ROLE OF CI, PHARMACY, NUCLEAR MEDICINE AND R&D

Research & Development

Standard Operating Procedure describing the role of the Chief Investigator, Pharmacy, Nuclear Medicine (Radiopharmaceuticals) and Research & Development Office in the setup and management of Clinical trials sponsored by West Hertfordshire Hospitals NHS Trust

SOP Number : SOP-08-05	**Effective Date:** October 2021
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1.0 BACKGROUND

This document sets out the procedures to be followed by all West Hertfordshire Hospitals Trust (WHHT) staff who conduct research studies and clinical trials at WHHT.

It provides guidance on the conduct of research studies and clinical trials to ensure compliance with the Trust's policies.

For trials sponsored by WHHT, the trial responsibilities are normally delegated to the Chief Investigator (CI). The CI takes on the primary responsibility for conducting clinical trials. The CI may delegate some or all of the trial activities to suitably qualified individuals, but remains ultimately responsible for the trial.

The Sponsor shall ensure that a drug trial does not start without essential documents in place and is authorised by the R&D Department. In addition a drug trial should not commence until a site initiation meeting has been completed.

2.0 PURPOSE

2.0.1 To outline what procedures have to be completed by Pharmacy, the R&D Office and the Research Team prior to conducting a drug trial sponsored by WHHT.

2.0.2 To outline what procedures have to be completed by Pharmacy, the R&D Office and the Research Team in implementing amendments within a drug trial sponsored by WHHT.

2.0.3 To outline what procedures are required to be completed by Pharmacy, the R&D Office and the Research Team at study closure for a drug trial sponsored by WHHT.

2.0.4 To clarify the roles and responsibilities of the Researchers, Pharmacy, Nuclear Medicine Department and the R&D Department during the setup and conduct of drug trials sponsored by WHHT.

2.0.5 To outline the methods of recording the delegated trial responsibilities.

3.0 APPLICABLE TO

Any Trust employee involved with clinical research including, but not limited to, Unit Heads, Chief Investigators (CI), Principal Investigators (PI), Consultants, Co-investigators, Clinical Trial Pharmacists, Research Managers, Statisticians, Research Nurses, Allied Health Professionals, Trial Coordinators, the RDSG & Data Managers.

Where reference is made to R&D Office or Pharmacy Department in this SOP, this refers to the WHHT R&D Office and to the WHHT Pharmacy. For multicentre studies, unless otherwise stated, the responsibilities should be outlined in a separate study agreement and is outside the scope of this SOP.

4.0 RESPONSIBILITIES

This section describes the roles and responsibilities of the R&D Office, Pharmacy and the CI in setting up a new Clinical Trial of an Investigational Medicinal Product (CTIMP) trial sponsored by WHHT.

The Sponsor shall ensure all WHHT sponsored clinical trials are conducted in accordance with the principles of Good Clinical Practice (GCP), Trust Policies, SOPs and UK regulations.

4.1 The Research and Development Department

The R&D Office shall ensure sponsored trials do not start without the following:

- Notice of acceptance of an MHRA Clinical Trial Authorisation (CTA) (including responses to remarks where applicable)
- Medicinal and Healthcare products Regulatory Agency (MHRA) authorisation for medical devices, where applicable
- Favourable ethical opinion/HRA approval
- Local R&D confirmation of Capacity and Capability (C&C)
- Sponsorship agreement
- Signed Clinical Trial Agreements (CTA) and/or collaboration agreements
- A study initiation meeting to ensure all essential documents are in place before the trial can commence (see SOP-18)

4.2 Pharmacy

The Pharmacy Department shall ensure it carries out all of the delegated responsibilities from the sponsor as follows:

- To safeguard subjects, health care professionals and the trust by ensuring that Investigational Medicinal Products (IMPs) are appropriate for use and are procured, handled, stored, transferred and used safely and correctly

- To ensure that IMPs are managed and dispensed to patients in accordance with the protocol and Sponsor requirements

- To ensure that all pharmacy clinical trials procedures comply with relevant guidelines and UK regulations

- To ensure all clinical trial activities are in accordance with any local Trust medicine management policies

- To ensure a designated member of pharmacy staff is appointed to have overall responsibility for the pharmacy clinical trials services and is documented within a delegation log and/or job description.

