMP and non-IMP trials, within one year of the conclusion of the research a summary of the final report must be submitted to the Research Ethics Committee. There is no standard form for this.

4.5.4 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.

5 Department of Research and Innovation Responsibilities

5.1 Where UH Bristol is the sponsor of a blinded research study in which the ***SAE/SUSAR*** has occurred and when applicable, the Research and Innovation Department will 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.*

5.2 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.

5.3 The Research and Innovation Department reserves the right to suspend or withdraw approval 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.

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

5.5 Non-IMP SUSARs

5.5.1 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.

5.6 SUSARs

5.6.1 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***.

5.6.2 The Research and Innovation Department will delegate responsibility to the research team to report all ***SUSARs*** that are fatal or life-threatening to:

- The Medicines and Healthcare products Regulatory Agency (MHRA)
- the competent authorities (equivalent of MHRA) of any EEA State, other than the United Kingdom, in which the trial is being conducted
- The research ethics committee that granted approval[1]

within seven days of becoming aware of the event.

5.6.3 The Research and Innovation Department will delegate responsibility to the research team to report any additional relevant information to the bodies described in section 5.6.2 within eight days of the report described in section 5.6.2 being made.

5.6.4 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 Medicines and Healthcare products Regulatory Agency (MHRA)
- The competent authorities (equivalent of MHRA) of any EEA State, other than the United Kingdom, in which the trial is being conducted
- The research ethics committee that granted approval[1]

within 15 days of becoming aware of the event.

5.6.5 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 post or email.

5.6.6 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.

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

5.7.1 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

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

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.

6 Assessment of Adverse Events

6.1 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.*

6.2 Causality

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 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. The investigator will also consult the Investigator Brochure or other product information.

- **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***.

6.3 Expectedness

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

- **Expected:** Reaction previously identified and described in protocol and/or reference documents e.g. Investigator Brochure, Summary of Product Characteristics (SmPC).
- **Unexpected:** Reaction not previously described in the protocol or reference documents.

NB The protocol must identify the reference documentation used.

6.4 Seriousness

An event is considered serious if it meets one or more of the following criteria:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect

7 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

Appendix 1 - Adverse Events template

UH Bristol Investigator's Template for recording Adverse Events v7.0

Full title of Study:			
Ethics No:		UH Bristol Study Reference no:	

Sheet number: _____ of _____

AE No:	Patient ID	Description of Event	Start date	Duration/End date	Outcome	**Sequelae
					☐ Resolved ☐ Ongoing ☐ Ongoing with sequelae**	

Assessment			
Intensity:	☐ mild ☐ moderate ☐ severe	Expectedness	☐ expected ☐ unexpected i.e. not described in protocol, product information or Investigator Brochure.
Causality: Relationship to study drug/device/ intervention	☐ not related ☐ unlikely to be related ☐ possibly related ☐ probably related ☐ definitely related	Seriousness	☐ Not serious ☐ Results in death* ☐ Life threatening* ☐ Results in hospitalisation or prolongation of existing hospitalisation* ☐ Results in disability or incapacity* ☐ Congenital anomaly or birth defect* ☐ Other (please specify)*

* Event is considered serious – report to the sponsor within 24 hours using the form provided. Where none is provided use the UH Bristol Research Related SAE/SUSAR Initial Report Form

RESEARCH SAFETY REPORTING POLICY - SAE/SUSAR REPORT FORM

An event/reaction is serious if it:

- results in death,
- is life threatening,
- results in persistent or significant disability/incapacity,
- requires hospitalisation,
- prolongs a current hospitalisation
- results in a congenital anomaly or birth defect.

This form must be used where UH Bristol is the sponsor of the research study in which the SAE has occurred or where no other form has been provided by the sponsor.

Instructions for completion of Initial and Follow up Report Forms (Appendices 3 & 4):

1. As soon as possible, and at the latest within 24 hours of becoming aware of event,
   - Complete the Initial Report Form and send to sponsor.
   - Where UH Bristol is sponsor;
     - email: research@uhbristol.nhs.uk OR
     - fax: 0117 342 0239
   - Where University Of Bristol is sponsor the form must be submitted to both UH Bristol (using details above) and the University of Bristol;
     - email: research.governance@bristol.ac.uk OR
     - fax: 0117 929 8383

   Please ensure that all sections have been completed.

