Portsmouth Hospitals University NHS Trust

Standard Operating Procedure (SOP) for Reporting Urgent Safety Measures in Clinical Research

For Completion by SOP Author	
Reference Number	PHU/RDSOP/006
Version	V3.0, 7th August 2023
Document Author(s)	Joe Shoebridge, R&D Manager Toni Baker, Research Facilitator
Document Reviewer(s)	Ian Gedge, Research Facilitator Sharon McCready, Trust Lead Research Nurse

For Completion by Research Dept., SOP Controller	
Name of Responsible Committee	Research Development Meeting
Issue Date	14th August 2023
Implementation Date	14th September 2023
Review date	14th September 2026
Electronic location	Research and Development - Research Office\Policies and SOPS\# Active SOPS

UNCONTROLLED DOCUMENT

The definitive versions of all Portsmouth Hospitals Trust SOPs, Templates and Forms for Research are online at http://www.porthosp.nhs.uk/research-department

If you are reading this SOP in printed form then you are reading an uncontrolled document. You must therefore verify that the version number and date given below are the most recent, by cross-checking with the Trust research website before proceeding with implementation.

Portsmouth Hospitals University NHS Trust is committed to ensuring that, as far as is reasonably practicable, the way we provide services to the public and the way we treat our staff reflects their individual needs and does not discriminate against individuals or groups on any grounds. This SOP has been assessed accordingly

CONTENTS

UNCONTROLLED DOCUMENT

1. INTRODUCTION

Regulation 30 of the Medicines for Human Use (Clinical Trials) Regulations 2004: SI 2004/1031 specifies that the Sponsor or Investigator may take appropriate urgent safety measures (USM) in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety.

This measure can be taken prior to seeking approval from competent authorities and ethics committees. However, for all studies, any USMs implemented must be reported to the Sponsor as soon as practicable. The Sponsor will then make immediate contact with the relevant regulatory authorities. In the UK this will be the Medicines and Healthcare products Regulatory Agency (MHRA) (where applicable, i.e. CTIMPs and MHRA notifiable trials) and the Research Ethics Committee (REC).

It is Trust policy that this process is followed for all research studies either sponsored by or hosted at Portsmouth Hospitals University NHS Trust (PHU). This Standard Operating Procedure (SOP) provides for how this shall be reported and by whom.

2. PURPOSE

The purpose of this document is to describe the SOP for implementing and reporting urgent safety measures for all research studies sponsored and hosted by PHU.

3. SCOPE

This SOP applies to all research studies Sponsored and/or hosted by PHU. This includes at other sites for which PHU is responsible.

USMs need only be reported to the MHRA if it is a Clinical Trial of an Investigational Medicinal Product (CTIMP) or a regulated trial of a medical device.

3.1. Who should use this SOP?

- All individuals involved in research studies taking place within PHU.
- All individuals involved in research studies taking place at another site, where PHU is the Sponsor.

3.2. When this SOP should be used

The process outlined in this SOP should be followed when an immediate hazard to the health or safety of a research participant(s) is identified and urgent changes in study conduct are either taken, or need to be implemented, before approval from the MHRA or the REC can be sought.

Such immediate hazards may occur as a result of the following examples:

- A Serious Breach in protocol, procedures or Good Clinical Practice (GCP).
- A series of adverse reactions or a single case of an unexpected serious adverse reaction or an increase in the intensity or frequency of expected events and reactions.
- Study devices producing erroneous measures.
- An expected Serious Adverse Reaction (SAR) with an unexpected outcome (e.g. death).
- Serious omissions in the approved protocol.

Urgent safety measures might include, for example:

- A temporary halt to the study at one site or study-wide.

UNCONTROLLED DOCUMENT

- An urgent change to study procedures.
- The addition of new 'unapproved' study procedures.

The Trust recognises that some external sponsors, networks, funders and employers may require the use of their own SOPs for the good governance of research. In such cases it is the responsibility of the Portsmouth Hospitals University NHS Trust user (including those individuals contracted to work on behalf of the Trust), to ensure that the external SOP does not conflict the SOP outlined below. If the external SOP contradicts the Trust's procedure then approval must be sought in writing from the Research and Development Manager.

In the event of an infection outbreak, flu pandemic or major incident, the Trust recognises that it may not be possible to adhere to all aspects of this document. In such circumstances, staff should take advice from their manager and all possible action must be taken to maintain ongoing patient and staff safety.

