

University Hospitals Bristol NHS Foundation Trust

Research Related Adverse Event Reporting Policy

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RESEARCH RELATED ADVERSE EVENT REPORTING

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1 Background

- 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 apply to all clinical trials involving investigational medicinal products (IMPs) 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.

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 Related Adverse Event Reporting Policy are not met, the Trust policy must be followed as a minimum.

3 Abbreviations and definitions

3.1 Abbreviations

AI	Adverse Incident
AE	Adverse Event
AR	Adverse Reaction
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SSAR	Suspected serious adverse reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
CTIMP	Clinical trial of an Investigational Medicinal Product
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
REC	Research Ethics Committee

3.2 Definitions

3.2.1 For definitions of **adverse incidents** (clinical, non-clinical and near misses) refer to section 3 of the UBHT Adverse Incident Reporting Policy & Guidelines.

3.2.2 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.

3.2.3 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.

3.2.4 An **unexpected adverse reaction** is an adverse reaction the nature and severity of which is not consistent with the information about the medicinal product/medical device/intervention in question set out –

(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.

Comment: 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.

3.2.5 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.

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

3.2.7 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.

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

3.2.9 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.

3.2.10 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

Flow diagram summarising the Investigator's responsibilities is available on the UH Bristol research web site. Research Guidance Sheet No. 10a - Safety – 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&D 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&D and MHRA (IMP studies and non-CE marked devices only) approval. The initial notification to the REC should be by telephone. Notice in writing to REC, R&D 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 Adverse Incident Reporting Policy and Guidelines.

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. A short assessment is provided as an example in appendix 1.
- 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 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 notified in a timely fashion. It is strongly recommended that this be at the same time as notifying the sponsor:
- The host organisation (where UH Bristol is both the sponsor and the host organisation only one report need be sent to the Trust Research and Innovation Department)
 - 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 Annual safety reports

- 4.3.1 For IMP studies, one year following the granting of a Clinical Trials Authorisation Certificate, and thereafter annually, the Chief Investigator with assistance from the Research and Innovation Department send an annual safety report to the:
- Medicines and Healthcare products Regulatory Agency (MHRA).
 - Research Ethics Committee that granted approval.

Appendix 6 and 7 provide guidance and templates for annual reports. For clinical trials that commenced before 1 May 2004, the reporting period starts with the issue date of the CTX letter or first DDX exemption letter by the MHRA (or previously by the Medicines Control Agency).

- 4.3.2 Each submission of an annual safety report to the main REC must be accompanied by the Safety Report form for CTIMPs available at:
[http://www.nres.npsa.nhs.uk/docs/forms/Safety_Report_Form_\(CTIMPs\).doc](http://www.nres.npsa.nhs.uk/docs/forms/Safety_Report_Form_(CTIMPs).doc)

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 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 main Research Ethics Committee. These reports will include information on the safety of participants. The form for providing these reports is available at:
[http://www.nres.npsa.nhs.uk/docs/forms/Progress_Report_Form_\(non-CTIMPs\).doc](http://www.nres.npsa.nhs.uk/docs/forms/Progress_Report_Form_(non-CTIMPs).doc)
- 4.4.3 For IMP studies, 1 year following the granting of a favourable ethical opinion and thereafter annually, the Chief Investigator will submit progress reports to the main 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 at:
[http://www.nres.npsa.nhs.uk/docs/forms/Progress_Report_Form_\(CTIMPs\).doc](http://www.nres.npsa.nhs.uk/docs/forms/Progress_Report_Form_(CTIMPs).doc)
- 4.4.4 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.

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 form available at:
[http://www.nres.npsa.nhs.uk/docs/forms/End_of_Study_\(non-CTIMP\).doc](http://www.nres.npsa.nhs.uk/docs/forms/End_of_Study_(non-CTIMP).doc)
- 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 UBHT is the sponsor this will be the Research and Innovation Department).
 - Medicines and Healthcare products Regulatory Agency (MHRA).
 - Research ethics committee that granted approval.
- This report will be submitted on the form available at:
<http://eudract.emea.europa.eu/docs/Declarationoftheendoftrialform170805withfields.doc>
- 4.5.3 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.

