Document Title: Adverse Event Reporting for Device Trials

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Summary of Amendments

Version Number	Modification:
V1.0	New SOP

Key related documents:	Trust Research Policy Trust Policy DN1 Document Control Procedures SOP012 (Adverse Event Reporting SOP071 Urgent Safety Measures

Key Points of this Document

1 Purpose and Contents

a. This document defines the medical device adverse event and medical device deficiency recording and reporting requirements for a clinical investigation plan (CIP) involving an unlicensed medical device or medical device already on the market that are being evaluated for new intended uses, new populations, new materials or following design changes. It covers research projects sponsored by Royal Papworth Hospital NHS Foundation Trust and those managed by Papworth Trials Unit Collaboration (PTUC) where sponsor responsibility for safety event reporting and recording has been delegated to PTUC.

b. The document details the requirements for medical device adverse event and medical device deficiency safety reporting to ensure compliance with the Medical Devices Regulations 2002 and the Medical Devices (Amendment) (Great Britian) Regulations 2023. Serious adverse event reporting under the Medical Device Directives 90/385/EEC and 93/42/EEC, ISO14155:2020 (Clinical Investigations of Medical Devices for Human Subjects-Good Clinical Practice) and the European Commission Guidelines on Medical Devices MEDDEV 2.7/3 (May 2015) as referenced by MHRA.

c. For non-Royal Papworth sponsored or non-PTUC managed studies the medical device adverse event and medical device deficiency reporting process directed by sponsor SOPs/Clinical Investigation Plan (CIP) must be followed.

2 Roles & Responsibilities

a. This SOP should be read in conjunction with PTUC SOP012 (Adverse Event Reporting).

b. All staff managing medical device research projects sponsored by Royal Papworth Hospital NHS Foundation Trust or managed by Papworth Trials Unit Collaboration (PTUC) must comply with the requirements set out in section 4.

3 Policy

a. This SOP is mandatory and, as per the Trust's Information Governance and Records Management framework, non-compliance may result in disciplinary procedures.

Medical Device Terms

Term	Definition
Malfunction	ISO14155: Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or the clinical investigational plan.
Medical device	MHRA definition of medical device, reference: Clinical investigations of medical devices – guidance for manufacturers April 2024: A 'medical device' means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: — diagnosis, prevention, monitoring, treatment or alleviation of disease, — diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap, — investigation, replacement or modification of the anatomy or of a physiological process, — control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

Event Definitions

Acronym:	**Full term:**	**Definition:**
AE	Adverse event	ISO14155 and MEDDEV2.7/3: Any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

		NOTE 1 This definition includes events related to the investigational medical device or the comparator. NOTE 2 This definition includes events related to the procedures involved. NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.
ADE	Adverse device effect	ISO14155 and MEDDEV2.7/3: adverse event related to the use of an investigational medical device NOTE 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
DD	Device deficiency	ISO14155 and MEDDEV2.7/3: inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer.
IB	Investigator's Brochure	ISO14155: compilation of the current clinical and non-clinical information on the investigational medical device(s) relevant to the clinical investigation.
SAE	Serious adverse event	ISO14155 and MEDDEV2.7/3: Any adverse event that a. Led to death, b. Led to serious deterioration of the subject, that either resulted in

