Plymouth Research and Development

NHS University Hospitals Plymouth NHS Trust

Standard Operating Procedure

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Title:	Safety reporting		
Approver		Document No:	T5
Name:	Chris Rollinson	Version No:	8.0
Signature:		Effective Date:	Jul-2022
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1. Purpose

To describe the procedure and responsibilities related to the collection, review, and reporting of serious and non-serious adverse events to ensure compliance with the UK and international regulatory requirements. Safety terms are defined in Appendix 1.

2. Scope

This Standard Operating Procedure (SOP) relates to Clinical Trials of Investigational Medicinal Products (CTIMPs), including non-Investigational Medicinal Products (nIMPs), and non-CTIMPs hosted, and/ or sponsored by University Hospitals Plymouth (UHP). The procedure for medical devices safety reporting is not described here, refer to SOP T14.

3. Responsibilities

Sponsor is responsible for the ongoing safety evaluation within the trial. Accountability for certain functions may be formally delegated in writing, where appropriate, to the Chief Investigator (CI) and/ or a Clinical Trials Unit (CTU).

Research Governance Manager (RGM) and Deputy RGM are the point of contact on behalf of the Trust where it is the study Sponsor.

Chief Investigator (CI) within their other delegated accountabilities, is responsible for informing PIs of relevant safety issues.

Principal Investigator (PI) has responsibility for reporting safety events or reactions to the study Sponsor or CTU (including abnormal laboratory results) that are identified in the protocol as critical to evaluations of safety in the trial. The PI is responsible for informing the site study team of all relevant safety issues.

Site study team members have responsibility for safety reporting as defined in the protocol.

4. Documents needed for this SOP

- CTIMP Safety Report form and non-CTIMP safety report form for UK ethics committee.
- SAE Reporting Form template

- Pregnancy Notification Form template

5. Related documents

- SOP T7 Urgent Safety Measures
- SOP T10 Recording of study data
- SOP T14 Clinical Investigations of Medical Devices
- SOP P16 Data management and IDMC
- SOP P18 Randomisation and blinding
- SOP SWPTS QMP 002 Reporting incidents, errors and adverse events and reactions
- TRW.HGV.POL.936.5 Incident Management Policy