5 Department of Research and Development Responsibilities

A flow diagram summarising the Research and Innovation Department's responsibilities is available on the UH Bristol research web site.

Research Guidance Sheet No. 10c - Safety – R&D responsibilities

- 5.1 Where UH Bristol is the sponsor of a blinded research study in which the **SAE/SUSAR** has occurred, 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 (refer to R&E Department internal SOP Recording and Reporting SAEs/SUSARs). 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 For IMP studies where UH Bristol is sponsor the Research and Innovation Department will code all SAEs reported using the Common Terminology Criteria for Adverse Events (CTCAE).
- 5.5 The Research and Innovation Department will maintain a record of all **SAEs** reported to the Department and where applicable the CTCAE codes.

5.6 Non-IMP SUSARs

- 5.6.1 Where UH Bristol is the sponsor of a blinded non-IMP study, the Research and Innovation Department will report all SAEs that are assessed as **non-IMP SUSARs** by either the investigator or the un-blinded assessor to the research ethics committee that granted approval within 15 days using the NRES Report of Serious Adverse Event form available at: [http://www.nres.npsa.nhs.uk/docs/forms/Safety_Report_Form_\(non-CTIMPs\).doc](http://www.nres.npsa.nhs.uk/docs/forms/Safety_Report_Form_(non-CTIMPs).doc)

5.7 SUSARs

- 5.7.1 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**.
- 5.7.2 The Research and Innovation Department will 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.
- 5.7.3 The Research and Innovation Department will 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.
- 5.7.4 The Research and Innovation Department will report all **SUSARs** that are not assessed as life threatening or fatal :
- 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 approval¹

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

within 15 days of becoming aware of the event.

5.7.5 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. Three copies should be provided of all enclosures, except for SUSAR reports (one copy only).

5.7.6 Each submission of a **SUSAR** report to the main REC must be accompanied by the Safety Report form for CTIMPs available at:

[http://www.nres.npsa.nhs.uk/docs/forms/Safety_Report_Form_\(CTIMPs\).doc](http://www.nres.npsa.nhs.uk/docs/forms/Safety_Report_Form_(CTIMPs).doc)

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.

5.8 Annual safety, annual progress and end of study reports

5.8.1 Where UH Bristol is sponsor, at the request of the Chief Investigator the Research and Innovation Department will assist the Chief Investigator in compiling the annual safety, 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, 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 2001** Research Governance Framework for Health and Social Care.
http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4008777&chk=dMRd/5
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/enterprise/pharmaceuticals/eudralex/vol-10/21_susar_rev2_2006_04_11.pdf

Appendix 1 - Adverse Events template

UH Bristol Investigator's Template for recording Adverse Events v3.4

Full title of Study:			
Ethics No:		UH Bristol Project Registration no:	

Sheet number : _____ of _____

AE No:	Patient ID	Description of Event	Start date	Duration/End date	Outcome	**Sequelae
					<input type="checkbox"/> Resolved <input type="checkbox"/> Ongoing <input type="checkbox"/> Ongoing with sequelae**	
Assessment						
Intensity:		<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe	Expectedness	<input type="checkbox"/> expected <input type="checkbox"/> unexpected i.e. not described in protocol, product information or investigator brochure.		
Causality: Relationship to study drug/device/intervention		<input type="checkbox"/> not related <input type="checkbox"/> unlikely to be related <input type="checkbox"/> possibly related <input type="checkbox"/> probably related <input type="checkbox"/> definitely related	Seriousness	<input type="checkbox"/> Not serious <input type="checkbox"/> Results in death* <input type="checkbox"/> Life threatening* <input type="checkbox"/> Results in hospitalisation or prolongation of existing hospitalisation* <input type="checkbox"/> Results in disability or incapacity* <input type="checkbox"/> Congenital anomaly or birth defect* <input type="checkbox"/> Other (please specify)*		
AE No:	Patient ID	Description of Event	Start date	Duration/End date	Outcome	**Sequelae
					<input type="checkbox"/> Resolved <input type="checkbox"/> Ongoing <input type="checkbox"/> Ongoing with sequelae**	
Assessment						
Intensity:		<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe	Expectedness	<input type="checkbox"/> expected <input type="checkbox"/> not expected i.e. not described in protocol, product information or investigator brochure.		
Causality: Relationship to study drug/device/intervention		<input type="checkbox"/> not related <input type="checkbox"/> unlikely to be related <input type="checkbox"/> possibly related <input type="checkbox"/> probably related <input type="checkbox"/> definitely related	Seriousness	<input type="checkbox"/> Not serious <input type="checkbox"/> Results in death* <input type="checkbox"/> Life threatening* <input type="checkbox"/> Results in hospitalisation or prolongation of existing hospitalisation* <input type="checkbox"/> Results in disability or incapacity* <input type="checkbox"/> Congenital anomaly or birth defect * <input type="checkbox"/> Other (please specify)*		

