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Pharmacovigilance 02: Adverse Event and Reaction Reporting

IT IS THE RESPONSIBILITY OF ALL USERS OF THIS SOP TO ENSURE THAT THE CORRECT VERSION IS BEING USED

All staff should regularly check the Research & Development Webpage for information relating to the implementation of new or revised versions. Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded version are promptly withdrawn from use unless notified otherwise by the SOP Controller.

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SOP reference:	R&D SOP Ph 03	
Version:	3.0	
Author:	Janet Forkes	signature
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	27/03/2018	
Implementation date of current version:	31 / 03 / 2018	
Date of Review:	01 / 05 / 2019	

The Gloucestershire Hospitals NHS Foundation Trust wishes to acknowledge York Hospitals NHS Foundation Trust and University Hospitals Bristol NHS Foundation Trust who gave permission to use their templates in the development of these SOPs.

Version History Log

This area will be updated with details of all changes made to the SOP whether due for full review or not.

Version	Details of Change	Date Implemented
1.0	Original	SOP 02
2.0	Reviewed and updated along with reorganisation into the Gloucestershire R&D Consortium suite of SOPs	10/02/2015
2.1	Review and addition of related SOPs	10/03/2017
3.0	Rebranding to GHNHSFT, updating of contact details and reference documents. Inclusion of section 5.2.2 SAEs for CTIMPS hosted by the Trust	31/03/2018

This SOP will be reviewed every two years unless changes to any relevant legislation require otherwise

Contents

1 Introduction, Background and Purpose

The Medicines for Human Use (Clinical Trials) Regulations 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 purpose of the SOP is to describe the adverse event reporting procedure that should be followed for CTIMPs sponsored by the Trust.

As well as research related adverse events, adverse incidents occur on research studies. It is important that research related adverse incidents are reported in the same way as non-research related adverse incidents (see Section 5.6).

2 Who Should Use This SOP

This SOP should be used by investigators involved in CTIMP trials sponsored or co-sponsored by the Trust, or where the R&D Department has contracted to provide pharmacovigilance services for a particular study.

For externally sponsored CTIMP studies hosted by the Trust, Adverse Event reporting will ICH GCP guidelines and follow the Sponsor's requirements with R&D department notification.

3 When this SOP is to be used

Recording and reporting of Adverse Events (AEs), including Adverse Reactions (ARs), Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs), and Suspected Unexpected Serious Adverse Reactions (SUSARs) should be managed in line with the reporting procedure of the sponsor of the research trial.

Where the Trust is the sponsor or co-sponsor, this SOP and the trial protocol must be followed.

4. Definitions

The following definitions are taken from the Medicines for Human Use (Clinical Trials) Regulations 2004.

4.1 Adverse Event

An adverse event is any untoward medical occurrence in a subject to whom a medicinal product 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/intervention, whether or not considered to be related to the medicinal product/ intervention.

Note: the definition of adverse event given above is that used in the clinical trials regulations however, for the avoidance of doubt, when following this SOP **all** AE/SAEs should be collected for all trial subjects from the commencement of any trial related procedures (including screening procedures). This is the default position for all Trust sponsored trials and any deviation from this must be agreed by the Sponsor prior to the start of the trial and documented accordingly.

4.2 Adverse Reaction

An adverse reaction is any untoward and unintended response in a subject to an investigational medicinal product 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 an IMP qualifies as an AR; there is evidence or argument to suggest a causal relationship.

Note: All adverse reactions are adverse events.

4.3 Unexpected Adverse Reaction

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

- in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC or SPC) for that product,
- in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

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.

4.4 Serious Adverse Event

An adverse event, adverse reaction, or unexpected adverse reaction is defined as serious if it:

- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect.

Comment: Life threatening in the definition of an SAE/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.

4.5 Suspected Unexpected Serious Adverse Reaction

A SUSAR is a suspected unexpected serious adverse reaction.

A SUSAR is a SAR which is also "unexpected", meaning that its nature and severity are not consistent with the information about the medicinal product in question set out:

- in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC or SPC) for that product;
- in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

Comment: All adverse events that are suspected to be related to an investigational medicinal product and that are both unexpected and serious are considered to be SUSARs.

4.6 Investigational Medicinal Product

An Investigational Medicinal Product (IMP) 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.

4.7 Non-Investigational Medicinal Product

Products that are not the object of investigation (i.e. other than the tested product, placebo or active comparator) may be supplied to subjects participating in the trial and used in accordance with the protocol. This might be preventative, diagnostic or therapeutic reasons and/or to ensure that adequate medical care is provided for the subject. These medicinal products do not fall within the definition of investigational medicinal products (IMPs) in Directive 2001/20/EC and are called non-investigational medicinal products (NIMPs).

