Standard Operating Procedure

SETUP AND MANAGEMENT OF PHASE I TRIALS

SETTING Trustwide (Adult Services)

AUDIENCE All research staff and staff undertaking Phase I clinical research within University Hospitals Bristol & Weston NHS Foundation Trust (UHBW)

ISSUE Phase I/First in Human trials require vigilant delivery and oversight. It is essential to clearly define the roles and responsibilities of staff undertaking Phase I/First in Human trials within UHBW in order to ensure safe and effective delivery.

Document History

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N/A - original	1.0	21/APR/2020	28/JUL/2020	Nicola Manning	Diana Benton (on behalf of TRG)
20/DEC/2021	1.1	20/DEC/2021	28/FEB/2022	Jess Bisset	Jake Harley

Version Number	Reason for change
Original V1.0	Original
V1.1	Minor amendment to include risk assessment checks for devices

1. Introduction

All investigational medicinal products (IMPs) must go through a series of trials before they can be licensed for use. This ensures that new treatments are safe, effective and in addition provides information on the how the body affects the drug, and how the drug affects the body.

Phase I studies are usually performed in a group of healthy volunteers and/or patients and the main purpose is to determine whether it is safe to proceed to efficacy studies. In some cases, such as cancer treatments, administration of the IMP to healthy volunteers would be considered unethical due to the expected risk-benefit profile, and in these cases the treatment is given to patients with the condition the IMP is being developed to treat.

Participants in a phase I study usually receive a single dose of an IMP, and subsequent patients are given the next highest dose providing pre-set safety criteria are met. Phase I studies are often the first time a substance is administered to a human (FIH), and in that case samples are usually collected to assess the pharmacodynamic (PD) and pharmacokinetic (PK) properties of the IMP.

Given the early stage in development of an IMP used in a phase I study, research staff and facilities must meet the standards for enhanced safety monitoring and reporting that are required in a phase I protocol.

Novel devices may also be used in a First in Human (FIH) trial with the same enhanced standards for safety monitoring and reporting required.

Any speciality within UHBW may undertake a phase I trial but only once arrangements for setup and conduct have been individually assessed using the guidance of this Standard Operating Procedure (SOP)

2. Purpose

The purpose of the SOP is to define the roles and responsibilities of staff undertaking Phase I/FIH trials within UHBW, unit requirements, and expectations around assessing feasibility and performing study visits

In Scope: All staff undertaking Phase I/FIH clinical research within UHBW
Out of scope: Staff working on research which is not defined as Phase I/FIH

3. Responsibilities

Principal Investigator (PI). Phase I trials require vigilant delivery and oversight. The PI must be appropriately experienced and trained to undertake the role for a Phase I study/FIH study (see section 5.2). The research team working with the PI must also have suitable experience and training to work on Phase I/FIH studies. All Principal Investigators for Clinical Trials of Investigational Medicinal Products (CTIMPs) and Clinical Investigations of Medical Devices must ensure they are familiar with SOP 008 Investigator oversight of Research by reading and signing confirmation of this.

Research and Innovation (R&I) Department. Staff involved in the approvals and feasibility must ensure that a robust risk assessment and evaluation of staff and facilities to be utilised for the Phase I/FIH clinical study are undertaken using the applicable workflow on Edge.

4. Abbreviations and Definitions

Abbreviations	
AHP	Allied Health Professional
ATIMP	Advanced Therapy Investigational Medicinal Product
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
ECG	Electrocardiogram
FIH	First in Human
GCP	Good Clinical Practice
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
MEMO	Medical Equipment Management Organisation
PI	Principal Investigator
PD	Pharmacodynamics
PK	Pharmacokinetics
PPE	Personal Protective Equipment
R&I	Research & Innovation
SOP	Standard Operating Procedure
UHBW	University Hospitals Bristol & Weston
UPH	Urgent Public Health