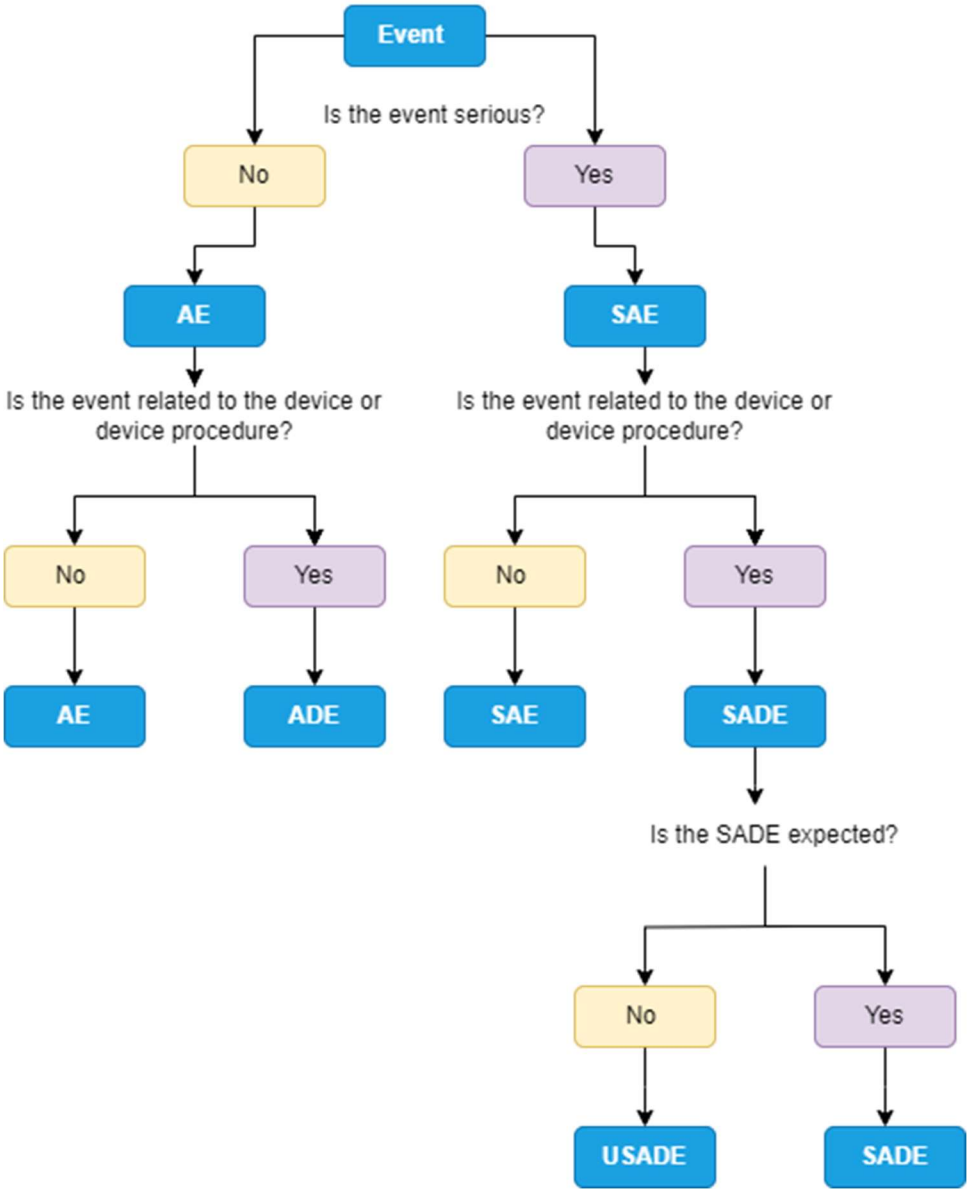
		1) A life-threatening illness or injury, or 2) A permanent impairment of a body structure or a body function, or 3) In-patient or prolonged hospitalisation, or 4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c. Led to foetal distress, foetal death or congenital abnormality or birth defect NOTE Planned hospitalisation for a pre-existing condition or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
SADE	Serious adverse device effect	ISO14155 and MEDDEV2.7/3: Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
USADE	Unanticipated serious adverse device effect	ISO14155: serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the Clinical Investigation Plan, Clinical Investigation Brochure, Risk Analysis Report or another appropriate document as anticipated.

Assessment Definitions

Assessment type:	Person responsible for undertaking assessment:	Explanation of assessment:
Seriousness	Member of the research team	An event is defined as being serious if it results in any of the following: • Death • Is life threatening • Results in hospitalisation • Hospitalisation is prolonged • Results in disability or incapacity • Consist of a congenital anomaly or birth defect • Is considered an important medical event by the investigator
Causality	PI or other delegated medically qualified member of staff	MEDDEV2.7/3: Assessment of the relationship between the use of the medical device (including the medical surgical procedure and the comparators) and the occurrence of each adverse event are categorised as: • Definitely related (would become a serious adverse device effect) • Probably related (would become a serious adverse device effect) • Possibly related (would become a serious adverse device effect) • Unlikely to be related (would remain a serious adverse event) • Not related (would remain a serious adverse event) If the event is deemed to be ***in any way related, i.e. by a selection of definitely, probably or possibly related,*** to the MEDICAL DEVICE OR PROCEDURE the categorisation of the SAE becomes a SADE. The Sponsor cannot downgrade an Investigator's causality assessment, if the sponsor disagrees that the event is related to the medical device or associated procedure, clarification will be sought from the Investigator. If the sponsor still disagrees, both opinions must be

		provided with the report. However, the sponsor may upgrade a PI's causality assessment.
Expectedness	Sponsor	Assessment of whether or not the observed SADE is anticipated or unanticipated. The event is deemed to be unanticipated if there is no mention of the event at the observed severity in the approved safety documentation. If the SADE is assessed as unanticipated it is then referred to as an Unanticipated SADE (USADE).