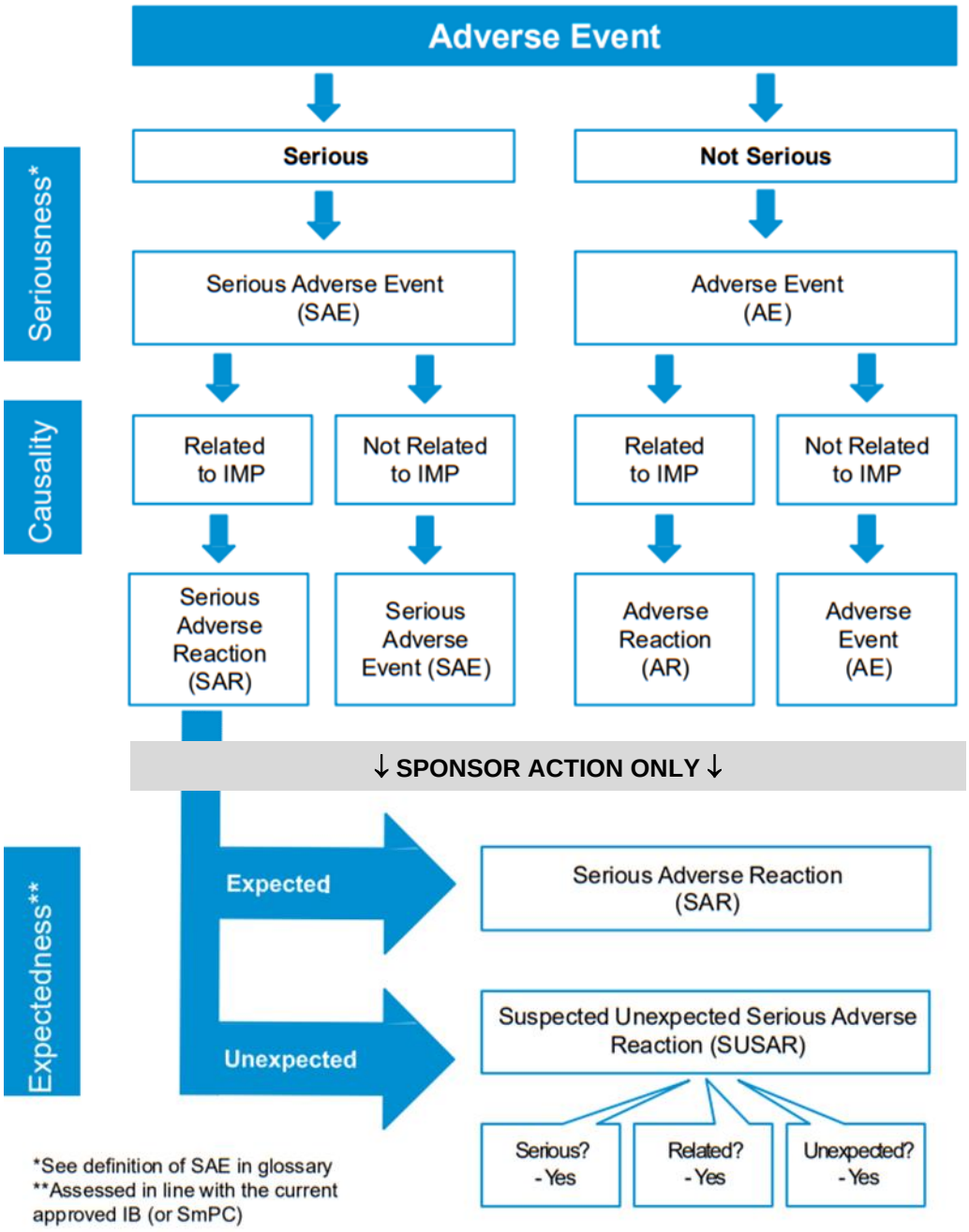
6. Acronyms

AE: Adverse Event
AR: Adverse Reaction
CA: Competent Authority
CAR T: Chimeric antigen receptor T cells
CI: Chief Investigator
CTIMP: Clinical Trials of an Investigational Medicinal Product
CTU: Clinical Trials Unit
DI: Designated Individual
EMA: European Medicines Agency
HRA: Health Research Authority
HTA: Human Tissue Authority
ICSR: Individual Case Study Report
IMP: Investigational Medicinal Products
ISF: Investigator Site File
MHRA: Medicines and Healthcare products Regulatory Agency
nIMP: Non-Investigational Medicinal Products*
PD: Person Designate
PI: Principal Investigator
SAE: Serious Adverse Event
SAER: Serious Adverse Event and Reaction
SAR: Serious Adverse Reaction
SOP: Standard Operating Procedure
Sub-I: Sub-Investigator
SUSAR: Suspected Unexpected Serious Adverse Reaction
SWPTS: South West Peninsula Transplant Service
TMF: Trial Master File
UHP: University Hospitals Plymouth

* Medicinal product used in the context of a clinical trial and not falling within the definition of an IMP

7. Process map(s)/ flow chart(s)

Safety reporting assessment flowchart:



