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 University of Cape Town Clinical Research Centre		Standard Operating Procedures
Title	Trial Participant Safety managing and reporting for clinical research	
Number	06	
Version	1	

	Name	Title	Signature	Date
Reviewer	B Wright	Project Manager	<i>BW</i>	5 May 2015
Authoriser	D Shamley	Director	<i>D Shamley</i>	5/5/2015
Effective date				5 May 2015
Review date				5 May 2018

1. Purpose

To describe the responsibilities and procedures for managing and reporting adverse events (AEs) in clinical trials of investigational products and other clinical research studies.

2. Scope

The Clinical Research Centre (CRC) will advise whether this document is mandatory for research where UCT's Faculty of Health Sciences (FHS) is the named sponsor, or where CRC facilities are used. In these circumstances the SOP is relevant for CRC staff and investigational team staff involved in the process of managing and reporting AEs. This SOP may, however, also be adapted for use for studies conducted by UCT clinical researchers where UCT is not the sponsor. NB All clinical research conducted at UCT must comply with the Faculty of Health Sciences Human Research Ethics Committee (HREC) SOPs regarding unanticipated problems involving risks to research participants and others, including AEs (<http://www.health.uct.ac.za/research/humanethics/about/>).

3. Templates/forms

CRC 6.1 Serious Adverse Event (SAE) form

CRC 6.2 Safety Assessment and Reporting Guideline

CRC 6.3 Safety reporting flowchart

CRC 6.4 FHS008: Internal Adverse Event or Unanticipated Problem reporting (HREC document)

CRC 6.5 Form FHS009: Reporting Form for Safety Information Investigator Brochure, Safety Information, DSMB Report, Hold on Study Activity (HREC document)

4. Glossary/definitions

See also: South African Good Clinical Practice (SAGCP) Guideline; ICH Guideline for Good Clinical Practice E6; ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A; the South African Medicines Control Council (MCC) Guidelines for Reporting AE/Drug Reactions.

THIS SOP REMAINS THE PROPERTY OF THE UCT CLINICAL RESEARCH CENTRE**Adverse event (AE)**

Any untoward or unfavourable medical or psychological occurrence in a participant, including any abnormal laboratory finding, symptom or disease. An AE does not necessarily have a causal relationship with the research or any risk associated with the research.

Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Clinical Research

Health-related research that involves people, their tissue (e.g. blood samples), behaviour and/or data.

Clinical Research Centre (CRC)

A centre located in UCT's FHS that provides advice and services to researchers in order to produce high quality clinical research. The CRC may agree to take on the role of sponsor for specific studies should certain criteria be fulfilled.

Clinical Trial (of an Investigational product)

Any investigation in human participants (including patients and other volunteers) intended to discover or verify the clinical, pharmacological and/or other pharmacodynamics effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining their safety and/or efficacy.

Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a clinical trial and the quality of the data produced (See South African Good Clinical Practice Guideline, Second Edition. 2006. Appendix C).

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A standard for clinical trials/studies which encompasses the design, conduct, performance, monitoring, termination, auditing, recording, analysis, and reporting and documentation of clinical trials/studies and which ensures that the trials/studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented and the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. The South African GCP Guidelines are also applicable, in whole or in part, to biomedical research in general.

Human Research Ethics Committee (HREC)

An independent body constituted of medical professional and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance on that protection by, among other things, reviewing and approving/providing favourable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. HREC's must be registered and accredited by the National Health Research Ethics Council (NHREC).

Investigational Medicinal Product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigator

An investigator who is the responsible leader of any site team is the Principal Investigator (PI), a South African-based scientist with sole or joint responsibility for the design, conduct, delegation of responsibilities, analysis and reporting. Sub-investigators are designated and supervised by the PI to perform critical study-related procedures and/or to make important study-related decisions. In the case of a multi-centre trial there must be a local PI attached to each site, while an investigator assigned responsibility for the coordination of investigators at different centres in a multicentre trial is termed a Coordinating (or National) Principal Investigator (CI).

Investigator's Brochure

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

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Files for each project containing key documents (such as Essential Documents for clinical trials). The Master File is in two parts – a Sponsor File and Investigator Site File (ISF).

Medicines Control Council (MCC)

A regulatory authority that was established in terms of the Medicines and Related Substances Act, 1965 (Act No. 101 Of 1965) to oversee the regulation of medicines in South Africa. Its main purpose is to safeguard and protect the public by making sure that all medicines that are sold and used in South Africa are safe, therapeutically effective and consistently meet acceptable standards of quality.