2. As soon as possible, and at the latest within five days of becoming aware of the event,
   - Complete the Follow up Report Form and send to sponsor.
   - Where UH Bristol is sponsor;
     - email: research@uhbristol.nhs.uk OR
     - fax: 0117 342 0239

   Where University Of Bristol is sponsor the form must be submitted to both UH Bristol (using details above) and the University of Bristol;
     - email: research.governance@bristol.ac.uk OR
     - fax: 0117 929 8383

   Please ensure that for SUSARs, all sections have been completed, and for other SAEs that sections 1, 2 and 3 have been completed.

   NB: Points 1 and 2 may be done together, if within 24 hours of becoming aware of the event.

3. Complete and return (as above) further Follow-up Report Form(s) for data collected later than five days post SAE until the SAE has resolved or a decision for no further follow up has been taken.

4. Initial and Follow up Report Forms must be signed off by the appropriate personnel and sent to the sponsor. Where UH Bristol is sponsor forms may be provided in paper, fax or electronic format. Paper copies to be sent to Research and Innovation, Level 3, UH Bristol Education Centre, Upper Maudlin Street, Bristol, BS2 8AE (not required if signatures on faxed copy). Faxed forms to be sent to 0117 342 0239 as detailed above. Electronic forms can be submitted via email to research@uhbristol.nhs.uk. Where the forms are submitted via email the scanned copy must include the signature of the CI/PI or alternatively be sent from the CI/PI email account as confirmation of signature.

5. For multi-centre studies where CI is not investigator making this report, send a copy of each form to the Chief Investigator.

6. Send a copy of each form to other bodies as required. e.g. Data Safety Monitoring Board.

7. Keep original forms in Investigator Site File (ISF).

8. Identifiable information must not be sent to sponsor unless; patient consent allows sponsor access, it is essential and it is sent via a secure method.

Appendix 3 - SAE initial report form

R&I use only: case reference number	

RESEARCH SAFETY REPORTING POLICY - SAE/SUSAR <u>INITIAL</u> REPORT FORM (Page 1 of 4)

1. Person making report	
Name:	
Job title/role in study:	
Email address:	
Telephone No:	

2. Details of study	
Full Title of Study:	Study site (e.g. Hospital name):
	UH Bristol R&I /UoB study reference No:

3. Details of subject affected by SAE/SUSAR
Subject study ID: Initials

4. Details of SAE/SUSAR (further space available in section 12)	
Full description of event/reaction, including body site, reported signs and symptoms and diagnosis where possible:	
Event is defined as serious because it (tick as many as apply): ☐ resulted in death ☐ is/was life-threatening ☐ resulted in persistent or significant disability/incapacity ☐ required hospitalisation ☐ prolonged an ongoing hospitalisation ☐ resulted in a congenital anomaly or birth defect ☐ other – please specify* **Please give further details in section 6 'Outcome'**	*Specify:

Maximum intensity (up until time of initial report)	Mild ☐	Moderate ☐	Severe ☐

Onset Date (when event became serious)	**Onset Time**	**End date**	**End time**	***OR* Duration**

Signature of person making report: _____Date:____/____/____

To be completed by the person filling in the SAE form					
UH Bristol R&I/UoB number:		*Subject ID/initials*		*Onset date of SAE*	

RESEARCH SAFETY REPORTING POLICY - SAE/SUSAR INITIAL REPORT FORM

Sheet number: _____of _____

5. Details of IMP/device/intervention(s) if applicable (further space available in section 12)									
Brand name:	Indication	Batch no.	Route (e.g. oral)	Form (e.g. tablet)	Total dose/24h (specify units)	Regimen (e.g. BD)	Start date & time	Stop date & time	Suspected cause of SAE /SUSAR? (Y/N)
For blinded studies, was the randomisation code broken?		☐	*Yes	☐	No				
*If yes, give details:									

Continue on new sheet if necessary; please identify how many sheets have been used.

Signature of person making report:_____Date:____/____/____

To be completed by the person filling in the SAE form					
UH Bristol R&I no.:		*Subject ID/initials*		*Onset date of SAE*	

Appendix 3 **RESEARCH SAFETY REPORTING POLICY - SAE/SUSAR INITIAL REPORT FORM** (page 3 of 4)

6. Outcome (further space available in section 12)		
☐ Resolved*	☐ Ongoing*	☐ Died* (give cause and PM details if available)
*Give details:		
Was the patient withdrawn from the study?	Yes ☐	No ☐

7. Location of (onset of) SAE (further space available in section 12)
Setting (e.g. hospital*, home, GP, nursing home):
*If SAE occurred on UH Bristol precinct give exact location:

8. Action taken and further information (further space available in section 12)
Please describe action taken (including details of IMP where applicable e.g. drug withdrawn etc…):
Other information relevant to assessment of case e.g. medical history, family history, test results.