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

**RESEARCH RELATED SAE/SUSAR REPORT FORM
(drugs, devices and interventions)**

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 0239one copy to Research and Innovation

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)one copy to Research and Innovation

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. Send a paper copy of the Initial and Full Report Forms with signatures to Sponsor. Where UH Bristol is sponsor send to Research and Innovation, Level 3, UH Bristol Education Centre, Upper Maudlin Street, Bristol, BS2 8AE (not required if signatures on faxed copy).
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 each form to other bodies as required. e.g. Data Safety Monitoring Board.
7. Keep original forms in Investigator Site File (ISF).

Appendix 3 - SAE initial report form

R&I use only: case reference number		Date report received by R&I	
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RESEARCH RELATED SAE/SUSAR INITIAL REPORT FORM

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1. Person making report					
Name:					
Job title/role in study:					
Contact address:					
Email address:					
Telephone No:					
Fax number:					
2. Details of study					
Full Title of Study:			Study site (e.g. Hospital name):		
			UH Bristol R&I Project Registration No:		
			Ethics No:		
			EudraCT No (IMP studies only):		
3. Details of subject affected by SAE/SUSAR					
Subject study ID	Initials	DoB	Gender	Weight	Height
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): <input type="checkbox"/> resulted in death <input type="checkbox"/> is/was life-threatening <input type="checkbox"/> resulted in persistent or significant disability/incapacity <input type="checkbox"/> required hospitalisation <input type="checkbox"/> prolonged an ongoing hospitalisation <input type="checkbox"/> resulted in a congenital anomaly or birth defect <input type="checkbox"/> other – please specify*			*Specify:		
Please give further details in section 6 ‘Outcome’					
Maximum intensity (up until time of initial report)		Mild <input type="checkbox"/>	Moderate <input type="checkbox"/>	Severe <input type="checkbox"/>	
Onset Date <small>(when event became serious)</small>	Onset Time	End date	End time	OR Duration	

Signature of person making report: _____ **Date:** ____ / ____ / ____

R&I use only: case reference number

To be completed by the person filling in the SAE form

UH Bristol R&I number: _____ Subject ID/initials _____ Onset date of SAE _____

RESEARCH RELATED SAE/SUSAR INITIAL REPORT FORM

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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: ____ / ____ / ____

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

6. Outcome (further space available in section 12)

<input type="checkbox"/> Resolved*	<input type="checkbox"/> Ongoing*	<input type="checkbox"/> Died* (give cause and PM details if available)
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*Give details:

Was the patient withdrawn from the study?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
---	------------------------------	-----------------------------

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)

<p>Is the SAE related to the drug/device/intervention?</p> <input type="checkbox"/> Not related <input type="checkbox"/> Unlikely to be related <input type="checkbox"/> Possibly related* <input type="checkbox"/> Probably related* <input type="checkbox"/> Definitely related*	<p>*If possibly, probably or definitely related, was the SAE unexpected?</p> <input type="checkbox"/> Yes ¹ <input type="checkbox"/> No ² <p>(Unexpected means not described in the protocol or other product information)</p>	<p>In addition to this form, and within 5 days:</p> <p>1 - Please complete and return all sections of the follow up report form.</p> <p>2 - Please complete and return sections 1, 2 and 3 of the follow up report form.</p>
---	--	---

10. Sponsor notification (only complete where sponsor is not UH Bristol)

Has the Sponsor been notified of the SAE/SUSAR?	<input type="checkbox"/> Yes, give date:
	<input type="checkbox"/> No ⁺