4. ABBREVIATIONS & DEFINITIONS

Abbreviation	Meaning
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
IRAS	Integrated Research Application System
MHRA	Medicines and Healthcare products Regulatory Agency
PHU	Portsmouth Hospitals University NHS Trust
PI	Principal Investigator
REC	Research Ethics Committee
SOP	Standard Operating Procedure
TMF	Trial Master File
USM	Urgent Safety Measure

Term	Definition
PHU Hosted Studies	Refers to an externally sponsored study for which PHU are acting as a recruiting site.
PHU Sponsored Studies	Studies which PHU have ultimate responsibility for the initiation, management of and financing for. PHU take primary responsibility for ensuring that the design of the study meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting.
Study Team	The people involved in the conduct of a research project. There may be different research teams for the project at different sites.
Urgent Safety Measure (USM)	An urgent safety measure taken by the sponsor or investigator in order to protect the subjects of clinical research against any immediate hazard to their health or safety.

UNCONTROLLED DOCUMENT

5. DUTIES AND RESPONSIBILITIES

Role	Responsibilities
All Studies (Hosted and Sponsored) Research team member	• To report to the Chief Investigator, the Research Office of the host Trust and Sponsor any hazards or USMs taken to protect the health and/or safety of study participants. Reporting procedures to be followed for hosted, externally sponsored studies should be those outlined in the study protocol. • To immediately implement any USMs as instructed in writing by the Sponsors or designated person to protect the health and safety of their study participants.
Where PHU is the Sponsor Chief Investigator	• To implement immediate changes to site level or study-wide procedures for the urgent protection of study participants. • To report all implemented USM to the Research Office, MHRA, REC, other research sites and team members within the required time frames. • To train Principal Investigators at all sites and any other study team members in this SOP, as applicable. This may be delegated to the local Principal Investigator or another appropriate individual.
Research Office staff on behalf of PHU as Sponsor	• To assist the Chief Investigator with reporting of the USM. • To review the USM and its implications. • To oversee the assessment and reporting process.
Research Governance & Risk Group (PHU)/ Sponsored Oversight Group (PHU)	• To review and assess the implications of all reported USMs, which have been implemented at PHU or during a PHU Sponsored study. ▪ The Sponsored Oversight Group meets monthly and will review USM on PHU Sponsored Studies as and when they occur. ▪ Records of these will be kept to be reviewed at the Research Governance and Risk Group when that meets on a quarterly basis.

6. PROCESS

6.1. PHU Hosted studies

The process for PHU Hosted studies is illustrated in section 10.1.

Upon identifying a hazard to research participants, requiring immediate action to protect their health or safety, the team member should consider putting a USM in place to protect the participants. **Wherever possible** they should first consult the protocol (for any explicit USM instructions), the CI and the Sponsor of the study. However, participant safety must come first, and immediate action taken to protect this.

Upon implementing a USM the study team must report the measure(s) to the Sponsor by following the instructions set out in the study protocol. Where there are no instructions, the investigator should document all decisions and notify the CI and Sponsor's Research office using the PHU template: Urgent Safety Measures (USM) Assessment, Record and Reporting Form.

All urgent safety measures implemented at PHU should be notified to and recorded by the Research Office.

6.2. PHU Sponsored studies

UNCONTROLLED DOCUMENT

The process for PHU Sponsored studies is illustrated in section 10.2

6.2.1. Procedure

USMs can be implemented immediately. Notification and/or approvals are not required prior to their implementation but must be actioned immediately afterwards.

Upon identifying a hazard to research participants, requiring immediate action to protect their health and safety, constituting a change in study conduct and a USM, the **research team member** should:

- Report the hazard and measures taken immediately to the Chief Investigator. Where the Chief Investigator is not available it must be reported to another delegated person or appropriate deputy. If no one on the delegation log is immediately available, please contact the Research Office or Senior Research Nurse team for advice if required.

- Document the hazard and any actions taken on the Urgent Safety Measures (USM) Assessment, Record and Reporting Form.

Upon notice of an implemented USM or a hazard that requires Urgent Safety Measures the **Chief Investigator** or delegated person should:

Immediately

- Telephone the MHRA's Clinical Trials Unit to discuss the issue with an MHRA safety scientist **(CTIMPs/MHRA notifiable studies only)**. Contact details are provided in the table below. In practice this will ideally be done in parallel to identifying the necessary corrective and preventative measures required and discussions with the safety scientist may inform these actions. If the call is not made at the time of intervention, the call should be ideally made within 24 hours of measures being taken- but no later than 3 days from the date that the measures are taken.
  When calling the MHRA the reporter will be expected to relay:

  1. The IRAS ID and/or the EudraCT number of; a. The trials for which USM action has been taken, b. Other ongoing trials with the same Investigational Medicinal Product(s) (IMP(s)) c. Trials run by a different Sponsor affected by the USM action.
  2. The affected IMP(s) - commercial or developmental names.
  3. Nature of the safety concern and whether it has been reported as a SUSAR.
  4. Which USMs have been taken and when.
  5. The number of UK subjects who are currently receiving the IMP, the number of subjects who received it and the number affected by the USM.
  6. Contact details in case of further questions.