Definitions	
ATIMP	An ATIMP as defined in Article 2(1) of Regulation 1394/2007 which is tested or used in a clinical trial (in accordance with Article 2(d) of Directive 2001/20/EC). If any researchers are unclear whether their trial involves an ATIMP they must contact the R&I department as soon as possible on 0117 342 0233
First in Human	A type of clinical trial in which a new drug or device is tested in humans for the first time.
Phase I Clinical Trial	Trials of an IMP in subjects (either healthy subjects or patients) who will not benefit from the IMP (except for life-threatening diseases). ABPI, 2018
Pharmacodynamics (PD)	The study of the effects of an IMP on the body and the mechanisms by which it acts (what the IMP does to the subject). ABPI, 2018
Pharmacokinetics (PK)	The study of the time course of the concentrations of an IMP and related substances in the blood and other parts of the body (what the subject does to the IMP). The concentrations depend on the processes of absorption (from the site of administration of the IMP), distribution in the tissues, metabolism (breakdown) and excretion (getting rid of it). ABPI, 2018

5. Procedure

The following outlines the procedure for undertaking both UHBW sponsored and externally sponsored Phase I/FIH clinical studies conducted within UHBW. The approval, planning and coordination of a Phase I/FIH clinical study must be done with full support and communication with R&I, the PI, clinical research team and the sponsor. In addition, the checklist in Appendix 1 must be completed, signed by the PI and submitted to R&I.

5.1 Feasibility

- When undertaking feasibility for a Phase I/FIH study all aspects of the study must be considered.
- Feasibility meetings should include all staff and departments involved in the conduct of the study. This is to ensure any barriers to the research study are identified quickly and that studies that are taken on by UHBW are appropriate for the participant group and specialities, resources and equipment, staffing and knowledge. Proper planning at this stage will make the approvals process more streamlined.
- **In addition,** the following points/actions must be considered:
    - Access to emergency teams
    - Principal Investigator (PI) must be working as a speciality consultant within respective clinical speciality
    - Need for clinically appropriate and safe inpatient facilities
    - 24-hour access to respective PI or Sub PI and medical team
    - Safe out of hours access to labs/lab equipment
    - Access to study IMP and out of hours pharmacy
    - For FIH involving devices -access to study device and out of hours MEMO
    - Additional training requirements of nursing staff
    - Access and engagement of specialised allied health professionals (AHPs, physiotherapy, dietetics, psychology etc.)
- For studies where the IMP is an ATIMP, a risk assessment must be completed and submitted for approval by UHBW ATIMP committee as per SOP_021 Review of Clinical Trials involving ATIMPs. Under exceptional circumstances (e.g., in cases of Urgent Public Health (UPH) research) if full review as per SOP_021is unmanageable the process must be discussed and agreed with the Chair of the ATIMP committee in advance.

5.2 PI Requirements

In addition to the usual requirements of acting as a principal investigator for a CTIMP and Clinical Investigation of a Medical Device, the following apply:

- The PI must be suitably qualified, with relevant clinical experience and expertise in the relevant patient population and previous research experience in early-stage CTIMPs and device trials.
- Normally, the principal investigator would be expected to have all of the following: (a) a postgrad medical qualification, (b) a higher research degree (PhD or MD) and (c) hold a permanent position as a hospital consultant or consultant senior lecturer in an academic unit.
- The PI has responsibility for the conduct of the study. Roles and tasks may also be delegated according to skills, qualifications and knowledge to other members of the research team and must be documented on the delegation log.
- The PI should delegate and support a sub-Investigator who will take on the same tasks as the PI, and who will be available at all times when the PI is not.

- The PI is responsible for receiving informed consent from participants enrolled in Phase I/FIH trials. However, if this is impractical (due to large numbers of participants or absence of PI) this may be delegated to senior medical colleagues with previous trials experience following detailed training from the PI and study team.
- The PI and other supporting physicians should be trained in managing and leading clinical emergencies.
- The PI should be contactable both within and out of normal working hours or should delegate this, (in the case of annual leave or absence), to a suitably trained colleague acting as the Sub PI.
- The PI or a delegated senior member of the research team/Sub PI should be available overnight for patient review if required.
- The PI must discuss potential risks of the study with clinical lead/ICU/Resuscitation lead for UHBW during the study set up process and inform of actual patient recruitment date and hospital visits.
- The PI should ensure processes are in place to inform ICU, site team, prior to admission and at time of admission of the following: patient details, study details and patient location in the event of an emergency requiring rapid review and/or resus team attendance. This will be completed in conjunction with the lead research nurse for the study.
- The PI should ensure that the sponsor has provided adequate emergency medical telephone support which should be available at all times.