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction

Any untoward medical occurrence that at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Standard Operating Procedure (SOP)

Detailed written instructions to achieve uniformity of the performance of a specific function.

Sponsor

An individual, a company, an institution, or an organisation which takes responsibility for the initiation, management, and/or financing of a clinical research project.

Unanticipated problems

An 'unanticipated' problem is any incident, experience or outcome that meets all the following three criteria:

- Unexpected in terms of its nature, severity or frequency, or the research population being studied; or if anticipated it is not fully addressed or specified in information provided to the HREC or to participants such as in initial protocol applications, any amendments, investigator brochures, scientific literature, product labelling, package inserts and HREC-approved informed consent documents or any existing documentation regarding the research conducted to date under the protocol;
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research);
- Suggests that the research places participants or others at a greater risk of physical, psychological, economic or social harm than was previously known or recognised.

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In summary, an unanticipated problem is:

Unexpected – not in the consent form, investigator's brochure, protocol package insert or label; or unexpected in its frequency, severity or specificity;

Related to the research – caused by, or probably caused by, or associated with a device;

Harmful – caused harm to participants or others, or placed them at increased risk of physical, psychological, economic or social harm.

Examples of unanticipated problems include:

- Loss of a laptop computer containing confidential information about participants or others.
- A spouse physically abused by his or her partner for taking part in the study.
- Publication in the literature or a Data and Safety Monitoring Report that indicates an unexpected change in the balance of risks and benefits in the study.
- Finding that laboratory reports on blood or other samples were in error.

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

5. Responsibilities and procedure

5.1. Safety monitoring of participants in clinical research, including clinical trials, is an ethical requirement. This involves appropriate prevention, monitoring, prompt reporting and management of adverse events (AEs).

5.2. The sponsor is responsible for the ongoing safety evaluation of an investigational product and should promptly notify in writing all relevant investigators, the Medicines Control Council (MCC) and HREC of any findings that could affect adversely the safety of participants, the trial conduct, or alter an approval/favourable opinion to continue the trial. Participants should also be informed. Accountability for any specific function involved may, however, be delegated in writing to the investigator.

5.3. Depending on the level of risk, the sponsor may appoint a medical monitor, trial safety group or independent data monitoring committee to periodically assess safety data and advise on whether a trial should be amended, suspended or terminated.

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- 5.4. The Principal Investigator (PI) takes responsibility for safety assessment and reporting at the site but may delegate aspects of the role to suitably qualified and experienced members of the team. This will be recorded and signed off by the PI on the delegation log.
- 5.5. By the time of trial/study start all staff that may play a part in the process of assessing and/or reporting safety data should receive adequate training according to their role. The training must be documented and roles must be allocated and signed off by the PI on the delegation log.
- 5.6. Safety assessments and reporting will be performed according to the approved protocol and current regulatory and ethical requirements (see <http://www.mccza.com/> and the CRC website for MCC requirements regarding the safety of investigational medicinal products; see <http://www.health.uct.ac.za/research/humanethics/sop/> for UCT HREC's requirements). However, the level of risk, including what is already known about an investigational product, will play a role; should the planned management and/or reporting of adverse events be different from that specified in the regulations, this should be justified in the protocol.
- 5.7. It should be clear to all medical staff working on a clinical trial as to:
- How AE reports are elicited from participants, graded and assessed in terms of relationship with an investigational product and their severity, and followed up.
 - How staff responds to AE reports in terms of medical care of participants and reporting within the site team.
 - That the site staff should, unless otherwise justified, report to the sponsor within 24 hours of becoming aware of an SAE.
 - Who takes responsibility for reporting to the regulatory authority, HREC(s) and (if relevant) a sponsor-specific oversight entity (e.g. trial safety group). NB if the sponsor assesses causality differently to the investigator the event should still be reported with both assessments. See the Safety Reporting flowchart (CRC 6.2) for a summary of timelines for reporting to the MCC and HREC.
 - Who is responsible for periodic safety reporting (e.g. 6 monthly line listings to MCC or HREC).
- 5.8. Appropriate template documentation (e.g. source documents, Case Record Forms, SAE forms) that complies with regulatory, ethical and the sponsor's requirements should be available; the template SAE form CRC 6.1 may be used or adapted as long as it remains compliant with regulatory and ethical requirements.