***Please note, you must inform the Sponsor within 24 hours of becoming aware of the event.**

Signature of person making report: _____ Date: ____ / ____ / ____

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

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: ___ / ___ / ___

R&I use only: case reference number		Date Received	
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To be completed by the person filling in the SAE form				
UH Bristol R&I no.:		Subject ID/initials		Onset date of SAE

Appendix 4 - SAE follow up report form

RESEARCH RELATED SAE/SUSAR FOLLOW UP REPORT FORM

(Page 1 of 3)

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 <input type="checkbox"/>	Moderate <input type="checkbox"/>	Severe <input type="checkbox"/>
	End date	End time	OR Duration
2. Outcome			
<input type="checkbox"/> Resolved*	<input type="checkbox"/> Ongoing*	<input type="checkbox"/> Died* (give cause and PM details if available)	
*Give details:			
Was the patient withdrawn from the study?		Yes <input type="checkbox"/>	No <input type="checkbox"/>
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) are accurate and complete

Appendix 4

R&I use only: case reference number	
-------------------------------------	--

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

RESEARCH RELATED SAE/SUSAR FOLLOW UP REPORT FORM

(Page 2 of 3)

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.

Signature of person making report: _____ **Date:** ____ / ____ / ____

Appendix 4

R&I use only: case reference number

To be completed by the person filling in the SAE form

UH Bristol R&I number:		Subject ID/initials		Onset date of SAE	
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RESEARCH RELATED SAE/SUSAR FOLLOW UP REPORT FORM

(Page 3 of 3)

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?	<input type="checkbox"/>	*Yes	<input type="checkbox"/>	No
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*If yes, give details:

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

Name of person completing report: _____

Signature of person making report: _____ **Date:** ____ / ____ / ____

SAE/SUSAR SPONSOR REPORT FORM

This page for Research and Innovation Use Only UH Bristol sponsored Studies
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Case reference number:	
UH Bristol Project Registration No:	
EudraCT No (IMP trials only):	

1. Sponsor assessment of causality		
<p>Is the SAE related to the drug/device/intervention?</p> <p><input type="checkbox"/> Not related <input type="checkbox"/> Unlikely to be related <input type="checkbox"/> Possibly related* <input type="checkbox"/> Probably related* <input type="checkbox"/> Definitely related*</p>	<p>*If possibly, probably or definitely related, was the SAE unexpected?</p> <p><input type="checkbox"/> Yes¹ <input type="checkbox"/> No²</p> <p>(Unexpected means not described in the protocol or other product information)</p>	<p>1 - Ensure all required sections of the follow up report form have been completed.</p> <p>2 - Ensure sections 1, 2 and 3 of the follow up report form have been completed.</p>
Comments:		
Name of person performing sponsor assessment ² :		Contact Number:
Signature of person performing sponsor assessment:		Date:

2. Administrative and sponsor details	
Date report received from investigator:	CTA/DDX number (if applicable):
<p>Name and Address of sponsor:</p> <p>University Hospitals Bristol NHS Foundation Trust Research and Development Department Level 3 UH Bristol Education Centre Upper Maudlin Street Bristol BS2 8AE</p>	<p>Contact person at Sponsor</p> <p>Name:</p> <p>Address: Same as sponsor.</p> <p>Telephone no: 0117 342 0233 Fax no: 0117 342 0239</p>

² 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 annual safety reports

For Annual Safety Report Form go to Appendix 7.

The safety report of a clinical trial should have three parts:

- A report on the subjects' safety in the concerned clinical trial.
- A line listing of all suspected SARs (including all SUSARs) occurred in the concerned trial.
- 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. 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 lumped 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 the 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 – Annual Safety Report Form