8. Procedure

Step	Action	Responsibility
1	Use risk-adapted approach within protocol design to tailor safety reporting requirements to reflect the safety data already available and align the use of the Investigational Medicinal Products (IMP), Investigation Medical Device or intervention relative to normal clinical care. This approach applies to all clinical trials and interventional studies sponsored by the Trust.	Sponsor and CI.
2	Follow the specific requirements of the protocol for identifying and recording adverse events including where pregnancy occurs. Document clearly all participant or investigator reported adverse events in the health record (or source data file for volunteers, refer to SOP T10): **S**ymptoms — what, start date, how it happened i.e. if a fall, was it due to tripping or dizziness? **M**edication — new medications, drug name, dose, frequency, start and stop date? **A**ctivities — participant work/ general day-to-day activities affected, was the participant admitted to or attended hospital/ GP, admission and discharge date/ time, scan and tests completed including results if available? **R**esolve — when did the symptoms resolve or return back to participants baseline, are there any investigations outstanding? **T**ell — immediately inform PI or Sub-Investigator (Sub-I), Sponsor if assessed as serious or event of interest, report on DATIX (for definitions of patient safety incidents that require reporting on DATIX refer to the Trusts Incident Management Policy) Assessment recorded of each reported event for: • Seriousness according to the definitions in the protocol • Causality of event, this assessment cannot subsequently be downgraded by others • Severity of event i.e. mild, discomfort, severe **The above assessments must be made by a medically qualified doctor or dentist whichever is most appropriate.**	PI and clinical research team.

Step	Action	Responsibility
	Immediately report all Serious Adverse Events (SAEs) including device deficiencies or events of interest, verbally or *via* email to the Sponsor or delegate (within 24 hours) even where not all necessary information has been obtained. An initial detailed written report must follow using sponsors template (if not provided use SAE Reporting Form) Completion of the initial SAE report can be performed by a Research Nurse. However, additional, and further information should be submitted as a follow-up SAE report to the Sponsor or delegate containing documented evidence that assessment decisions were made by a medically qualified doctor. This can be demonstrated by the PI or Sub-I counter signing the SAE form and entries made in the health record or source data file. Check no participant-identifiable information is contained within the SAE report to the Sponsor or delegate unless the participant has specifically consented to this. Maintain a separate ongoing log for each participant. Follow-up all adverse events until resolution or the end of study, as defined by the protocol. An event maybe considered as 'resolved' if it clinically resolves, ceases to be 'serious' or stabilises.	
3	Report pregnancy for a study participant or partner of a participant to Sponsor or delegate using sponsors template (if not provide use Pregnancy Notification Form). Pregnancy does not meet the definition of a SAE, unless a congenital anomaly or defect. Follow up pregnancy until the end of the pregnancy (to collect pregnancy outcome) provided informed consent has been obtained.	PI and clinical research team.
4	Receipt, acknowledgement, and review of reported SAEs must be in place including the assessment of expectedness on using the Reference Safety Information (RSI) current at the time of the event. Assessment of causality on behalf of the Sponsor is carried out by the CI on all SAEs. Under no circumstances should the CI downgrade the study site PI or Sub-I opinion. Both opinions should be recorded. Track and follow-up SAEs that are on-going or missing key information with study site staff in a timely manner. Tracking systems can include a spreadsheet or calendar reminders/ alerts.	RGM, Deputy RGM or delegate.

<table>
<tr><th>Step</th><th>Action</th><th>Responsibility</th></tr>
<tr><td>5</td><td>Un-blind treatment codes (for double-blind trials) prior to expedited reporting to the Competent Authority (CA) and ethics committees.

Maintain blind for persons responsible for the ongoing conduct of the study, or for analysis and interpretation of results. Site PI/ Sub-I should only receive unblinded information if necessary for safety reasons. Refer to SOP P18.</td><td>RGM, Deputy RGM or delegate.</td></tr>
<tr><td>6</td><td>Expedited reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs), to the relevant Member State CA and ethics committee:

• within 7 days after the Sponsor or delegate first aware of a fatal or life-threatening event
  ○ additional relevant information must be reported within 8 calendar days of the initial report
• within 15 days after the Sponsor or delegate first aware of an event not fatal or life-threatening

N.B. in the case of ethics committees in the UK, only report in expedited fashion SUSARs occurring in UK.

Receipt of new, significant information on an already reported case, the clock starts again.