9. Causality and Expectedness (to be completed by physician)		
Is the SAE related to the drug/device/intervention? ☐ Not related ☐ Unlikely to be related		***In addition to this form, and within 5 days:*** [1]**For unexpected SAEs, if event ongoing, please complete and return all sections of the follow up report form.** [2]**For expected SAEs, if event ongoing, please complete and return sections 1, 2 and 3 of the follow up report form.**
☐ Possibly related* ☐ Probably related* ☐ Definitely related*	***If possibly, probably or definitely related, was the SAE unexpected?** ☐ Yes[1] ☐ No[2] (Unexpected means not described in the protocol or other product information)	

10. Sponsor notification (only complete where sponsor is not UH Bristol)	
Has the Sponsor been notified of the SAE/SUSAR?	☐ Yes, give date: ☐ No[+]
[+]***Please note, you must inform the Sponsor within 24 hours of becoming aware of the event.***	

11. Additional information (refer to section number)	
Section no.	Further information

12. Chief/Principal Investigator, or delegated physician (at this site)	
Name:	
Job title/role in study:	
Contact address:	
Email address:	
Telephone No:	
Fax number:	
Signature:	
I confirm that the contents of this form (pages 1, 2, 3 ± 4) are accurate and complete	

Please tick this box if additional pages have been used: ☐

Signature of person making report: _____Date:____/____/____

(Page 4 of 4)

R&I use only: case reference number	

To be completed by the person filling in the SAE form					
UH Bristol R&I/UoB no		*Subject ID/initials*		*Onset date of SAE*	

Appendix 4 - SAE follow up report form

RESEARCH SAFETY REPORTING POLICY - SAE/SUSAR FOLLOW UP REPORT FORM

(Page 1 of 4)

1. Further details of SAE/SUSAR			
Further details of event/reaction, including body site, reported signs and symptoms and diagnosis where possible:			
Maximum intensity (up until time of follow up report)	Mild ☐	Moderate ☐	Severe ☐
	End date	**End time**	***OR* Duration**

2. Outcome		
☐ Resolved*	☐ Ongoing*	☐ Died* (give cause and PM details if available)
*Give details:		

Was the patient withdrawn from the study?	Yes ☐	No ☐

3. Additional action taken and further information since initial report
Please describe further action taken:

Further information or missing data relevant to assessment of case e.g. medical history, family history, test results.

Signature of person making report:_____Date:____/____/____

Name (please print):_____
Job title:_____

Signature of Chief /Principal Investigator or delegated physician: Name (print please): I confirm that the contents of this form (pages 1± 2/3/4) are accurate and complete

Appendix 4

To be completed by the person filling in the SAE form					
UH Bristol R&I /UoB number:		*Subject ID/initials*		*Onset date of SAE*	

RESEARCH SAFETY REPORTING POLICY - SAE/SUSAR FOLLOW UP REPORT FORM (Page 3 of 4)

Sheet number: _____of _____

4. CONCOMITANT MEDICATION – details of administration of other medication concurrent with the IMP(s)/device/intervention.								
Brand name:	Indication	Route (e.g. oral)	Form (e.g. tablet)	Total dose/24h (specify units)	Regimen (e.g. BD)	Start date & time	Stop date & time	*Or* duration of treatment

Continue on new sheet if necessary; please identify how many sheets have been used.
Name of person making report: _____
Signature of person making report: _____Date:____/____/____

To be completed by the person filling in the SAE form					
UH Bristol R&I/UoB number:		*Subject ID/initials*		*Onset date of SAE*	

RESEARCH SAFETY REPORTING POLICY - SAE/SUSAR <u>FOLLOW UP</u> REPORT FORM

Sheet number: _____of _____

5. STUDY IMP – details of administration. **NB complete for IMP studies only**									
Brand name:	Indication	Batch no.	Route (e.g. oral)	Form (e.g. tablet)	Total dose/24h (specify units)	Regimen (e.g. BD)	Start date & time	Stop date & time	*Or* duration of treatment
For blinded studies, was the randomisation code broken?		☐	*Yes	☐	No				
*If yes, give details:									

<u>Continue on new sheet if necessary; please identify how many sheets have been used.</u>
Name of person completing report: _____
Signature of person making report: _____Date:____/____/____