Decision making flow diagram



Key

AE Adverse Event
ADE Adverse Device Effect
SAE Serious Adverse Event
SADE Serious Adverse Device Effect
USADE Unanticipated Serious Adverse Device Effect

4 Procedure

4.1 Adverse Event Recording and Reporting

a. The recording and reporting of AEs must be clearly defined in the clinical investigation plan (CIP) and timelines dictated within this must be adhered to.

b. All AEs will be recorded within the trial database.

c. All AEs must also be recorded within the patient's electronic health record, for full details on how to complete this for Royal Papworth Hospital patients refer to the Trust intranet.

d. The investigator must assess all AEs for seriousness and causality.

e. The investigator is required to report any ADEs that are identified in the CIP as critical to the safety of the trial to the sponsor as soon as practical.

f. The sponsor or delegated representative is required to keep a detailed record of all AEs reported by the investigator.

g. It will be the responsibility of the sponsor or delegated representative to assess if an increase of ADEs merit an urgent safety measure or requires expediated reporting to the MHRA. Refer to MHRA website for more information https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device

4.2 Device Deficiency Recording and Reporting

a. The scope of DD recording must be clearly defined within the CIP.

b. As a minimum any DD which might lead to/have led to the death of a patient or user or to a serious deterioration in their state of health, if circumstances had been less favourable or measures hadn't been taken to prevent it, must be recorded and reported.

c. Refer to the definition of seriousness on Page 6 for what constitutes a serious deterioration in health of a patient or user.

d. All DD will be recorded within the trial database. The database must have the capability to record safety events that occur in device users (including the study team) and patients.

e. DD should be reported in the same manner as SAEs. Refer to Section 4.3.2.

4.3 Serious Adverse Events

4.3.1 Recording

a. The process for recording and reporting SAEs must be documented in the CIP.

b. All serious adverse events should as a minimum be recorded from the point when procedures for the medical device under investigation have started, following receiving participant consent.

c. For non-CE/UKCA marked devices, and those devices with CE/UKCA marking but that are being used outside of their intended purpose, all SAE/SADE/USADEs will be recorded within the trial database.

d. All SAEs must also be recorded within the patient's electronic health record. Refer to the intranet for guidance on how to do this for Royal Papworth Hospital patients.

e. Recording should include as a minimum the following parameters:

1. Patient ID code
2. Unique SAE ID code
3. Event Term (Using MedDRA Preferred Term)
4. Full description of the event
5. Date of the medical device procedure/or first use of device
6. Event duration (start and end dates)
7. Action taken/treatment given
8. Causality (i.e. relatedness to the medical device and the relatedness to the device investigational procedure*) in the opinion of the Investigator.
9. Expectedness – whether the event would be considered anticipated, as listed in the CIP, IB, risk analysis report or other appropriate documentation) at the same level of severity).
10. Event status (resolved/resolved with sequelae/ongoing/death.

*complications of procedures are considered not related if the procedure would have been applied to the patient in the absence of investigational device/application.

f. Only a medically qualified person involved in the clinical investigation at the trial site can complete the causality assessment.

g. The expectedness assessment should be completed by a medically qualified sponsor representative such as the Director of R&D for RPH Sponsored studies or the Director of PTUC for studies managed by PTUC with delegated responsibility for safety recording and reporting from an external sponsor.

