SAEs (Hosted)

Research & Development

Standard Operating Procedure for Identifying, Recording and Reporting Serious Adverse Events in Trust Hosted Drug Clinical Trials

SOP Number : SOP-05-09	**Effective Date:** October 2021
Version Number: v09	**Review Date:** 2-3 years

1.0 BACKGROUND

This document sets out the Adverse Event (AE) reporting procedures to be followed by all West Hertfordshire Hospitals Trust (WHHT) staff who are involved in setting up and running research studies managed by West Hertfordshire Hospitals Trust.

It provides guidance on the responsibilities delegated to the Chief Investigator (CI) by the Sponsor regarding adverse event reporting.

2.0 PURPOSE

This SOP relates to Serious Adverse Event (SAE) recording and reporting requirements for WHHT hosted Clinical Trials for an Investigational Medicinal Product (CTIMPs). This SOP describes the procedures for identifying, recording and reporting AEs and SAEs. The reporting requirements for SAEs to the Principal investigator (PI), Sponsor and the R&D Office are described.

3.0 APPLICABLE TO

Any WHHT personnel involved with clinical research including, but not limited to, Unit Heads, Chief Investigators (CI), Principal Investigators (PI), Co-Investigators, Consultants, Clinical Trial Pharmacists, Research Managers, Statisticians, Research Nurses, Allied Health Professionals, Trial Coordinators, Administrative Staff & Data Managers.

4.0 RESPONSIBILITIES

For WHHT hosted clinical trials, the responsibility for pharmacovigilance is with the sponsor/CI.

Any research staff who observe an adverse event is responsible for notifying the PI/DI within 24 hours of knowledge, or, as stated in the protocol.

5.0 PROCEDURE

5.1 Recording and Reporting Adverse Events (AE)

5.1.1 An AE 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.

5.1.2 An Adverse Reaction (AR) is any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

5.1.3 All AEs and ARs should be recorded in the source data (medical records or case report forms (CRFs)), as stated in the protocol.

5.1.4 AEs and ARs should be reviewed by a clinician.

5.1.5 The severity of AEs and ARs should also be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version stated in the protocol. Please ensure that the highest grading is used for recording purposes.

5.1.6 The PI/DI should ensure compliance for assessing AEs and ARs as described in the Sponsor agreement and protocol.

5.1.7 Events considered serious, should follow procedures outlined in 5.2.

5.2 Recording and Reporting Serious Adverse Events

5.2.1 A SAE or Serious Adverse Reaction (SAR) must be recorded and reported according to the protocol.

5.2.2 **Seriousness assessment**

The PI/DI should review whether the event is **serious**, i.e. if the event results in one or more of the criteria listed in the definitions or has been identified within the protocol or reference document (e.g. Investigator's Brochure (IB) or Summary of Product Characteristics (SPC) as an SAE.

5.2.3 Any research staff who observe an SAE is responsible for notifying the PI/DI within 24 hours of knowledge, or, as stated in the protocol.

5.2.4 The PI/DI should record the event as stated in the protocol (e.g. CRF/SAE form).

5.2.5 SAEs and SARs must also be reported to the Sponsor within 24 hours, or within the timeframes stated in the protocol.

5.2.6 **Causality assessment**

The PI/DI should assess the causality of the event, by considering whether the event has any relationship to the administered study medication, as follows:

- Events which are **Definitely, Probably or Possibly** related are Serious Adverse Reactions
- Events which are **Unlikely or Unrelated** are Serious Adverse Events

5.2.7 **Expectedness assessment**
Generally, the **expectedness assessment** is completed by the Sponsor. However, for reporting purposes, the CI/DI should assess the expectedness using the reference safety information stated in the protocol (IB or SPC). SARs should be considered as unexpected if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information for the IMP.

5.2.8 Current versions of the SPC should be printed and a hard-copy kept in the Trial Master File (TMF). (see SOP-06) Research teams should check periodically for updates to the SPC in the Electronic Medicines Compendium website.