4.8 Adverse Incident

An adverse incident (AI) is any incident/accident, near miss or untoward event which had or may have had, the potential to cause harm, dissatisfaction or injury to persons, loss or damage to property. This definition includes hazards, accident, ill health, dangerous occurrences and near misses.

5. Chief Investigator/ Principal Investigator responsibilities in the event of Adverse Events

5.1 All Adverse Events

The CI/PI must ensure that the dignity, rights, safety and wellbeing of subjects are given priority at all times and must take appropriate action to ensure the safety of all staff and participants in the study. The CI/PI will consider what actions, if any, are required and in what timeframe.

In the event of an adverse event, the CI/PI/Co-Investigator (Co-I) (or delegated member of research team) must review all documentation (e.g., hospital notes, laboratory and diagnostic reports) relevant to the event. The investigator will make an assessment of intensity, causality, expectedness and seriousness. Detailed guidance on making this assessment is given in section 6.

Except where the protocol states otherwise, all adverse events/reactions should be recorded in detail to allow analysis at a later stage. A template for recording adverse events is provided (Appendix 1 for research team use and Appendix 2 for R&D department use for Trust Sponsored trials). Adverse events will also be recorded in the patient's medical notes where possible and that this includes the assessment of causality, severity and seriousness.

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.

The Investigator should keep an ongoing log of adverse events in the ISF that must be made available to the Sponsor on request (see Appendices 3 and 4) and on the local trial management system EDGE.

At the conclusion of the sponsored trials all adverse event/reactions, recorded during a study must be subject to statistical analysis and that analysis and any subsequent conclusions included in the final study report.

5.2 Serious Adverse Events (SAEs)

5.2.1 For CTIMPS Sponsored by the Trust

Immediately after becoming aware of a serious adverse event (and within 24 hours) a member of the research team must notify the R&D Department. Written reports should be made by completing a Research Related SAE/SUSAR Initial Report Form (Appendix 1). The initial report will include as much information as is available at the time and should be signed by a suitable qualified medical doctor, usually the PI or delegated investigator, to confirm their review and assessment of the SAE . This form must be faxed to the R&D Department. For the avoidance of doubt, the date that the initial notification is issued to the R&D Department is day 0 of the reporting timescales. The R&D Department will acknowledge receipt

of the SAE notification by noon of the following working day. If acknowledgement of the SAE is not received by the Investigator by this time then it is the responsibility of the Investigator to contact the R&D Department immediately. On receipt of a notification of an SAE/SUSAR the Sponsor's R&D Department will follow the MHRA and REC guidelines.

In the event that the R&D Department fax is unresponsive please email the completed form to ghn-tr.glos.rdsu@nhs.net . This email address is checked every working day. This email notification must ONLY be used in the event that the R&D Department fax is unresponsive.

In addition the following bodies must also be notified in a timely fashion where applicable. It is strongly recommended that this be at the same time as notifying the sponsor:

- The host organisation R&D Department
- The Chief Investigator
- Any other persons or bodies specified in the protocol or clinical trial agreement (e.g. Data Monitoring Committee)

The only exception is where the protocol or Investigator Brochure identifies the event as not requiring immediate reporting. Laboratory parameters may also require reporting within the same timescales as SAEs and these should be specified in the protocol.

The Investigator (or delegated person) will provide any information missing from the initial report within five working days of the initial report to the R&D Department and the bodies specified above (where applicable).

After the initial report the investigator is required to actively follow up the subject until either

(i) the SAE resolves, or

(ii) (ii) the Sponsor and CI/PI agree that no further follow-up is required.

This decision must be documented.

Investigators (or delegated persons) will provide follow-up information, each time new information is available, using a Research Related SAE/SUSAR Follow-up Report Form (Appendix 2)

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

Although there is no requirement for expedited reporting of SAEs that are not deemed to be related to the intervention and unexpected, they must be documented in Development Safety Update Reports and Annual Progress Reports as detailed in the R&D SOP Pharmacovigilance 01- Safety Reporting.

The Investigator must maintain an up to date log of all SAEs using the ISF SAE log and EDGE SAE workflow. This log will be reconciled with the R&D

Department's log during trial monitoring. The frequency of this reconciliation may be defined in the trial monitoring plan. As a minimum, reconciliation will take place as part of the database check prior to database lock.

For SAEs that are deemed 'possibly, probably or definitely related' and 'unexpected' refer to section 5.3 below.

5.2.2 For CTIMPS hosted by the Trust

The reporting requirements of the research protocol will be followed for reporting SAEs. A copy of the SAE CRF will be sent to the R&D Department on the conclusion of the SAE or the end of the reporting requirements as defined in the study protocol. These will be logged and reviewed on a quarterly basis by the R&D Senior Management Team.