- To ensure all pharmacy staff involved in clinical trial activities have their roles and responsibilities documented within a delegation log/signature log which is counter signed by the designated member stated above.

- To ensure research pharmacy staff training records are maintained up-to-date and have proof of GCP training (updated every 2-3 years).

4.3 The Nuclear Medicine Department

The Nuclear Medicine Department (Radiopharmaceuticals) shall ensure it carries out all of the delegated responsibilities from the Sponsor as follows:

- To safeguard subjects, health care professionals and the Trust by ensuring that radionuclides are appropriate for use and are procured, handled, stored, transferred and used safely and correctly

- To ensure that radionuclides are managed and dispensed in accordance with the protocol and Sponsor requirements

- To ensure that the above points are conducted in accordance with the relevant guidelines and UK regulations

- To ensure all clinical trial activities are in accordance with any local Trust policies

- To ensure a designated member of Nuclear Medicine is appointed to have overall responsibility for the radiopharmaceutical services and is documented within a delegation log and/or job description

- To ensure all Nuclear Medicine staff involved in clinical trial activities have their roles and responsibilities documented within a delegation log/signature log which is counter signed by the designated member stated above

- To ensure nuclear medicine staff training records are maintained up-to-date and have proof of GCP training (updated every 2-3 years).

4.4 The Chief Investigator or Delegated Individual (DI)

The CI/DI shall ensure the following delegated responsibilities are carried out:

- Ensure Pharmacy (Clinical Trials Pharmacist/DI) is involved in reviewing clinical trial agreements and/or pharmacy charges
- Receive MHRA and ethics approval for the study
- Receive confirmation of WHHT sponsorship for the study prior to study start
- Provide a copy of the MHRA Clinical Trial Authorisation (CTA) application form in draft, prior to requested authorisation to the R&D Office
- Receive RDSG approval and R&D confirmation of C&C for the study prior to study start
- Receive Gene Therapy Advisory Committee (GTAC) or Administration of Radioactive Substances Advisory Committee (ARSAC) approvals where applicable
- Agreement including pharmacy charges

5.0 PROCEDURE

5.1 Research and Development Office

The R&D Office shall ensure that all WHHT sponsored CTIMPs have RDSG and Trust R&D confirmation of C&C prior to patient recruitment and study start. As part of the research governance process, the following documentation will be sent by the study team (Trial Coordinator/Data Manager) to pharmacy (Lead Clinical Trials Pharmacist) to be retained within the Pharmacy Study File:

- Copy of Clinical Trial Authorisation Application
- Clinical Trial Authorisation – Notice of Acceptance
- MHRA approval of response to CTA remarks (if applicable)
- GTAC/Ethics Approval
- Copy of signed Clinical Trials Agreement

The R&D Office shall circulate a list of all new amendments requiring approval by the RDSG as part of the RDSG agenda.

For WHHT sponsored trials, the study team should ensure approval of any protocol amendments relating to IMP management are reviewed and approved by Pharmacy before submission to R&D. Where IMP management responsibility is delegated to a third party other than the WHHT Pharmacy, the study team should ensure that the changes are approved by delegated parties.

All approved new and amended protocols shall be uploaded to the Trust intranet by the R&D Department upon approval.

The R&D department shall attend a trial initiation visit with the study team/coordinating centre and pharmacy (where applicable) prior to study commencement.

The R&D Department shall also ensure a study close out meeting is conducted prior to closure. The R&D Department shall ensure the CI/PI submits an End of Trial Notification form to the MHRA and ethics committee within 90 days of study closure or 15 days for early termination (see SOP-21).

The R&D Department shall also ensure that all essential documents are in place before they authorise the team to archive trial documentation in accordance with Sponsor and regulatory requirements. (see SOP-17)

5.2 Chief Investigators

The CI shall not start a drug trial sponsored by WHHT without confirmation of C&C from the R&D Office.