5.2.9 IBs should either be kept in the site file or in a central file with a file note stating the current version and its location.

5.2.10 When IBs are updated with a change to the safety information, this should be treated as a substantial amendment (see SOP-09). An electronic copy of the IB should also be forwarded to the R&D Office with the associated documentation.

5.2.11 The PI/DI should ensure that the seriousness, causality and severity assessments are documented according to the protocol.

5.2.12 SAEs and SARs must be reported to the Sponsor within 24 hours of knowledge, or as stated in the protocol.

5.2.13 SAEs should be followed-up until resolution or as stated in the protocol.

5.2.14 The SAE flow chart (appendix 2) can be used to assess SAEs.

5.2.15 At the annual R&D update teams will be asked to submit numbers of SAEs for review by the Trust R&D Steering Group (RDSG).

5.3 Recording and Reporting SUSARs

5.3.1 Events identified as serious, related and unexpected, should be classed as Suspected Unexpected Serious Adverse Reactions (SUSARs) and should be reported to the Sponsor within 24 hours of knowledge, or as stated in the protocol.

5.3.2 The Sponsor will decide if a SAR or an SAE is a SUSAR and will inform the authorities accordingly.

5.3.3 If there is any suspicion that a Non-IMP interacts with an IMP, then this should be reported to the sponsor as a possible SUSAR.

5.3.4 If a SUSAR report form has not been provided by the Sponsor, please use the form attached as Appendix 3.0.

5.3.5 At the annual R&D update teams will be asked to submit numbers of SUSARs for review by the Trust RDSG.

5.4 Urgent Safety Measures (USMs)

5.4.1 A USM taken by the Sponsor or investigator in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety.

5.4.2 The PI/DI must notify the Sponsor immediately should they believe that an urgent safety measure needs to be implemented.

5.4.3 The Medicines and Healthcare products Regulatory Agency (MHRA) and Healthcare Research Authority (HRA) must be notified by the Sponsor immediately, and in any event within 3 days, that such a measure has been taken and the reasons why it has been taken.

5.4.4 USMs may be taken without prior notification to the MHRA / HRA. However, the PI/DI must inform the R&D Office of the new events, the measures taken and the plan for further action as soon possible.

5.4.5 If a USM form has not been provided by the Sponsor, a form for notifying the R&D Office of Urgent Safety Measures is attached as Appendix 4.0.

5.5 Pregnancy

5.5.1 Pregnancy in itself is not regarded as an AE unless there is suspicion that the study medication may have interfered with the effectiveness of the contraceptive or that it might be harmful to the foetus.

5.5.2 Should a pregnancy occur, it should be recorded and reported in accordance with the procedures described in the protocol.

5.5.3 In the event of a pregnancy, a pregnancy report form should be completed with the PI/DI's signature and sent to the Sponsor. Should the Sponsor not provide a form, please use the Pregnancy Notification Form attached as Appendix 5.0.

5.5.4 The mother should be followed-up during the course of the pregnancy and the baby should be followed-up for a minimum of three months after birth, or as stated in the protocol.

5.5.5 The mother should give consent for additional follow-up during the course of the pregnancy and once the baby is born.

5.5.6 Similarly, if the partner of a patient on a clinical trial becomes pregnant, the baby should be monitored for at least three months after birth. Consent needs to be obtained for this additional follow-up.

5.5.7 Any event meeting the serious criteria (death, life-threatening, congenital abnormality, birth-defects) should be reported as an SAE, according to the protocol.