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- 5.9.** UCT HREC's own reporting form for unanticipated problems (including AEs) must also be submitted. See CRC 6.4 and 6.5
- 5.10** Should the investigator decide that there are safety concerns that require an immediate amendment to the protocol or conduct of the research he/she should communicate this to site(s) staff without delay. Then, as soon as possible, he/she will inform the sponsor, MCC, HREC(s) and any other relevant parties as to what the safety concern was, what measures were taken and what the next steps will be (e.g. to submit a protocol amendment or notice of trial suspension, termination).
- 5.11** Essential documents relating to safety assessment and reporting should be maintained in the Mater File.

6. Document history:

Version No.	Date	Reviewer	Details of changes

THIS SOP REMAINS THE PROPERTY OF THE UCT CLINICAL RESEARCH CENTRE**CRC 6.1 Serious Adverse Event Form**

When reporting dates use dd/mmm/yy

Submit SAE reports to: _____

Protocol ID: _____

Participant study number: _____

Participant details

Participant initials:	Male	Female	<input type="checkbox"/> Initial report <input type="checkbox"/> Follow-up report	Date of this report:
Date of birth or age at time of event			Weight at time of event (if known): _____ kg	Date PI notified of event:

Investigator details

Investigator name: _____	Phone #: _____
Study Site Address: _____ _____	

Investigational product(s)

Name (indicate if unblended or not)	Batch number	Dose & frequency	Route	Start date/time	Stop date/time (or ongoing)	Indication for use	Causality assessment

* Causality: 1=Definite, 2=Probable, 3=Possible, 4=Unlikely, 5=Unknown

Concomitant medicines/treatments at time of event, i.e. not to treat event (or attach copy of relevant case record form)

Name	Dose & frequency	Route	Start date/time	Stop date/time (or ongoing)	Indication for use	Possibly causal? Yes/No

Event onset date:	Event onset time:	Event resolved date:	Event resolved time:
Event description: (including dates of hospitalisation, diagnosis and de-challenge/re-challenge, where available)			
If necessary please continue event description on Supplementary Information Sheet <input type="checkbox"/> Mark (x) if used			

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Protocol ID:

Participant study number:

Why was the event serious? (mark ALL that apply X)		Outcome at the time of this report	
Fatal		Resolved	
Life-threatening		Recovered with long term sequelae	
New/prolonged in-patient hospitalisation		Condition worsened	
Persistent or significant disability/incapacity		Not available	
Congenital anomaly / birth defect		Fatal	
Medically significant otherwise		If outcome was fatal, date of death: _____	
Required intervention to prevent one of the above outcomes		Autopsy findings (or attach): _____	

Treatment of event (or attach copy of concomitant medication CRF)

Name of medication/treatment	Dose & frequency	Route	Start date/time	Stop date/time (or ongoing)	Indication for use

Relevant laboratory/diagnostic tests:

Date	Test	Results (or pending)

Relevant Medical History - continue on Supplementary Information Sheet

Date	Disease/surgery

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Protocol ID:

Participant study number:

SUPPLEMENTARY INFORMATION

Please indicate the section to which supplementary Information refers:

Reporter (Title and name): _____

Signature: _____ Date: _____

For Sponsor use:


Date received in house:

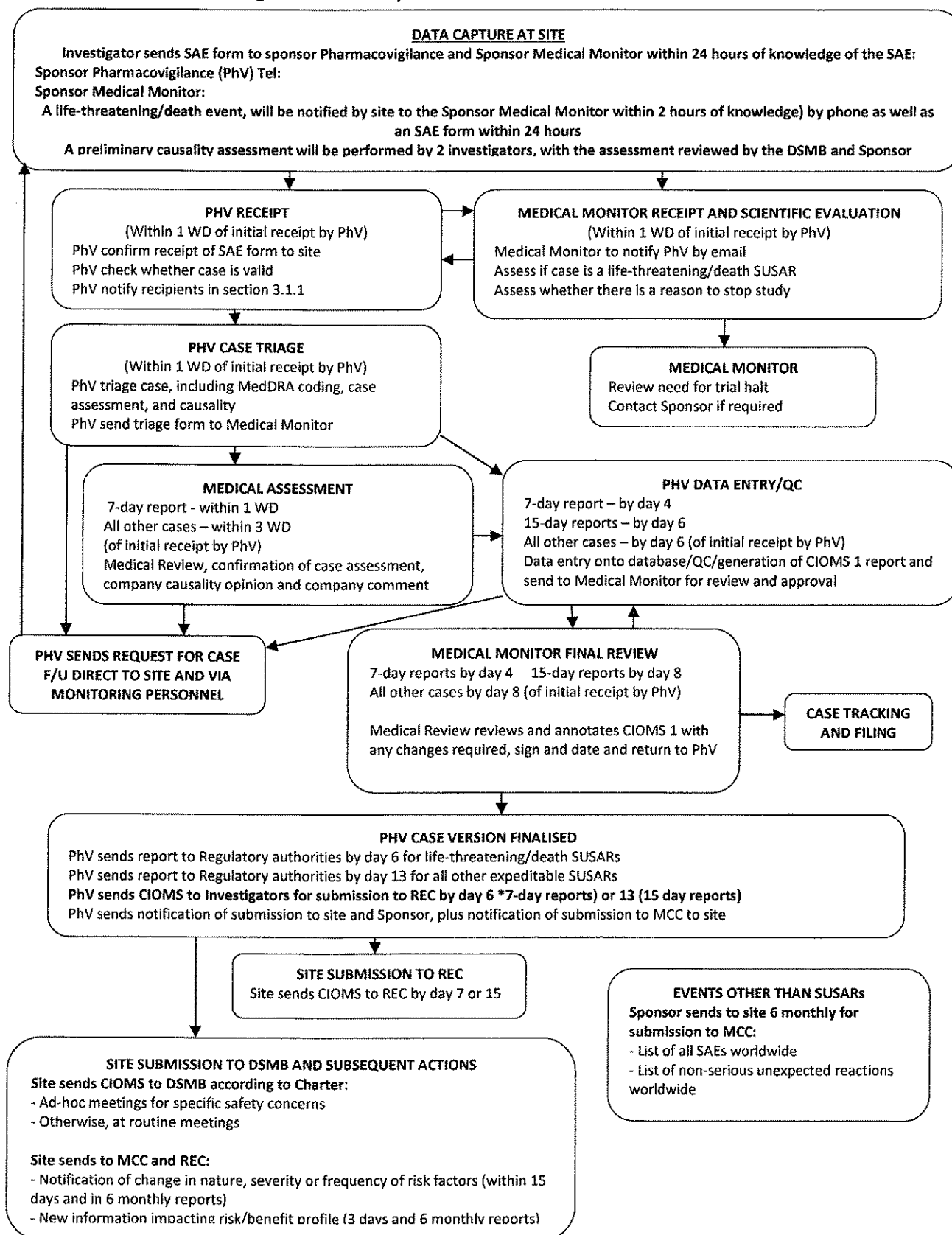
Date reviewed:

Reviewer's name/role:

Recommended action:

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	University of Cape Town Clinical Research Centre		CRC 6.2 Safety assessment and reporting guideline
Trial number		Sponsor	
<p>Process for elicitation and management of adverse event (AE) reports:</p> <ol style="list-style-type: none"> 1. AEs will be assessed from screening and recorded throughout the trial unless otherwise stated in study protocol. 2. AEs will be recorded whether spontaneously reported, observed by the trial staff or elicited by general questioning. 3. At screening and admission, participants will be instructed to report changes in health they experience. 4. AEs will also be elicited by indirect questioning (although no leading questions will be asked) during study days, usually at meal times and at discharge, with such questions as "How are you?" or "Is anything bothering you?". 5. Abnormal findings will be carefully considered and any participant who, in the judgment of the investigator may not safely complete the study, will be withdrawn. 6 AEs will be followed up until resolution or agreement between the PI and the Sponsor Medical Monitor. 7. SAEs, non-serious unexpected reactions and changes in nature, severity or frequency of risk factors, and new information impacting the risk/benefit profile should be documented and reported. See process flowchart 8. In addition, other anticipated problems that increase the risk of harm to participants or others (see UCT Faculty of Health Sciences REC document FHS008hlp) should be reported within 7 calendar days of the investigator learning of occurrence. 			

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CRC 6.4**FHS008: Internal Adverse Event or Unanticipated Problem reporting**

HREC office use only (FWA00001637; IRB00001938)			
<input type="checkbox"/> Report is noted and filed - no further action required.			
This serves as notification that all changes and documentation described below are noted and approved			
Chairperson of the HREC signature		Date	

Principal Investigator to complete the following:**1. Protocol Information**

Date (when submitting this form)	
HREC REF Number	
Project Title	
Protocol number (if applicable)	
Principal Investigator (PI)	
Department / Office Internal Mail Address	

2. Documents for acknowledgement

<p>Please itemise on the page below, all documents including revised version numbers and dates, which need to be noted or acknowledged. This page will be detached, signed and returned to the PI as notification of the HREC's approval. (If any protocol amendments occur please separately complete the Amendment Form FHS006)</p>

3. Description of Internal Adverse Event (tick ✓)

Definitions and timelines for reporting internal (on site) adverse events and unanticipated problems are posted on the HREC website.