5.3 Unit requirements

- The unit must be assessed for suitability in relation to the trial procedure and this review must take place before UHBW involvement is agreed.
- The unit must be easily accessible to the cardiac arrest team in emergency situations.
- The unit should have a resuscitation trolley stocked and checked as per current UHBW guidance and all staff should be aware of its location.
- The unit should always have at least two nursing staff present at all times and more depending on the number of participants, and the schedule, risk and intensity of the study investigations.
- Staff must be competent to perform the observations and clinical requirements that are required by the protocol in order to maintain patient safety.
- Nurses caring for the participants must be Good Clinical Practice (GCP) and protocol trained and signed on the study delegation log.
- All nursing staff must be anaphylaxis trained and have anaphylaxis kits available to use if required. Oxygen and suction must also be available and functioning.
- Equipment required for the study must be available and in good working order, such as vital signs monitors, ECG machines, thermometers and pulse oximeters. These should be maintained, calibrated and checked as per current UHBW guidance.
- All study equipment, including that provided by external study sponsors should be checked by MEMO (as appropriate) and agreement given prior to trial start for its use.
- The unit should have emergency buzzers and nurse call buzzers in all areas where participant care will be undertaken.
- The unit must have door locks for toilets that can be opened from the outside in case of emergencies.
- The unit should have height and tilt adjustable beds available. In some cases, fully reclining chairs are acceptable, but this is dependent on the study requirements.

- Within the unit there should be areas to which there is restricted access (staff access only). This includes areas for IMP and equipment storage, sample handling and storage and other relevant functions.

5.4 Study Visits

For IMP trials: unit staff should work with the PI and the research team to:

- Ensure the responsible delegated doctor has been booked to attend the visit and that their attendance has been confirmed prior to the visit occurring.
- Ensure contact details are available for the relevant clinical/emergency team.
- Ensure a process for rapid unblinding is in place (if applicable).
- Ensure the Investigational Medicinal Product (IMP) is present and stored according to protocol and pharmacy guidelines.
- Ensure that in situations where there is an infection risk the most up to date infection control guidance in relation to Personal Protective Equipment (PPE) can be followed.
- Ensure that IMP is administered as per protocol guidelines and in line with any dose restrictions or dosing schedule.
- Ensure the drug administration log has been completed.
- Monitor the temperature of drug fridges or locked cupboards where the IMP will be stored and record this as per the specific study protocol.
- Monitor participants according to clinical need and protocol requirements.
- Conduct all study interventions as per protocol including sample taking and processing.
- Ensure that any lab samples are clearly labelled, logged and sent to the lab within the protocol required time frame.
- If patient is being cared for within a ward area by the respective clinical team, ensure full and concise handover of study specific patient and protocol requirements to ward staff and medical team on call, (PI responsibility).

For device trials:

- Ensure device(s) are present and stored according to protocol and MEMO guidelines
- Ensure device(s) are used according to manufacturer and Protocol guidelines

6. Dissemination and training in the SOP

This SOP will be disseminated to applicable research staff (including R&I) and will be available on the R&I website.

All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP. The personal training log of the individual (and the Investigator Site File/Trial Master File if required) should be completed to document that the content of this SOP has been read and understood as described in *SOP 007 Research Training*.

REFERENCES	ABPI Guidelines for Phase I Clinical Trials (2018 Edition) Clinical Trials Directive 2001/20/EC EMA Guideline on strategies to identify and mitigate risks for first in human clinical trials with investigational medicinal products (Revision 1, 2017) MHRA, Good Clinical Practice Guide 2012
RELATED DOCUMENTS AND PAGES	SOP_008 Investigator oversight of research SOP_021 Review of Clinical Trials involving ATIMPs Latest versions of these documents can be found on the R&I section of UHBW's website: http://www.uhbristol.nhs.uk/research-innovation/for-researchers/templates-and-sops/
AUTHORISING BODY	Trust Research Group
SAFETY	N/A
QUERIES AND CONTACT	Research Matron or Research Operations Manager via 0117 342 9873 or research@uhbw.nhs.uk