  (Where any of this information is not available at the time of the call, this should be provided as soon as possible after).

  7. Telephone the Research Office to notify the Sponsor of all decisions/actions taken/planned.
  8. Document all decisions taken and their assessment of the impact, on the USM Assessment, Record and Reporting Form

Within 24 hours of Telephone (initial) Notification

- Email the USM Assessment, Record & Reporting Form to the Research Office.

.

As soon as possible but in all cases within 3 days

- Notify the REC by telephone (all studies). For studies not submitted via combined review (i.e. non-MHRA notifiable studies) the notification should set out what measures have been taken and why. This information should be relayed to the REC

UNCONTROLLED DOCUMENT

who provided the initial approval for the study using the REC safety reporting cover sheet, which is available on the HRA website- Safety reporting – Health Research Authority (hra.nhs.uk)

For studies that were submitted via combined review (MHRA notifiable studies) the USM notification should be submitted via IRAS. Information on how to do so is available on IRAS- IRAS User Guide - Reporting during research (myresearchproject.org.uk).

- Notify the MHRA in writing (CTIMPS/MHRA notifiable studies only).This notification should be made via IRAS as above.
- Notify any other sites and all local study team personnel (including support departments).

As soon as possible but non-urgent

- Inform study funder if external funding has been sourced.

NOTE: Timelines exist except where a disease is (a) pandemic and (b) a serious risk or potentially serious risk to human health). In the event of a pandemic the timeline is amended to *'as soon as possible'.*

6.2.2. Substantial Amendments

Following written notification to the appropriate regulatory bodies a substantial amendment is also required. The substantial amendment covering the changes made as part of the USM is anticipated within approximately **2 weeks** of notification to the MHRA/REC.

The USM related substantial amendment must only include changes required as part of the urgent safety measure- no other study amendments are permitted to be made at the same time (unrelated changes may result in rejection of the substantial amendment).

If the trial predated the combined review process, then the substantial amendment should be submitted using the MHRA Submissions via the Human Medicines Tile (selecting 'Clinical Trial' as the Regulatory Activity and 'CT – Amendment' from the Regulatory sub activity dropdown list).

For MHRA notifiable studies which were submitted via the combined review process, or for non-MHRA notifiable studies, the substantial amendment should be made via IRAS- IRAS Help - Maintaining your approvals - Amendments (myresearchproject.org.uk).

Records of all correspondence to the MHRA and REC should be both filed in the TMF and sent to the Research Office. The Research Office can provide support during the preparation of the substantial amendment and submit on behalf of the CI and Sponsor for PHU sponsored studies.

Contact details:

Chief Investigator	Contact details should be present within the site file
Research Office	Telephone: 02392 286236 Email: research.office@porthosp.nhs.uk Please write in the subject box 'Notice of Urgent Safety Measure' and set as 'High Importance'
MHRA	Telephone: 0203 080 6456 Email: clintrialhelpline@mhra.gov.uk

UNCONTROLLED DOCUMENT

REC	This should be to the main REC that approved your study and will differ from study to study. If you are unsure, please contact the Research Office or refer to the REC approval letter in the TMF.

6.3. Notifying Study Participants

The study participants must be informed of the USM and given the opportunity to continue in the study with the modified procedures or withdraw from the study. Study participants may be contacted initially by phone and then informed in writing of the rationale for the USM and the steps taken or new procedures required to minimise the risk. In the case where the study participant has since deceased, no further action is required.

All correspondence must be documented in the participant's medical records, USM form and the case report form (where applicable).

Participants who are willing to continue in the study must be re-consented. A full record of all communication with participants must be maintained.

6.4. Temporary halt of a trial

If the CI and Sponsor decide that the hazard necessitates a temporary halt to the study, the CI must notify the Research Office, REC and MHRA within 15 days of the halt. A substantial amendment must be submitted, and this may be included on the same substantial amendment form as the notification of the urgent safety measure if appropriate. Notice of a temporary halt should make clear what specifically has been halted, (i.e. recruitment, or an interruption of the treatment of patients currently on the study) and the reasons for all decisions made.