6.0 RELATED DOCUMENTS

- SOP-01- SOP on SOPs
- SOP-02- SAEs (Sponsored)
- SOP-06- Trial Master File
- SOP-07- Research Staff Training
- SOP-09- Amendments
- SOP-10- Serious Breaches (Sponsored)
- detailed guidance is available on the MHRA website
- Detailed guidance on the request to the competent authorities of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end-of-trial (CT-1). (2010/C 82/01)

7.0 APPENDICES

Appendix 1.0 - Definitions
Appendix 2.0 - SAE reporting flowchart
Appendix 3.0 - SUSAR report form
Appendix 4.0 - Urgent Safety Measures form
Appendix 5.0 - Pregnancy Report Form

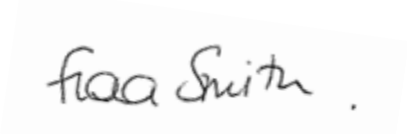
8.0 REVISION CHRONOLOGY

Revision Chronology:		
Version Number	**Effective Date**	**Reason for Change**
SOP-05-09	**October 2021**	1. Change from general Standard Operating Procedures (gSOP) to SOP 2. Removal of the '10.0 Agreement' from the template - all agreement signatures will be collated on a new 'SOP Signature Sheet Document' 3. Amendments following end of Brexit transition period 4. Other minor amendments and clarification of terms following review
gSOP-05-08	**10/2017**	Minor amendments following review
gSOP-05-07	**01/10/2015**	Minor amendments following review
gSOP-05-06	**22/05/2014**	Minor amendments following review
gSOP-05-05		SOP modified for use within ENHT & WHHT

gSOP-05-04 (MVCC)		SOP modified for implementation at MVCC
gSOP-05-04	**01/10/2011**	1. Section 4.2 – location of SPCs and IBs. 2. Section 4.3 - if a SAR is suspected to be caused by a non-IMP interacting with an IMP, then this should be considered a SUSAR. 3. Section 5.0 - a section on Urgent Safety Measures has been added. 4. Section 6.0 – reporting pregnancies. Pregnancies should be followed-up until the baby is at least three months old. 5. The SUSAR report form version 3.3 July 09 has been updated to version 4.0 29th August 2011 and attached as Appendix 2.. 6. The form for reporting Urgent Safety Measures is attached as appendix 4.0.
gSOP-05-03	**02/03/2010**	Sponsor upgraded SUSARs to be reported to R&D if research team is aware of this escalation
gSOP-05-02	**01/08/2006**	1. Review /update of overall SOP format 2. Unexpected SAE reporting requirement to R&D is not required

9.0 AUTHORSHIP AND APPROVAL

Author

Signature  **Date** 28/10/2021

R & D Steering Group Approval

Signature  **Date** 28/10/2021

Appendix 1: Definitions

Adverse Event (AE)
An unfavourable outcome that occurs during or after the use of a drug or other intervention, but is not necessarily caused by it.

Adverse Reaction (AR)
Any untoward and unintended response to an investigational medicinal product related to any dose administered. Comment: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product would qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship.

Chief Investigator (CI)
The investigator with overall responsibility for the research. In a multi-site study, the CI has co-ordinating responsibility for research at all sites. All applications for ethical review should be submitted by the CI.

Clinical Trial of Investigational Medicinal Product (CTIMP)
A clinical trial that is within the scope of the UK Medicines for Human Use (Clinical Trials) Regulations 2004. An investigation in human subjects, other than a non-interventional trial, intended: a) to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products, b) to identify any adverse reactions, or c) to study absorption, distribution, metabolism and excretion, with the object of ascertaining the safety and/or efficacy of those products.

Delegated Individual (DI)
An individual delegated by a person of responsibility to carry out their task(s).

Pharmacovigilance
The science relating to the detection, assessment, understanding and prevention of the adverse effects of medicines.

Principal Investigator (PI)
The investigator responsible for the research site. There should be one PI for each research site. In the case of a single-site study, the chief investigator and the PI will normally be the same person.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)
Any adverse event or adverse reaction that results in:

- death
- is life-threatening*
- requires hospitalisation or prolongation of existing hospitalisation

- results in persistent or significant disability or incapacity
- or is a congenital anomaly or birth defect

Comment: Medical judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important adverse events/reactions 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 of the other outcomes listed in the definition above, should also be considered serious.