Follow same reporting arrangements for nIMPs when:

• possibility of a reaction between a nIMP and IMP or it might be linked
• might be linked to either nIMP or IMP, but cannot be attributed to only one of these
• reaction associated with the nIMP is likely to affect the safety of the participants (urgent safety measure, refer to SOP T7)

Submission of SUSARs to the Medicines and Healthcare products Regulatory Agency (MHRA) via the electronic (e)SUSAR or Individual Case Study Report (ICSR) online tool. The reporting system to be used is defined by where the trial is being carried out:

<table><tr><td>UK sites</td><td>MHRA eSUSAR system only.</td></tr><tr><td>International sites</td><td>ICSR - submission file must be uploaded to European Medicines Agency’s (EMA) EudraVigilance platform, available to all Member State CAs. Direct reporting to a Member State CA may still be necessary.</td></tr></table></td><td>RGM, Deputy RGM or delegate.</td></tr>
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Step	Action	Responsibility
	Inform study site PIs in a concise and practical way of any SUSARs that occur in relation to an IMP for all studies with the same Sponsor. SUSARs may be collated into line listing in periods warranted by the nature of the research, however PIs must be kept fully informed of all safety information in a timely manner.	
7	Report SAEs occurring in research other than CTIMPs within 15 days to the main ethics committee, where in the opinion of the CI the event is: • "related" - resulted from administration of any of the research procedures, and • "unexpected" - not listed in the protocol as an expected occurrence Use the SAE report form for non-CTIMPs published on the Health Research Authority (HRA) website. Activities relating to material for human application, for example CAR T cells, are also subject to safety reporting where considered 'Serious' (see Appendix 1 definition of SAEARs). Any serious adverse events must be reported within 24 hours to the Trusts Designated Individual (DI) or Person Designate (PD) for onward reporting to the Human Tissue Authority (HTA). For further details refer to SOP SWPTS QMP 002.	RGM, Deputy RGM or delegate
8	Review of SUSAR reports or line listing supplied by Sponsor or delegate, normally evidenced through signing and dating the paper report or a receipt (if provided by the Sponsor). Disseminate all relevant safety issues to the site study team and maintain safety reports in the Investigator Site File (ISF)	PI and clinical research team.
9	Retain all records of safety reports including any follow up information for Trust Sponsored studies in the Trial Master File (TMF) for Sponsor oversight purposes.	RGM, Deputy RGM or delegate

9. Changes from last revision

SOP template change and merge of QA7 Reporting of SUSARs in Clinical trials of Medicinal Products for UHPNT UK Sponsored Studies with T5.

Appendix 1: Definitions of terms used in safety reporting

Term	Definition
AE Adverse event	Any untoward medical occurrence whether or not related to a medicinal product or intervention.
AR Adverse reaction	Any untoward and unintended response related to a medicinal product or intervention.
SAE, SAR Serious adverse event, serious adverse reaction	Any serious event or reaction that: • results in death • is life-threatening* • requires hospitalisation/ prolongs a hospital stay • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect • is otherwise considered medically significant by the investigator (non-CTIMPS only) 'Important Medical Event' may also be considered serious if the jeopardise the participant or require an intervention to prevent one of the above consequences. * 'life-threating' in the definition of 'serious' refers to an event where the patient was at risk of death at the time of the event.
SAEAR Serious adverse event and reaction	SAE: Any untoward occurrence which may be associated with the procurement, testing, processing, storage or distribution of tissue or cells intended for human application and which, in relation to a donor of tissue or cells intended for human application or a recipient of tissue or cells: a) might lead to the transmission of a communicable disease, to death, or life-threatening, disabling or incapacitating conditions; or b) might result in, or prolong, hospitalisation or morbidity. SAR: An unintended response, including a communicable disease, in a donor of tissue or cells intended for human application or a recipient of tissue or cells, which may be associated with the procurement or human application of tissue or cells and which is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.
SUSAR Suspected unexpected serious adverse reaction	Any SAR which is not consistent with the information about the medicinal product set out in: • Summary of Product Characteristics (SmPC), only applicable for products with marketing authorisation • Investigator's Brochure (IB) • Trial specific RSI document
RSI Reference safety information	Information used for assessing whether an adverse reaction is expected. This is contained in either the IB, SmPC or trial specific RSI document.