5.3 Suspected Unexpected Serious Adverse Reactions

Where the SAE has been deemed by the Investigator or Sponsor (taking advice from an independent medical expert where necessary) to be 'possibly, probably or definitely related' and 'unexpected' additional expedited reporting requirements exist.

For all multi-site studies the CI must inform all PI of SUSARs occurring on the study. It is the responsibility of the CI to communicate all information to the PIs, in particular any information that could adversely affect the safety of subjects. This notification must be documented.

The R&D Department will (on behalf of the Sponsor) notify the MHRA and REC of SUSARs within the specified reporting timescales. However, the R&D Department reserves the right to delegate this responsibility to the CI and this decision will be documented.

5.4 Events involving comparator drugs and study procedures

Often more than one drug is used in a clinical trial in order to meet the objectives of the trial and when considering patient safety ALL drugs used are of interest.

All comparator drugs and placebos are considered IMPs for the purpose of this SOP and are subject to the same reporting requirements as the test drug. Non investigational medicinal products (NIMPs) used in the trial may also be subject to reporting requirements and details should be provided in the study protocol.

The following scenarios when an adverse reaction to a NIMP would require reporting:

- If the adverse reaction is suspected to be linked to an interaction between a NIMP and an IMP and is serious and unexpected
- If a SUSAR is reported and it might be linked to either a NIMP or an IMP but cannot be attributed to only one of these

- If an adverse reaction associated with the NIMP is likely to affect the safety of the trial subjects

SARs associated with a NIMP should be reported to the Marketing Authorisation Holder (MAH) in order that this information may be used in the MAH's ongoing safety monitoring procedures.

A SAR associated with a NIMP which does not have a Marketing Authorisation in the UK must be notified to the appropriate licensing authority.

In some circumstances trial subjects may experience an SAE which is not related to the study product but which is related to the research (such as a study procedure). Such SAEs must be reported to the Sponsor using the SAE initial report form (See Appendix 1).

5.5 Reporting a Pregnancy

The requirement to follow up a pregnancy reported in a female trial subject, or in the partner of a male trial subject during the course of the study must be assessed during the risk assessment process.

For CTIMP studies the procedure to be followed in the event of a pregnancy being reported must be detailed in the protocol and approved by the Sponsor.

As a minimum, the Investigator must ensure follow-up of the pregnancy and inform the Sponsor of the outcome of the pregnancy. It may be necessary to monitor the development of the new-born for an appropriate period post-delivery which will be defined during the development of the trial protocol.

A pregnancy should be initially reported to the Sponsor using the initial SAE reporting form (see Appendix 1) within 7 days of becoming aware of the pregnancy.

5.6 Adverse Incidents

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. Research related Adverse Incidents must therefore be reported in accordance with the Trust's own Adverse Incident Reporting Procedure/System DATIX. An example of a research related adverse incident may be lost drugs. This is not an AE but should be reported as an AI.

Events that are both Adverse Incidents and Adverse Events MUST be reported independently following both processes and procedures previously outlined.

All Adverse Incidents that are reported as occurring on research studies taking place in the Trust are reviewed by the R&D Department and are reported to the R&I Forum.

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/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 (AR).**

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. Other SOPs and related documents

R&D SOP MR 03 Trial management system - using EDGE
R&D SOP TD 01 Research documentation and file management

Appendix 1

https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

RESEARCH RELATED SAE/SUSAR INITIAL REPORT FORM (Page 1 of 3)

R&D use only: case reference number		Date report received by R&D	

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

2. Details of study	
Title:	R&D Ref:
	Ethics No:
	EudraCT No (CTIMP studies only):

3. Details of subject affected by SAE/SUSAR (enter details available without unblinding subject)						
Participant study ID	Hospital Number	Initials	DOB	Gender	Weight	Height

4. Details of SAE/SUSAR			
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 ☐ required hospitalisation ☐ prolonged an ongoing hospitalisation ☐ resulted in persistent or significant disability/incapacity ☐ resulted in a congenital anomaly or birth defect ☐ other – please specify*		*Specify:	
Maximum intensity (up until time of report)	Mild ☐	Moderate ☐	Severe ☐

Onset Date	Onset Time (if known)	End date	End time (if known)

Date Investigator aware of SAE	Date SAE Initial report Faxed	Time SAE Initial report faxed

Signature of person completing page:		Date:	
Print name:		Job title:	

RESEARCH RELATED SAE/SUSAR INITIAL REPORT FORM (Page 2 of 3)

5. Outcome		
☐ Resolved*	☐ Ongoing*	☐ Died* (give cause and PM details if available)
*Give details:		
Was the patient withdrawn from the study?	Yes ☐	No ☐

6. Location of (onset of) SAE
Setting (e.g. hospital*, home, GP, nursing home):
Exact location:

7. Action taken and further information
Please describe action taken:
Other information relevant to assessment of case e.g. medical history, family history, test results.