4.3.2 Reporting

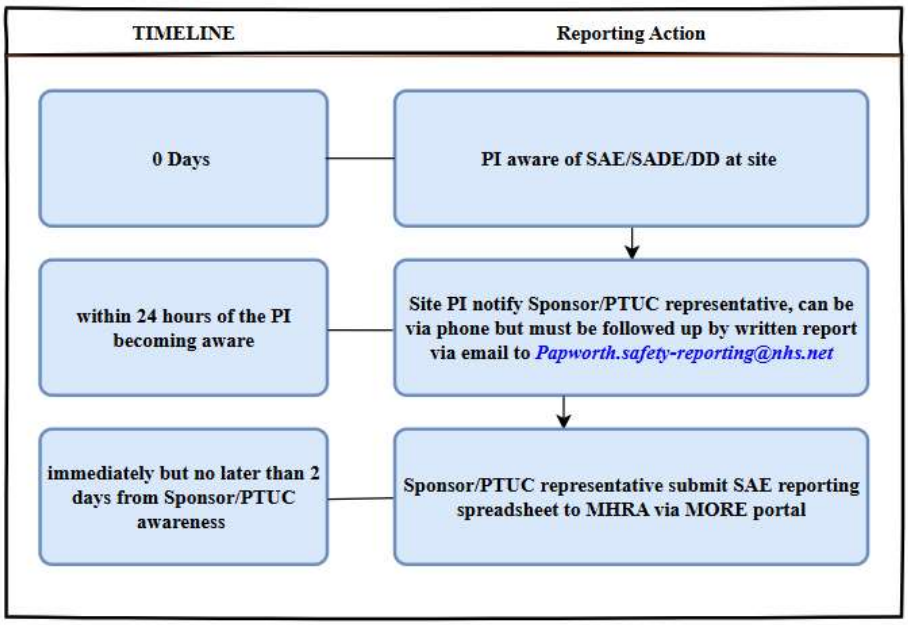
a. For all non-CE/UKCA marked devices (and CE/UKCA marked devices used outside of their intended purpose) all SAE/SADEs require expediated reporting to the MHRA.

b. Expediated reporting to MHRA is completed by entering the safety event details into an SAE reporting spreadsheet (refer to MHRA website for approved template: https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device) which is then submitted to the MHRA via an online submission portal called the MORE portal. For further details see Section 4.7.

c. **Fatal or Life-threatening SAE/SADE/DD**. In the case of a fatal or life-threatening SAE/SADE/DD where there is imminent risk of death, serious injury or serious illness and action needs to be taken to protect other patients, the Sponsor/PTUC representative should be notified immediately (within 24 hours of the investigator becoming aware of the event). Initial communication can be via telephone but should be followed up by written notification sent to the Royal Papworth Hospital (RPH) Sponsor safety reporting mailbox; Papworth.safety-reporting@nhs.net.

d. The Sponsor/PTUC delegated representative should notify the MHRA immediately, but not later than 2 calendar days following the date the sponsor/PTUC is made aware of the new reportable event or new information in relation to an already reported event. See diagram below:

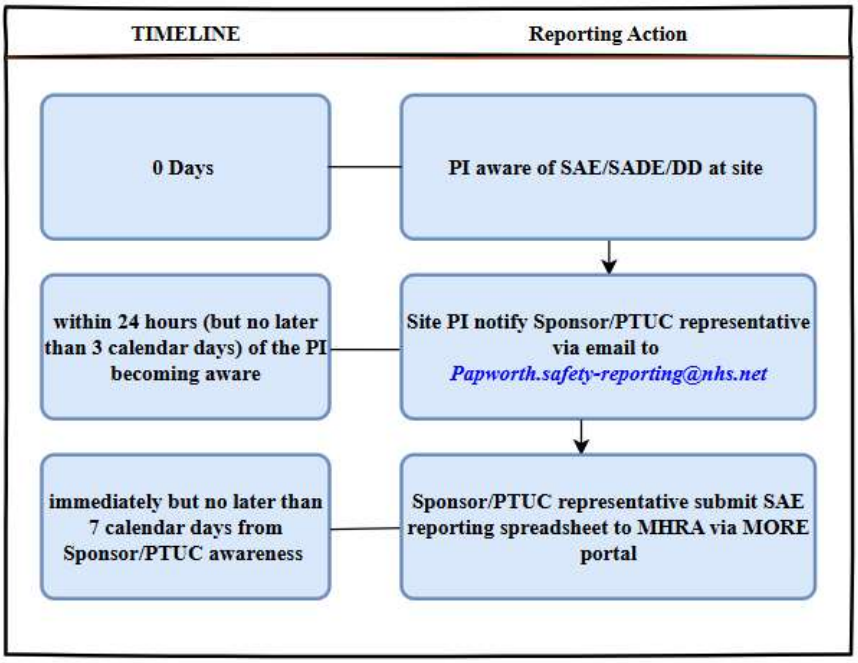
Diagram of reporting timeline for Fatal or life-threatening SAE/SADE/DD



e. **Non-fatal or non-life-threatening SAE/SADE**. In the event of a non-fatal or non-life-threatening SAE/SADE/DD the site PI should immediately notify the RPH Sponsor safety reporting mailbox; Papworth.safety-reporting@nhs.net (within 24 hours, but no later than 3 calendar days after the investigational site teams awareness of the event).