6.5. Re-starting the trial

The CI and Sponsor may decide to re-start the study if it has been shown safe to do so. This should be done by submitting a substantial amendment to the Research Office, REC and MHRA (where applicable), including supporting evidence that it is now safe to resume the study. All approvals and permissions should be secured prior to re-starting.

6.6. Study termination

If the CI and Sponsor decide not to re-start the temporarily halted study, the CI should submit an End of Trial declaration form and submit this to the REC and MHRA (where applicable) providing the reason why. This should be done within 15 days of the date of termination.

6.6 Research Office Procedure

On receiving a telephone notice of an urgent safety measure

Research Office staff should:

- Instruct the caller to notify the CI (where not the CI) and provide them with an Urgent Safety Measures Assessment, Record & Reporting Form.
- Select the Urgent Safety Measures Tracker Sheet in the Templates folder on the shared 'G' drive and record details of the telephone call.

UNCONTROLLED DOCUMENT

- Immediately notify the Director of Research, Deputy Director of Research or the Research & Development Manager. Should both be unavailable an appropriate senior member of staff should be notified (for example the Trust Lead Research Nurse, Head of Research Operations or a Research Facilitator).

- Follow the tracker sheet and record all actions.

- Save the tracker, and any associated correspondence, in the study folder on the G-drive.

- Acknowledge receipt of USM notifications.

The Research and Development Manager will contact the CI to discuss actions taken and check their compliance with the procedures outlined in section 6.2, recording all actions on the tracker sheet

Where there is uncertainty with regards to any USMs required, an Independent Medical Assessor will be contacted immediately. This person will usually be determined by the Research Director, CI, Medical Director, Chair of the study Data Safety Monitoring Committee or in rare cases the PI.

7. TRAINING REQUIREMENTS

All research staff should be trained in this procedure. Evidence of training shall be required for PHU sponsored CTIMP/MHRA notifiable studies and Research Office staff.

"The Research Dept., will endeavour to notify staff of SOP developments that may be relevant to them. SOPs are available on the Research department website. Updates on SOPs will feature in Research newsletters and communications and disseminate at local research meetings. It is the responsibility of all research active staff to ensure that they read the issued updates that may be relevant to them.

When a new SOP is authorised, or when an existing SOP is revised, self directed training must be carried out by all staff to which the SOP is relevant and this training documented in their training record. A template is provided to support this process. A study specific SOP training plan will be developed for investigators on high risk PHU Sponsored studies.

Staff should take time to read and fully understand the SOP and relevant documents, ensuring that they are able to implement the SOP when required. If clarification is needed then the trainee should approach their line manager and the SOP Controller who will arrange additional training. All staff should complete their training prior to the published implementation date which will normally be between 2-6 weeks after publication.

All staff are responsible for maintaining their own SOP Training Records and copies must be made available to line managers, the SOP Controller or study monitors on request."

8. REFERENCES AND ASSOCIATED DOCUMENTATION

Associated Documents:

- Template - Urgent Safety Measures Assessment, Record & Reporting Form.

Reference:

- Medicines for Human Use (Clinical Trials) Regulations 2004: SI 2004/1031
- MHRA guidance: https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#urgent-safety-measures
- Register to make submissions to the MHRA - GOV.UK (www.gov.uk)
- Urgent Safety Measures (ct-toolkit.ac.uk)

UNCONTROLLED DOCUMENT

- Safety reporting - Health Research Authority (hra.nhs.uk)
- IRAS User Guide - Reporting during research (myresearchproject.org.uk)
- IRAS Help - Maintaining your approvals - Amendments (myresearchproject.org.uk)