Signature of person completing page:		Date:	
Print name:		Job title:	

RESEARCH RELATED SAE/SUSAR INITIAL REPORT FORM (Page 3 of 3)

8. Causality and Expectedness (to be completed by physician)		
Is the SAE related to the drug/device/intervention? ☐ Not related ☐ Unlikely to be related ☐ 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 reference document such as IB or SmPC)**	**1 - The SAE is a SUSAR. Please complete and return all sections of the follow up report form when further information is available and complete R&D/F47 immediately.** **2 - The SAE is not a SUSAR. Please complete and return the follow up report form when further information is available.**

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

Signature of person completing page:		**Date:**	
Print name:		**Job title:**	

10. 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 are accurate and complete	

Appendix 2
https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

RESEARCH RELATED SAE/SUSAR FOLLOW UP REPORT FORM

R&D Use only:

Trial:		SAE reference number	Issued by R&D for initial SAE report
Report number:	e.g. Followup 1	Date Received	dd-mm-yyy

To be completed by the person filling in the SAE form					
Date of initial report		*Participant study ID*		*Participant initials*	

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 ☐

2. Outcome		
☐ Resolved*	☐ Ongoing*	☐ Died* (give cause and PM details if available)
*Give details (include end date and time where applicable):		
Was the patient withdrawn from the study?	Yes ☐	No ☐

3. Additional action taken and further information since initial report
Please describe further action taken:
Has the investigator assessment in the initial report form changed (provide reason):

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

Signature of Chief /Principal Investigator or delegated physician: Name (print please): Date: I confirm that the contents of this form are accurate and complete

Appendix 3

https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

RESEARCH RELATED SAE/SUSAR SPONSOR REPORT FORM

R&D Reference Number:	
Short Study Title:	
EudraCT Number:	
SAE reference number issued by R&D:	

1. Sponsor assessment of causality		
List the reports considered when making the Sponsor assessment		☐ Initial report ☐ Follow up report #1 ☐ Follow up report #2 ☐ Other .....
Is the SAE related to the drug/device/intervention? ☐ Not related ☐ Unlikely to be related ☐ 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 i.e. IB or SmPC)	1 - The SAE is a SUSAR. Proceed with unblinded assessment and complete sections 2 and 3. 2 - The SAE is not a SUSAR. Complete section 3.

2. Unblinding	
Name of individual who requested blind is broken:	
Request made to:	
Date request made:	
Information provided by:	
Information received by:	
Date information received:	
Location information filed by R&D:	
Names of all individuals who aware of result of unblinding:	
Comments:	

3. Administrative and sponsor details	
Name of person performing sponsor assessment:	Contact Number:

Signature of person performing sponsor assessment:	Date:
Name of Sponsor Representative	Contact Number:
Signature of Sponsor representative:	Date:

Study Title:	**Chief/Principal Investigator:**
R&D Reference Number:	**EUDRACT Number:**

AE/SAE Reference number	Participant ID	Date of Event dd-mm-yyyy	Brief Description of Event	SUSAR (Y/N)	Initials of individual making entry

Appendix 4

AE Log

AE/SAE Reference number	Participant ID	Date of Event dd-mm-yyyy	Brief Description of Event	SUS AR (Y/N)	Initials of individual making entry

Appendix 5 SAE LOG

Study Title:	**Chief/Principal Investigator:**
R&D Reference Number:	**EUDRACT Number:**

AE/SAE Reference number	Participant ID	Date of Event dd-mm-yyyy	Brief Description of Event	SUS AR (Y/N)	Initials of individual making entry

Appendix 6

RESEARCH RELATED ADVERSE EVENT RECORDING TEMPLATE

STUDY TITLE:	
EudraCT No:	
Ethics Reference:	
R&D Reference:	

PATIENT/VOLUNTEER ID:

AE NUMBER FOR THIS PARTICIPANT:

Description of Event	Start date:	End date: (where no end date exists as patient concludes involvement in the study with ongoing AE then insert NR here)

Assessment			
Intensity:	☐ mild ☐ moderate ☐ severe	Expectedness	☐ expected ☐ unexpected i.e. not described in protocol, SmPC or IB
Causality: Relationship to study drug/ 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 and/or R&D Unit within 24 hours using the SAE/ SUSAR reporting forms provided by the Sponsor . Where none is provided use the Research Related SAE/SUSAR Initial Report Form