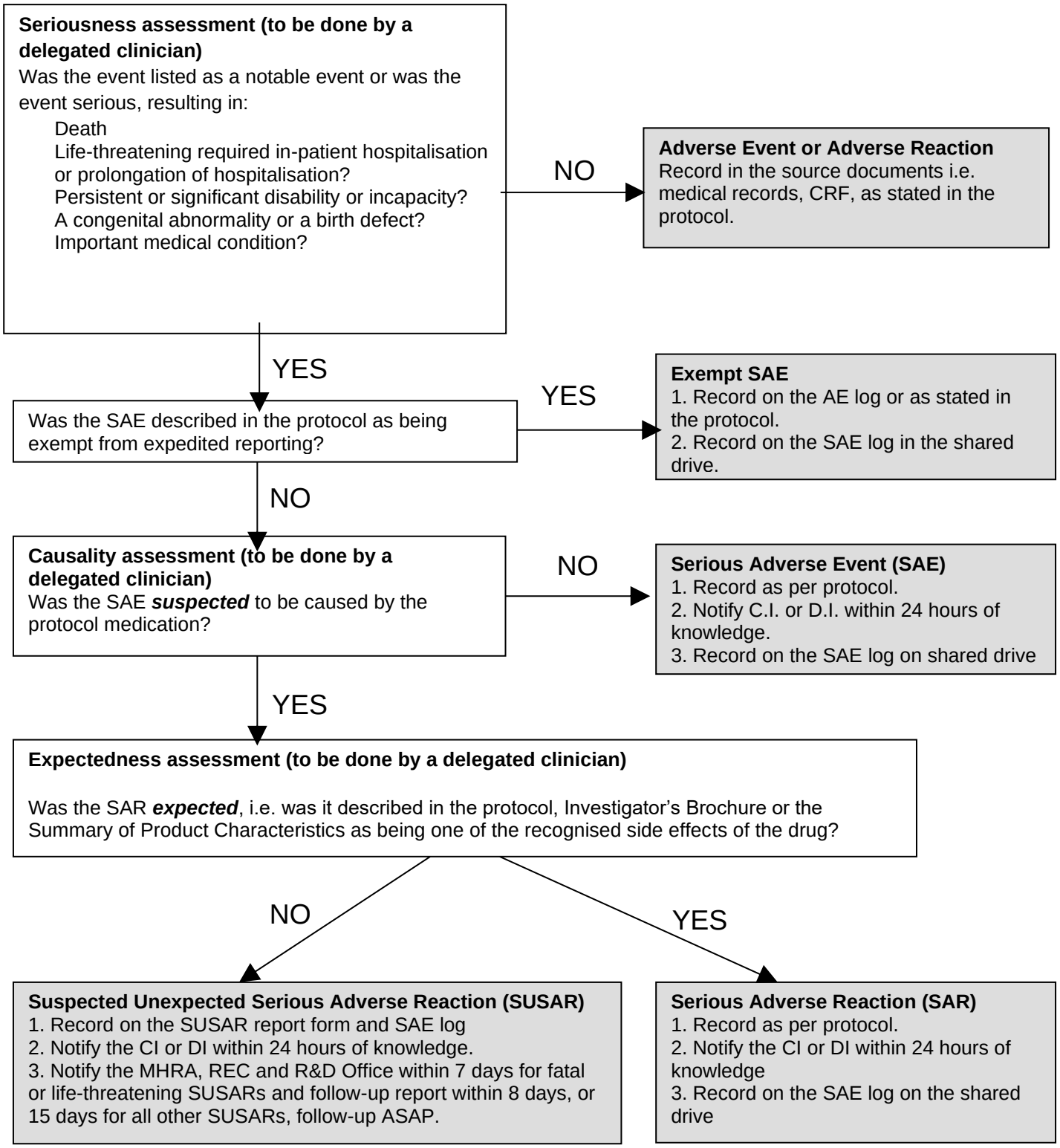
* Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of a Serious Adverse Event/Reaction.