Appendix 5 - SAE/SUSAR Sponsor report form

SAE/SUSAR SPONSOR REPORT FORM

This page for Research and Innovation Use Only
UH Bristol sponsored Studies

Case reference number:	
UH Bristol Project Registration No:	
EudraCT No (IMP trials only):	

1. Sponsor assessment of causality

Is the SAE related to the drug/device/intervention? ☐ Not related ☐ Unlikely to be related		[1]For unexpected SAEs, ensure all required sections of the follow up report form have been completed. [2]For expected SAEs, ensure sections 1, 2 and 3 of the follow up report form have been completed.
☐ Possibly related* ☐ Probably related* ☐ **Definitely related***	***If possibly, probably or definitely related, was the SAE unexpected? ☐ Yes[1] ☐ No[2] (Unexpected means not described in the protocol or other product information)	
Comments:		
Name of person performing sponsor assessment*		Contact Number:
Signature of person performing sponsor assessment:		Date:

2. Administrative and sponsor details

Date report received from investigator:	
Name and Address of sponsor: University Hospitals Bristol NHS Foundation Trust Research and Development Department Level 3 UH Bristol Education Centre Upper Maudlin Street Bristol BS2 8AE	Contact person at Sponsor Name: Address: Same as sponsor. Telephone no: 0117 342 0233 Fax no: 0117 342 0239

* Where the assessment has been performed by the Data Safety Monitoring Board, give the name of the Chair and attach a list of names of the members of the Board who participated in the assessment.

Appendix 6 - Guidance on content of Development Safety Update Reports

For Development Safety Update Report (DSUR) form go to Appendix 7.

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.

The DSUR should have three parts:
Part 1: Analysis of the subjects' safety in the concerned clinical trial(s) with an appraisal of its ongoing risk benefit.
Part 2: A line listing of all suspected SARs (including all SUSARs) occurred in the concerned trial, including all serious adverse reactions from third countries
Part 3: An aggregate summary tabulation of suspected SARs that occurred in the concerned trial

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) 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			

Appendix 7 – Development Safety Update Report Form

DEVELOPMENT SAFETY UPDATE REPORT FOR IMP STUDIES – UH BRISTOL SPONSOR – UK STUDIES

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 provided electronically on disk and sent to:

- Medicines and Healthcare products Regulatory Agency (MHRA):
  Information Processing Unit, Area 6, MHRA, 151 Buckingham Palace Road, Victoria, London SW1W 9SZ

And either submitted electronically via email or provided electronically on disk to:

- Research Ethics Committee that granted approval.

A copy should be placed within the Investigator Site File

Instructions for completion:

- Two months prior to the submission due date, **R&I will notify the Chief Investigator that a DSUR is due**, and advise the due date.
- **R&I will notify investigator of the location of the applicable template for completion**
- The **CI should complete sections 2, 7, 8, 9 and 10**.
- The **CI should return the completed form** to the Research Management Office, Level 3, Education Centre, Upper Maudlin Street, Bristol BS2 8AE or to R&DSponsorship@UHBristol.nhs.uk **within 21 days of notification**.
- **R&I will check the forms** for completeness**, complete section 11** if necessary and **liaise with the CI** over **finalising the report**, **gain signatures** and **return to the CI**.
- **The CI should submit the completed forms electronically on disk to** Information Processing Unit, Area 6, MHRA, 151 Buckingham Palace Road, Victoria, London SW1W 9SZ.
- A safety report form for the Research Ethics Committee should also be completed for CTIMPs. This form is available to download from the HRA website.

NB unblinded information must not be revealed to the CI or research team if it would compromise the study.

Appendix 7 **DEVELOPMENT SAFETY UPDATE REPORT FORM - IMP STUDIES – UH Bristol SPONSOR - UK**

1. Details of Sponsor			
Organisation:	University Hospitals Bristol NHS Foundation Trust		
Contact person:	Head of Research & Innovation/Research Operations Manager		
Contact address:	Research and Innovation, Level 3, Education Centre, Upper Maudlin Street, Bristol BS2 8AE		
Email address:	research@uhbristol.nhs.uk		
Telephone No:	0117 342 0233		
Fax number:	0117 342 0239		
Signature:			
Name:		Date:	
2. Details of person completing report (if different to above)			
Name:			
Job title/role in study:			
Contact address:			
Email address:			
Telephone No:			
Fax number:			
Signature:			
Name:		Date:	
3. Details of DSUR			
Report number:			
Period Covered:			
Date of report:			
4. Details of IMP			
IMP(s):			
Dosage, form, route of administration:			
Supplier:			
Marketing status:			