ANNUAL SAFETY REPORT FORM FOR IMP STUDIES – UH BRISTOL SPONSOR – UK STUDIES

Instructions for Researchers

1. One year following the granting of a Clinical Trials Authorisation Certificate, and thereafter annually³, complete sections 1-5 of the Annual Safety Report Form - IMP Studies – UH Bristol Sponsor – UK.
2. In addition, complete Safety Report form for CTIMPs available at:
[http://www.nres.npsa.nhs.uk/docs/forms/Safety_Report_Form_\(CTIMPs\).doc](http://www.nres.npsa.nhs.uk/docs/forms/Safety_Report_Form_(CTIMPs).doc)
3. *If there have been no reports of any Serious Adverse Events:*
Cross through section 6 and mark as not required. Sign and date comment.
Send the completed forms to:
 - Medicines and Healthcare products Regulatory Agency (MHRA), Clinical Trials Unit, 12-2, MHRA, Market Towers, 1 Nine Elms Lane, London SW8 5NQ.
 - The Research Ethics Committee that granted approval (NB An annual progress report may also be required. See section 4.5 of the Trust Research Related Adverse Event Reporting Policy).
 - UH Bristol Research and Innovation Department, Level 3, Education Centre, Upper Maudlin Street, Bristol, BS2 8AE
4. *If SAEs have been reported during the study:*
Send part completed forms to the Research Management Office, Level 3, Education Centre, Upper Maudlin Street, Bristol BS2 8AE.

Instructions for Research and Innovation Department

5. On receipt of a part completed Annual Report Form, complete 'Causality' and 'Expectedness' columns for all SSARs reported to the Trust and where an unblinded assessment has been performed by UH Bristol.
6. Complete section 6.
7. Send the completed forms to:
 - Medicines and Healthcare products Regulatory Agency (MHRA), Clinical Trials Unit, 12-2, MHRA, Market Towers, 1 Nine Elms Lane, London SW8 5NQ.
 - The Research Ethics Committee that granted approval.
8. Inform CI.
NB Do not provide the CI with any information that could unblind and compromise the study.

³ For clinical trials that commenced before 1 May 2004, the reporting period starts with the issue date of the CTX letter or first DDX exemption letter by the MHRA (or previously by the Medicines Control Agency).

1. Details of Sponsor			
Organisation:			
Name of person to contact:			
Contact address:			
Email address:			
Telephone No:			
Fax number:			
2. Details of person making report (if different to above)			
Name:			
Job title/role in study:			
Contact address:			
Email address:			
Telephone No:			
Fax number:			
3. Details of study			
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:			
4. 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:	

Signature of person making report: _____ Date: ____ / ____ / ____

UH Bristol R&D Project Registration No:		Ethics No:	
EudraCT No:		CTA No: (If CTA not yet issued, DDX no.)	

Appendix 7

ANNUAL SAFETY REPORT FORM - IMP STUDIES – UH Bristol SPONSOR - UK

(Page 2 of 4 unless stated otherwise)

Page _____ of _____

4. Report on subjects' safety in CTIMP	
Are there any new findings ⁴ related to the safety of the IMP treatments in this trial?	Yes <input type="checkbox"/> No <input type="checkbox"/>
If yes, provide details ⁵ :	
Have there been any other experiences with this IMP that could affect the subjects' safety?	Yes <input type="checkbox"/> No <input type="checkbox"/>
If yes, provide details ⁶ :	
Is it necessary to amend the protocol, patient information sheet, consent form or investigator brochure?	Yes <input type="checkbox"/> No <input type="checkbox"/>
If yes, give details and rationale:	

Signature of person making report: _____ **Date:** ____ / ____ / ____

⁴ New findings refers to information not already present in the investigator's brochure or for licensed drugs the summary of product characteristics.

⁵ 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.

⁶ 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.

UH Bristol R&D Project Registration No:	Ethics No:	EudraCT No:	CTA No (If CTA not yet issued, DDX no.):
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Appendix 7

ANNUAL SAFETY REPORT FORM - IMP STUDIES – UH Bristol SPONSOR - UK

(page 3 of 4 unless stated otherwise)

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

5. Line listing of Suspected Serious Adverse Reactions (SSARs)												
Study Subject Id	AE No.	Age	Sex	Details of IMP(s) list all		Route	Details of SSAR		Description of adverse event	Outcome	Causality ⁹	Expected ¹⁰ (Yes/No)
				Name of IMP	Dose		Date of onset ⁷	Dates of IMP treatment ⁸				

Signature of person making report: _____ Date: ___/___/___

Signature of R&D person completing report (if applicable): _____ Date: ___/___/___

⁷ 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.

⁸ If not available, best estimate of treatment duration

⁹ Possibly, probably or definitely related. Only required where sponsor assessment differs from investigator assessment

¹⁰ 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&D 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.