Appendix 2.0: SAE reporting flowchart

Please carry out the following assessments for all adverse events.



Appendix 3.0: SUSAR Report Form Version 7.0 2021

Date received by R&D Office	ID

Local Lead Researcher: **Department :** **Your reference:**

RD No. __ __ __ __ **Short title of study:**

Details of SUSAR - please provide details or circle all that apply.

1) Patient's Trial ID Number __ __ __ __

2) Is this a Trust patient? Yes No

3a) Patient's age ___ ___ **b) Gender** Male Female

4) Medical History

5) Concomitant Medication:

6)Details of SAE:

_____
_____
_____

7) Type of AE Report: Initial Report Follow up report

8) Date of onset: __ __/__ __/__ __ **Time of onset:** _ _ : _ _ **Date event resolved:** __ __/__ __/__ __ **still ongoing - - - - - - - - - -**

9) Trial drug : **Date of last dose:** _ _ / _ _ / _ _ _ _ **Time of last dose:** _ _ : _ _

10a) Event terms and CTCAE grading:

10b) Which version of the CTCAE was used? Version 5.0 Version 6.0

11) Seriousness assessment (please circle)

Death Life-threatening Hospitalisation or Prolongation of existing hospitalisation

Disability Congenital abnormality Important medical event

12) Causality assessment by CI/ PI- is there a possible causal relationship between this adverse event and the trial drug?

Causality / Trial Drug	Definitely	Probably	Possibly	Unlikely	Unrelated

13) Severity of event: Mild Moderate Severe

14) Outcome: Recovered Recovering Recovered with sequelae Not recovered Unknown Fatal

15) Expectedness assessment by CI/ PI – is this event expected as described in the protocol, Investigator's Brochure (IB) or Summary of Product Characteristics (SPC)?

Expectedness / Trial Drug(s)	Expected*	Unexpected

*(Expected events do not need to be reported to the R&D Office)

16) Please indicate which document(s) were used to check expectedness: Protocol IB SPC

For all SUSARs and SAEs please notify the sponsor as per their requirement. Where the Trust is the sponsor, please notify the MHRA and Research Ethics Committee of all SUSARs, in line with the Trust SOP SOP-02.

Local Lead Researcher Comments: (View on SUSAR and the implications for ongoing trial.)

Sponsor Assessment of Causality and Expectedness

Sponsor approval of Causality Assessment (Please circle): Yes No

If 'No' please provide details:

Sponsor approval of Expectedness Assessment (Please circle): Yes No

If 'No' please provide details:

Recommended Actions (where required):

Sponsor Representative Signature…… **Date**____/____/____

For Trust sponsored trials, please provide dates that this event was reported to:

MHRA __ __/__ __/__ __ **Main REC** __ __/__ __/__ __ **Other participating sites (for multi-centre studies)** __ __/__ __/__ __

For Trust hosted studies please give the date this event was reported to the sponsor __ __/__ __/__ __

CI/PI/DI signature…… **Date**____/____/____

Print Name ……

Return completed form, with accompanying Serious Adverse Event Report Form to: the R&D Department

Appendix 4.0: Notification of Amendment for Urgent Safety Measures

*Please complete this form to the R&D Office as soon as possible after implementation of Urgent Safety Measure. This form should only be in exceptional circumstances, for example to protect the participants from an **immediate** hazard to their welfare or safety*

Part A – Where to Send your Request

To: R&D Office

R&D Office use only

Date received:

Part B – Your Details

From:	
Tel:	
Fax:	
Email:	

Part C – Sponsor Details (please tick)