9. VERSION HISTORY LOG

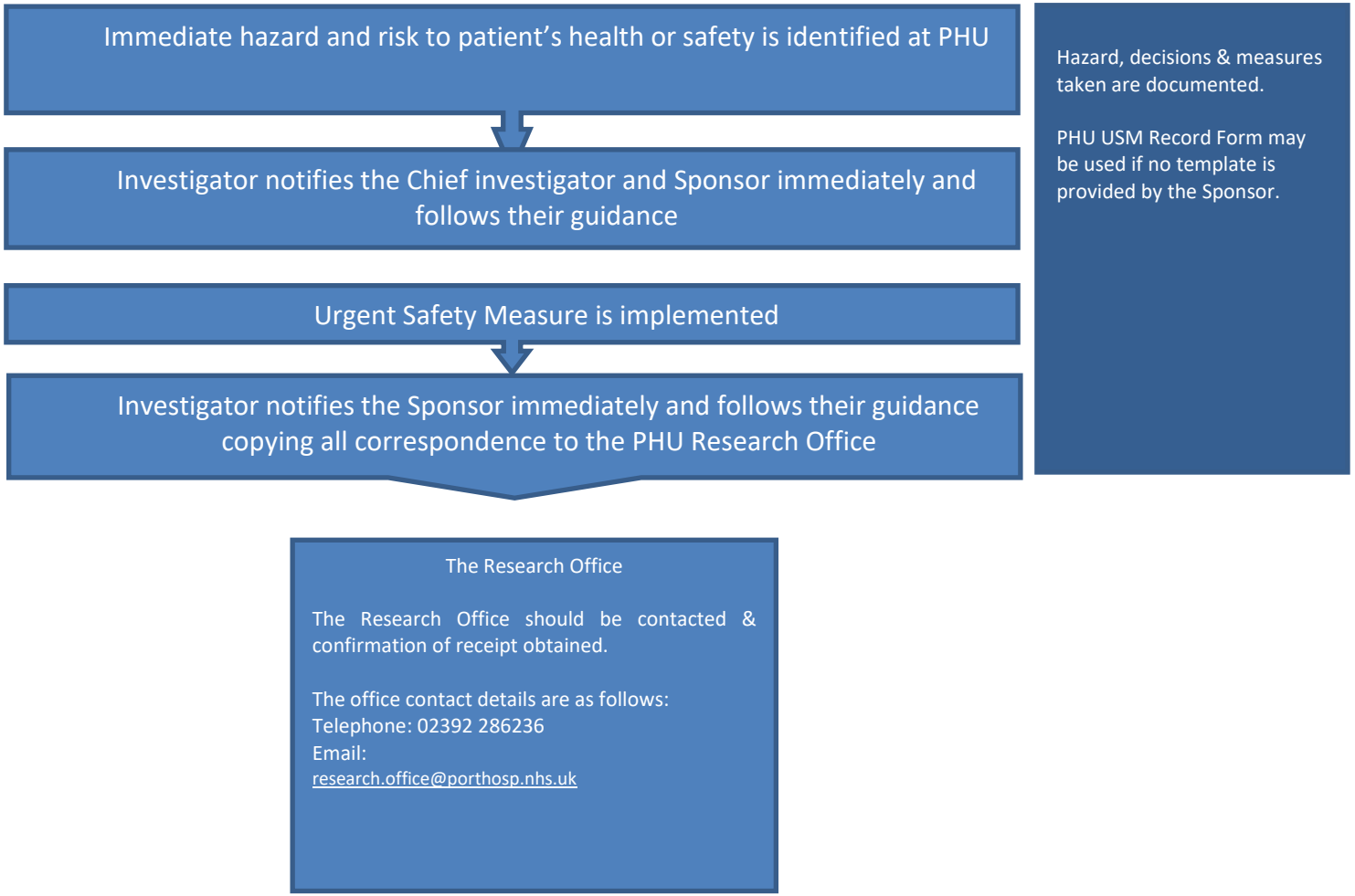
This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of Significant Changes
1.0	01/07/2012	N/A
1.1	07/04/2016	Additional information regarding SOP training added
2.0	16/12/2019	Updated notification procedures for MHRA and REC Removed use of whiteboard in the R&I Office Updated R&I office and MHRA contact details Corrected typographical errors Changed Research Office to R&I Office
3.0	07/08/2023	Updated notification procedures for MHRA and REC Updated submission guidance for amendments Changed R&I Office to Research Office Updated USM definition Updates Trust logo and acronym