f. The Sponsor/PTUC delegated representative should notify the MHRA immediately, but not later than 7 calendar days after awareness. See diagram below:

Diagram of reporting timeline for non-fatal or non-life-threatening SAE/SADE/DD



g. The device manufacturer should be informed within 24 hours of Sponsor/PTUC representative awareness of a SAE/SADE/USADE or device deficiency or as agreed in the study's communication agreement.

h. There is no requirement to inform the REC of the occurrence of a SAE/SADE or DD.

4.4 Unanticipated Serious Adverse Device Effect Reporting

a. Unanticipated events are those that are not listed as expected (anticipated) events for the medical device under investigation.

b. The Sponsor/PTUC representative should be notified immediately (within 24hours of the investigator becoming aware of the event) of the occurrence or suspected occurrence of a USADE.

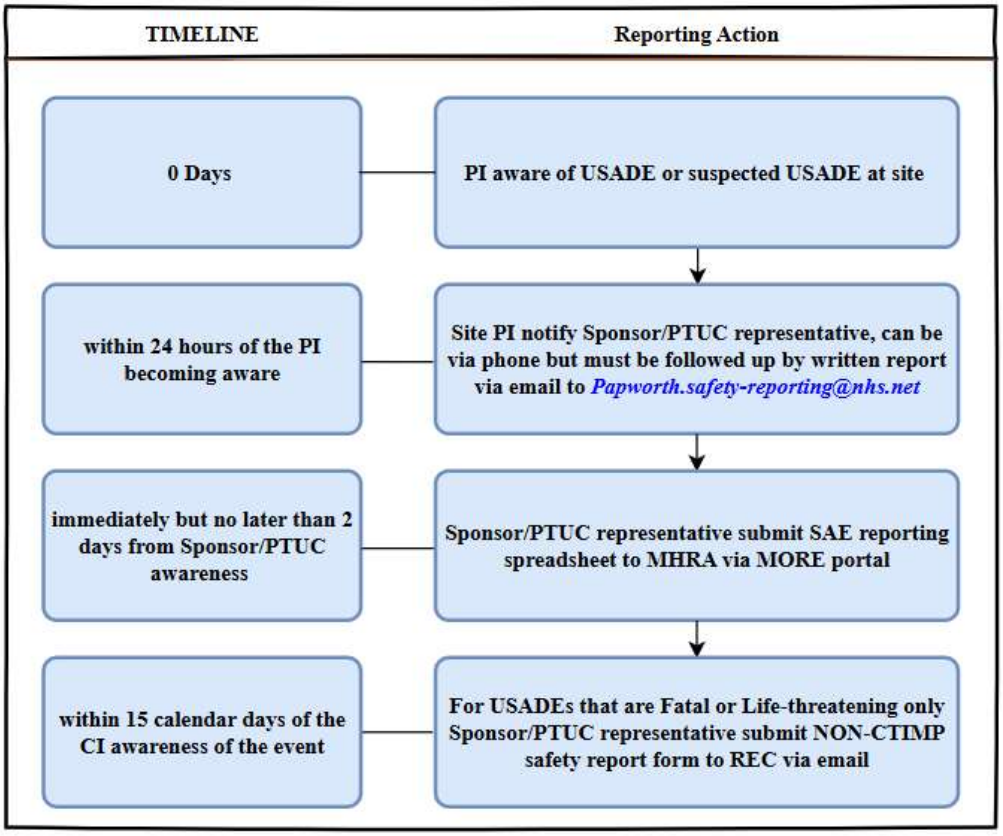
c. Initial communication can be via telephone but should be followed up by written notification sent to the RPH Sponsor safety reporting mailbox; Papworth.safety-reporting@nhs.net.

d. All USADEs must be reported to the MHRA immediately but no later than 2 calendar days following the date the sponsor/PTUC is made aware of the new reportable event or of new information in relation to an already reported event.

e. Reporting of USADE to the MHRA is completed using the same SAE reporting table used for reporting SAE/SADE, via the MORE portal.

f. **For USADEs that are fatal or life threatening** the Non-CTIMP safety report form (available from the HRA website) should be emailed to the REC who originally approved the clinical investigation plan, within 15 calendar days following the chief investigators awareness of the event.