Trust-sponsored ☐

Trust-hosted (please specify below) ☐

_____

_____

Part D – Study Details

Trial Name:	

CTIMP **OR** non-CTIMP (please delete as appropriate)						
RD reference number:	RD					
Chief Investigator:						
Principal Investigator:						

Part E – Urgent Measures

Measures taken:
Date effective from:

Why have these measures been taken:

Chief Investigator Signature	
Date	

Appendix 5.0: Pregnancy Notification Form version 2.0 13th January 2013

RD number _ _ _ _	**Your reference**
Short title of study	
Chief Investigator	**Department**
Patient's Trial ID Number __ __ __ __	**Date of birth** ___ ___ / ___ ___ /___ ___

1. MATERNAL INFORMATION			
Date of Birth	_ _/_ _/_ _ _ _		
Date of last menstrual period	_ _/_ _/_ _ _ _		
Expected Date of Delivery	_ _/_ _/_ _ _ _		
Method of contraception:			
Was contraception used as instructed?	Yes	No	Uncertain

2. MEDICAL HISTORY
Include information in familial disorders, known risk factors or conditions that may affect the outcome of the pregnancy. (If none, mark as N/A)

3. PREVIOUS OBSTETRIC HISTORY

(provide details on all previous pregnancies, including termination or stillbirth)
Gestation Week Outcome including any abnormalities

1

2

3

Patient's Trial ID Number __ __ __ __ Date of birth ___ ___ / ___ ___ /___

4. DRUG INFORMATION

Drug name	Dose	Route	Date start	Date stopped

5. PRENATAL INFORMATION

Have any specific tests, e.g. amniocentesis, ultrasound, maternal serum AFP, been performed during the pregnancy so far?

Yes No Not known

If Yes, please specify test date and results:

Test type and date _ _/_ _/_ _ _ _

Result

6. PREGNANCY OUTCOME

Patient's Trial ID Number __ __ __ __ **Date of birth** ___ ___ / ___ ___ /___ ___

7. MATERNAL PREGNANCY ASSOCIATED EVENTS

If the mother experiences an SAE during the pregnancy, please indicate here and complete an SAE form, complete with CI's signature.

8. CHILD OUTCOME

(**a) Abortion** Yes No

If Yes

Therapeutic Planned Spontaneous

Please specify the reason and any abnormalities (if known):

Date _ _/_ _/_ _ _ _

(b) Delivery Yes No

If Yes

Normal Forceps/Ventouse Caesarean

Date of delivery _ _/_ _/_ _ _ _

Delivery at week:

Delivery was: Normal Abnormal Stillborn

Please give dates and details of any abnormalities

Sex Male Female
Height cm
Weight kg
Head circumference cm

AGPAR score

1minute _ _ 5 minutes _ _ 10 minutes _ _

Patient's Trial ID Number __ __ __ __ **Date of birth** ___ ___ / ___ ___ /___ ___

9. ASSESSMENT OF SERIOUSNESS (OF PREGNANCY OUTCOME)

Not serious

Serious :

a) Mother died/baby died b) Life-threatening c) Involved prolonged inpatient hospitalisation

d) Results in persistent or significant disability/incapacity

e) Congenital anomaly/birth defect f) Other significant medical events

Date of death: _ _/_ _/_ _ _ _

10. ASSESSMENT OF CAUSALITY(OF PREGNANCY OUTCOME)

Please indicate the relationship between the trial drugs and the pregnancy outcome

Causality / Trial Drug(s)	Definitely	Probably	Possibly	Unlikely	Unrelated

Could the trial drugs have interfered with contraception?

a) Yes b) No c) Maybe

11. ANY ADDITIONAL INFORMATION

12. DETAILS OF PERSON SUBMITTING THIS REPORT

Signature …… Date _ _/_ _/_ _ _ _

Please print name ……..

CI/PI signature…… Date _ _/_ _/_ _ _ _