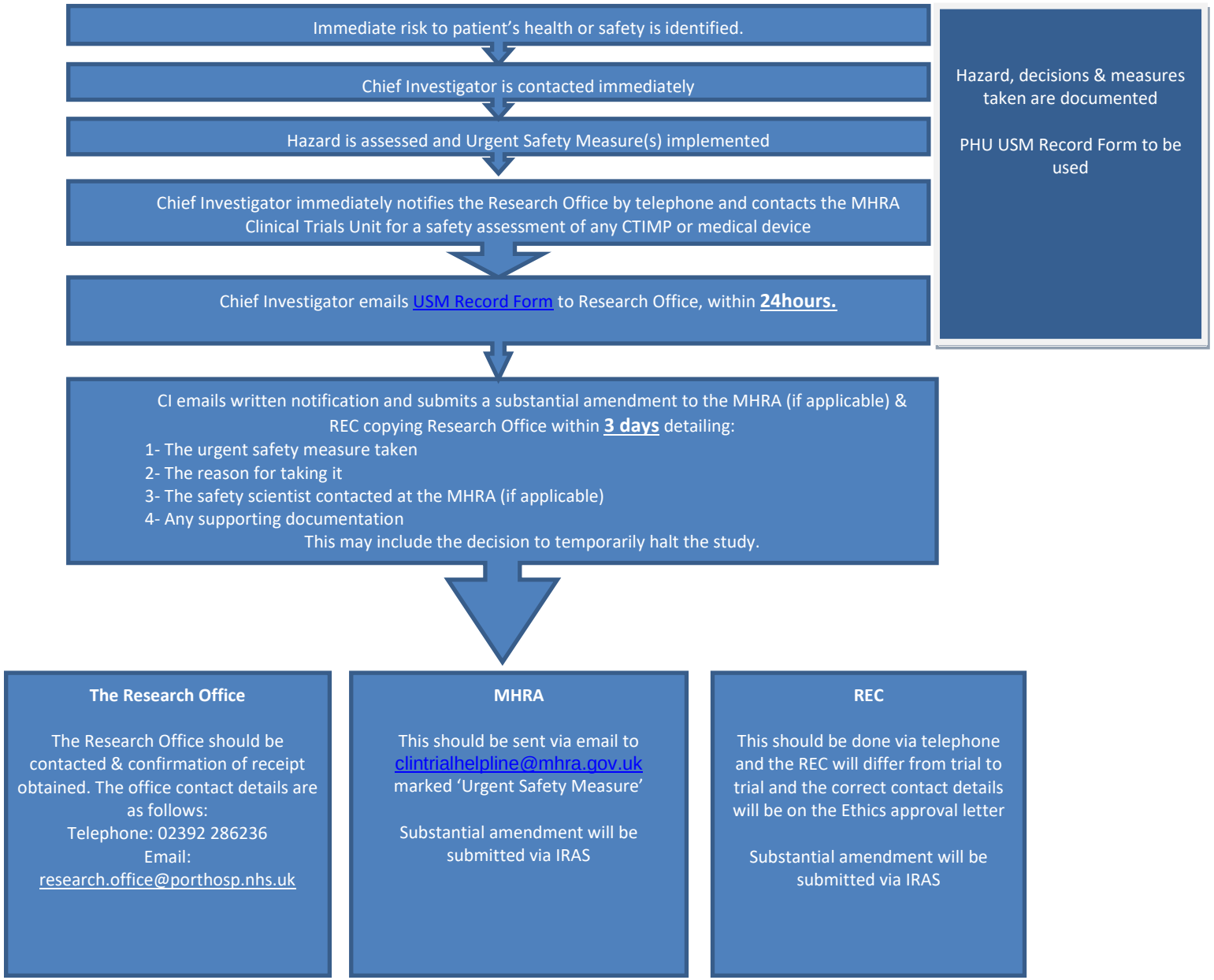
UNCONTROLLED DOCUMENT

10. APPENDICES

10.1. Hosted study flowchart



10.2. PHU Sponsored study flowchart



10.3. Training Record

Portsmouth Hospitals University NHS Trust

CONFIRMATION OF SOP TRAINING RECORD

A copy of this record may be kept in your personal training file to confirm your training in a specific SOP. The research department or your line manager may request copies to verify your training. If required by a study Sponsor a record may also need to be kept in the Trial Master Files (TMF) or Investigator Site Files (ISF).

SOP Details: To be completed by the SOP Controller	
Title of SOP	Reporting Urgent Safety Measures in Clinical Research
Reference Number	PHU/RDSOP/006
Version	V3.0, 7th August 2023
Issue Date	14th August 2023
Implementation Date	14th September 2023

Personnel Details	
Name	
Job Title & Research Role	
Date of Training	
Nature of Training	Self Directed/Delivered by etc
Records of any meetings to clarify details in SOP	

Signatures
I confirm that I have read and consider myself to be sufficiently trained in the above Standard Operating Procedure with regards to my individual roles and responsibilities Signature of Trainee …… Date ……
I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities Signature of Trainer …… Date ……

UNCONTROLLED DOCUMENT

Additional Notes & Signatures
Signature of Trainer (where appropriate) I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities Signature of Trainer …… Date ……

UNCONTROLLED DOCUMENT