Appendix 1: Phase I/FIH trial set-up checklist

Study Title:	Sponsor:
Commercial/Non-Commercial:	Study Number:
PI:	Research Team/Lead Nurse:

Requirement	Individual Responsible	Actioned?		Comments
		YES (Date each criterion please)	**No** (Provide further details in comments and discuss with R&I)	
Study Team				
Suitable PI identified?	Sponsor/divisional research lead/R&I			
Lead Research Nurse Identified?	PI/R&I			
Is the PI suitably qualified, with relevant clinical experience and expertise in the relevant patient population and previous research experience in early-stage CTIMPs and/device trials?	Sponsor/R&I			
Sub-Investigator identified?	PI			
Are all study staff Good Clinical Practice (GCP) and protocol trained and signed on the study delegation log?	PI/Lead Research Nurse			
Are the research nurses competent to perform the observations and clinical requirements that are required by the protocol in order to maintain patient safety?	Lead Research Nurse			
Are the PI and other supporting physicians trained in managing and leading clinical emergencies?	PI			

Study Title:	Sponsor:
Commercial/Non-Commercial:	Study Number:
PI:	Research Team/Lead Nurse:

Requirement	Individual Responsible	Actioned?		Comments
		YES (Date each criterion please)	No (Provide further details in comments and discuss with R&I)	
Feasibility				
Feasibility meeting arranged, including all staff and departments involved in the conduct of the study?	Sponsor/PI/Lead Research Nurse			
Is the study an ATIMP? If yes has a risk assessment been completed and submitted for approval by UHBW ATIMP committee?	PI/R&I			
Is there an appropriate process in place for receiving informed consent?	Sponsor/PI			
Is there appropriate support from the labs available (including out of hours)?	PI			
Is there access to study IMP (including out of hours)?	PI			
Is there access to study device(s)? (if applicable)	PI			
Safety				
Is there 24-hour access to PI/Sub-I and emergency medical team?	PI			
Is there a process for rapid unblinding (if applicable)?	Sponsor/PI			
Is the PI or delegated individual available overnight for patient review (if required)?	PI			
Has the PI discussed potential risks of the study with clinical lead/ICU/Resuscitation lead?	PI			
Are there arrangements in place to inform ICU/site team of hospital visit dates?	PI/Lead Research Nurse			

Is there adequate emergency medical telephone support provided by the sponsor (including out of hours)?	Sponsor/PI			
Is there appropriate PPE available and clear guidance on its use?	Lead Research Nurse			

Study Title:	Sponsor:
Commercial/Non-Commercial:	Study Number:
PI:	Research Team/Lead Nurse:

Requirement	Individual Responsible	Actioned? YES (Date each criterion please)	Actioned? No (Provide further details in comments and discuss with R&I)	Comments
Unit				
Is the unit easily accessible to the cardiac arrest team in emergency situations?	PI/Lead Research Nurse			
Does the unit have a resuscitation trolley?	PI/Lead Research Nurse			
Are research nurses anaphylaxis trained with anaphylaxis kits available?	PI/Lead Research Nurse			
Is Oxygen and suction available and in working order?	PI/Lead Research Nurse			
Are an adequate number of research nurses available to support the study schedule and intensity of the study investigations?	PI/Lead Research Nurse			
Is the equipment required available and in good working order?	PI/Lead Research Nurse			
Have MEMO given authorisation for the trial, and performed any required safety checks?	PI/Lead Research Nurse			
Does the unit have emergency buzzers and nurse call buzzers in all areas where participant care will be undertaken?	PI/Lead Research Nurse			
Does the unit have door locks for toilets that can be opened from the outside in case of emergencies?	PI/Lead Research Nurse			
Does the unit have height and tilt adjustable beds available and/or fully reclining chairs?	PI/Lead Research Nurse			

Does the unit have restricted access (staff access only) to areas for IMP, device and other equipment storage, sample handling and storage?	PI/Lead Research Nurse			

PI Signature:	**Print:**	**Date:**