Page _____ of _____

5. Details of CTIMPs covered by report			
UH Bristol R&D Project Registration No:		Ethics No:	
EudraCT No:		CTA No: (If CTA not yet issued, DDX no.)	
Full Title of Study:			
Date of MHRA approval:			
UH Bristol R&D Project Registration No:		Ethics No:	
EudraCT No:		CTA No: (If CTA not yet issued, DDX no.)	
Full Title of Study:			
Date of MHRA approval:			
UH Bristol R&D Project Registration No:		Ethics No:	
EudraCT No:		CTA No: (If CTA not yet issued, DDX no.)	
Full Title of Study:			
Date of MHRA approval:			

6. Details of non-interventional studies using IMP (if applicable)			
UH Bristol R&D Project Registration No:		Ethics No:	
Full Title of Study:			

7. Summary of Serious Adverse Events (SAEs)		
Number of SAEs	In reporting year:	In total:
No. of SSARs	In reporting year:	In total:
No. of SUSARs	In reporting year:	In total:

8. Report on subjects' safety in CTIMP(s), including urgent safety measures, serious breaches of GCP, temporary or early halt of trial due to safety concerns.	
EudraCT No:	
Are there any new findings[2] related to the safety of the IMP treatments in this trial?	Yes ☐ No ☐
If yes, provide details[3]:	
Have there been any other experiences with this IMP that could affect the subjects' safety?	Yes ☐ No ☐
If yes, provide details:	
Is/was it necessary to amend the protocol, patient information sheet, consent form or investigator brochure?	Yes ☐ No ☐
If yes, give details (including amended version numbers and dates) and rationale:	
Summary (including information gained from non-interventional studies and other sources, if applicable):	

[2] New findings refers to information not already present in the investigator's brochure or for licensed drugs the summary of product characteristics.
[3] When relevant, the following points should be considered: relation with dose, duration, time course of the treatment; reversibility; evidence of previously unidentified toxicity in the trial subjects; increased frequency of toxicity; overdose and its treatment; interactions or other associated risks factors; any specific safety issues related to special populations, such as the elderly, the children or any other at risk groups; positive and negative experiences during pregnancy or lactation; abuse; risks which might be associated with the investigation or diagnostic procedures of the clinical trial.

9. Overall safety assessment

Evaluation of risks:

Benefit-risk considerations:

Conclusions, including current management of risks and actions for future risk management if required::

Appendix 7 **DEVELOPMENT SAFETY UPDATE REPORT FORM - IMP STUDIES – UH Bristol SPONSOR - UK**

Page _____ of _____ continue on new sheet if necessary; please identify how many sheets have been used.

10. Line listing of Suspected Serious Adverse Reactions (SSARs)

Study Subject Id	AE No.	Age	Sex	Details of IMP(s) list all Name of IMP	Dose	Route	Details of SSAR Date of onset[4]	Dates of IMP treatment[5]	Description of adverse event	Outcome	Causality[6]	Expected[7] (Yes/No)

[4] If not available, best estimate of time to onset and route of administration. For an ADR known to occur after cessation of therapy, estimate of time lag if possible.
[5] If not available, best estimate of treatment duration
[6] Possibly, probably or definitely related. Only required where sponsor assessment differs from investigator assessment
[7] Results of unblinded assessment with reference documentation (e.g. investigator brochure, summary of product characteristics). For blinded studies where the research team are all blinded this information should be completed last by UH Bristol R&I Department and the report sent directly to the main REC and MHRA. Unless required for safety reasons this information must not be provided to blinded investigators.

DEVELOPMENT SAFETY UPDATE REPORT FORM - IMP STUDIES – UH Bristol SPONSOR – UK

(to be completed by Research and Innovation)

Page _____ of _____ continue on new sheet if necessary; please identify how many sheets have been used.

11. Aggregate Summary Table of SSARs		
Category e.g. Allergy/Immunology	**Adverse Event** e.g. Autoimmune reaction	**Total No. of Reports**

RELATED DOCUMENTS Name of document
DMS address ie http://nww.avon.nhs.uk/dms/download.aspx?did=nnnn

SAFETY If there are unusual or unexpected safety concerns (to staff or patient), emphasize them here

QUERIES Contact xxxx ' Ext nnnn / Bleep nnnn – this does not need to be the author, but whoever might be best placed (particularly 24/7) to answer a query.