<input type="checkbox"/>	Fatal or life-threatening adverse event or drug reaction
<input type="checkbox"/>	Serious and unexpected, non-fatal adverse event or drug reaction
<input type="checkbox"/>	Expected adverse event or drug reaction occurring at a greater than expected frequency or severity

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<input type="checkbox"/>	Serious and unanticipated adverse device reaction	
<input type="checkbox"/>	Unanticipated problem that increases risk of harm to participants	
<input type="checkbox"/>	New information that might impact the conduct of a clinical study	
3.1 Please provide a brief description of the event		
3.2 This report is		<input type="checkbox"/> Initial <input type="checkbox"/> Follow up
3.3 In the opinion of the local PI, is this event related to the study drug, device, or procedure? (tick ✓ one)		
<input type="checkbox"/>	Not related	
<input type="checkbox"/>	Unlikely	
<input type="checkbox"/>	Possibly	
<input type="checkbox"/>	Probably	
<input type="checkbox"/>	Definitely	
3.4 Action taken (tick ✓ all that apply)		
<input type="checkbox"/>	Hospitalisation	
<input type="checkbox"/>	Study treatment altered (e.g. drug dose changed)	
<input type="checkbox"/>	Study treatment stopped/ device removed	
<input type="checkbox"/>	Study blind broken	
<input type="checkbox"/>	Monitoring progress	
<input type="checkbox"/>	Removed from study	
<input type="checkbox"/>	Other. Describe in Section 3.1	
3.5 Outcome (tick ✓ all that apply)		
<input type="checkbox"/>	Complete resolution	
<input type="checkbox"/>	Ongoing/ unresolved	
<input type="checkbox"/>	Partial recovery	
<input type="checkbox"/>	Disability or impairment (permanent)	
<input type="checkbox"/>	Disability or impairment (may improve with time)	
<input type="checkbox"/>	Death	
<input type="checkbox"/>	Other. Describe in Section 3.1	

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a) MCC notified	<input type="checkbox"/> Yes	<input type="checkbox"/> No
b) Are any protocol revisions required?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
c) Should the consent/assent form(s) be amended?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
d) Will currently enrolled participants be notified of this event?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Note: If yes to any of the above (points b-d), please enclose an Amendment Form (FHS006) and revised documents with all revisions highlighted in bold or italics.		

5. Signature

My signature certifies that I will maintain the anonymity and/ or confidentiality of information collected in this research. If at any time I want to share or re-use the information for purposes other than those disclosed in the original approval, I will seek further approval from the HREC.			
Signature of PI		Date	

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CRC 6.5**Form FHS009: Reporting Form for Safety Information**
Investigator Brochure, Safety Information, DSMB Report, Hold on Study Activity

HREC office use only (FWA00001637; IRB00001938)			
<input type="checkbox"/> Report is noted and filed.			
Signature of HREC Chair		Date	

Principal Investigator to complete the following:**1. Protocol information**

Date (when submitting this form)		HREC REF Number	
Project Title			
Protocol number (if applicable)			
Principal Investigator			
Department / Office Internal Mail Address			

2. Type of submission (tick ✓)

<input type="checkbox"/>	Investigator Brochure Version #:
<input type="checkbox"/>	Data Safety Monitoring Board Report
<input type="checkbox"/>	Safety Information or Publication
<input type="checkbox"/>	Audit Report (with significant findings)
<input type="checkbox"/>	Hold on Study Activity initiated by:
	<input type="checkbox"/> MCC/FDA/EMEA
	<input type="checkbox"/> Sponsor <input type="checkbox"/> PI

3. Evaluation of information (tick ✓)

Information in this report changes the study risk	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Information in this report requires an amendment to the study protocol	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Information in this report requires an amendment to the informed consent/assent forms	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Information in this report includes a significant new finding which may affect participants' willingness to take part	<input type="checkbox"/> Yes	<input type="checkbox"/> No

(If yes to any of these questions please see note below)

Note: Please attach this report to an appropriate amendment application form (FHS006) where relevant with the required protocol and consent/assent revisions. The amendment application form must include a clean copy of the revised documentation and a copy with changes highlighted in bold or italics.

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4. Please provide a brief description of all potential changes in study risk or benefit arising from this submission:

5. List of Proposed Documents with Revised Version Numbers and Dates

(If any protocol amendments occur please separately complete form FHS006).

6. Signature

My signature certifies that the above is complete and correct.

Signature of PI		Date	
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