Diagram of timeline for USADE reporting



g. The sponsor should also ensure that all investigators responsible for the conduct of the clinical investigation are informed of the occurrence of a USADE. This should be done in a timely manner to ensure that investigators are kept fully informed of all safety information.

h. Clinical Investigations of medical devices are typically open-labelled studies, although in some cases the active device may be implantable and associated with variable periods of activity across patient cohorts. Unblinding might have to be considered in the event of a USADE, although this should be avoided where possible, however patient safety must take priority.

4.5 Urgent Safety Measures

a. The CI and PI have the authority to deviate from the CIP if doing so relates to the immediate safety of a participant, where continuing to follow the CIP would put that participant at risk.

b. This is classed as an urgent safety measure. For further details on reporting please refer to PTUC SOP071 Urgent Safety Measures.

4.6 Quarterly and Annual Safety Reports

a. A requirement of the MHRA is that both quarterly and annual cumulative summary reports of SAE events are submitted for the trial via the MORE portal using the templates provided on the MHRA website.

b. Refer to original non objection letter to see if further reporting requirements are stipulated.

c. It is worth noting that the MHRA has the right to withdraw a written notice of no objection if, in its opinion, the serious adverse events reported give rise to issues of public health (UK MDR 2022: Regulation 16(6) and Regulation 29(5).

4.7 MORE Portal Access

a. All SAEs/SADEs/USADEs/DDs and safety reports are submitted to the MHRA using the MORE portal.

b. Each submission of the SAE report template should be saved as a PDF file (with the submission date in the file name) and saved in the electronic folders and a copy printed for the Sponsor TMF.

c. Access to the platform is managed by R&D for RPH Sponsored studies so please contact a member of the R&D QA team (papworth.randdqa@nhs.net) for advice on registering for an account.

d. For studies where PTUC are taking responsibility for reporting to MHRA individuals can create a 'submitter' account by registering directly on the MORE portal by going to the following website more.mhra.gov.uk/login and selecting 'create an account'.

e. For options given for *Account type* and *Select Other User Group*, responses of 'other' and 'other-submitter' should be checked retrospectively. Once all the personal details and password are completed select the 'create user' tab. You should now be able to submit files to the MHRA via the Report Submission function.

f. Once a report has been submitted you are able to access the Report Management function to see successful delivery of reports. From here you can select individual report summaries to be downloaded as a PDF files for saving and printing in the TMF (alongside the submitted SAE report).

5 Risk Management / Liability / Monitoring & Audit

a. The R&D SOP Committee will ensure that this SOP and any future changes to this document are adequately disseminated.

b. The R&D Department will monitor adherence to this SOP via the routine audit and monitoring of individual clinical trials and the Trust's auditors will monitor this SOP as part of their audit of Research Governance. From time to time, the SOP may also be inspected by external regulatory agencies (e.g. Care Quality Commission, Medicines and Healthcare Regulatory Agency).

c. In exceptional circumstances it might be necessary to deviate from this SOP for which written approval of the Senior R&D Manager should be gained before any action is taken. SOP deviations should be recorded including details of alternative procedures followed and filed in the Investigator and Sponsor Master File.

d. The Research and Development Directorate is responsible for the ratification of this procedure.

Further Document Information

Approved by: *Management/Clinical Directorate Group*	Research and Development Directorate
Approval date: *(this version)*	Current approved version date
Ratified by Board of Directors/ Committee of the Board of Directors:	STET
Date:	N/A
This document supports: *Standards and legislation*	Medicines for Human Use (Clinical Trials) Regulations 2004 and all associated amendments. UK Policy Framework for Health and Social Care Research (2023)

Equality Impact Assessment: Does this document impact on any of the following groups? If YES, state positive or negative, complete Equality Impact Assessment Form available in Disability Equality Scheme document DN192 and attach.

Groups	Disability	Race	Gender	Age	Sexual orientation	Religious & belief	Other
Yes/No	NO	NO	NO	NO	NO	NO	NO
Positive/Negative							

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