The CI/DI shall provide copies of regulatory and other essential documentation upon request to the R&D Office and Pharmacy.

The CI/DI shall provide a copy of the MHRA CTA application form to the R&D Office.

The CI/DI shall provide all approved protocols and amendments to Pharmacy as outlined: draft protocols should be submitted in accordance with the timelines specified by Pharmacy; copies of the final protocol should also be submitted to Pharmacy.

The CI/DI shall also ensure study amendments are not implemented until all regulatory approvals and R&D/RDSG approvals are granted.

The CI/DI shall send a copy of the annually updated Investigator's Brochure (IB) to Pharmacy and the R&D Office.

The CI/DI must delegate responsibilities to the Pharmacy Department for the:

- Correct receipt and recording of deliveries of trial medicines
- Safe handling, storage and dispensing of trial medicines
- Return, disposal and destruction of unused products where applicable
- Reconciliation of delivery records with usage and return of unused stock
- Safe keeping of randomisation information including emergency code breaks
- Provision of information to trial subjects on how to take study medication
- Dispensing of trial medication to patients
- Preparation of proforma
- Ensuring drug re-call is carried out as per Sponsor/participating site pharmacy SOP when drug safety alert is issued.
- Maintaining log of drug batch

This delegation should be clearly documented within the trial delegation log and/or agreements.

In exceptional circumstances, the CI/DI may need to store clinical trial medication in a clinical area. The Chief Pharmacist must authorise this deviation from the policy and put in place a procedure to ensure the minimisation of risk and local compliance with the medicines policy.

The CI/DI shall ensure that if there are any changes in the trial status, these changes are immediately notified to Pharmacy and the R&D Office.

The CI/DI shall ensure that any issues with IMP management are notified to Pharmacy and the R&D Office immediately.

The CI/DI shall notify the R&D Department of the intent to close a study and arrange a close out meeting with the R&D Department to ensure the trial is closed in accordance with Sponsor and regulatory requirements.

5.3 Pharmacy

A designated member in Pharmacy shall ensure that all new clinical trial protocols and CTA applications are reviewed prior to study approval.

Pharmacy shall ensure all sponsored CTIMP clinical trials have a pharmacy study file setup and maintained as per the pharmacy SOP.

Before the commencement of a clinical trial, Pharmacy must ensure that the trial has regulatory (MHRA) approval and Trust R&D approval. The trial must also have been given a favourable opinion by the appropriate Research Ethics Committee (REC).

Pharmacy will carry out risk assessments for each clinical trial and put procedures in place to minimise the predictable risks from trial medication to patients and staff.

Pharmacy will ensure that all clinical trial medicines have been manufactured in a licensed production unit in accordance with Good Manufacturing Practice (GMP), are of suitable quality and fit for purpose. The presentation and labelling of clinical trial medication must be acceptable for use within the Trust. Pharmacy shall also ensure all conditions outlined in the MHRA CTA notice of acceptance letter have been met.

Pharmacy shall ensure that the source of all CTIMPs within a study are checked. Pharmacy shall ensure Qualified Person (QP) certificates and GMP compliance statements are in place.

The Pharmacy shall ensure all Clinical Trials Agreements (where applicable) are reviewed and approved by a pharmacist.

Pharmacy shall keep in regular contact with the R&D Department during the trial progress and ensure that the R&D Office is notified immediately of any issues regarding trial status change, IMP supply and management.

Pharmacy shall ensure that prior to dispensing; the protocols on the Trust intranet are checked to ensure they are working to the current version.

Pharmacy shall ensure that the research staff and/or other relevant departments are informed that the dispensed CTIMPs should only be administered locally. The CTIMPs cannot be sent to other organisations without a risk assessment and written authorisation from the pharmacy (Clinical Trials Pharmacists) where applicable. If this is agreed the Pharmacy shall then ensure that the CTIMPs are transported appropriately, in accordance with GMP cold-chain procedures. The Pharmacy should also ensure trained personnel will administer the IMP in accordance with the protocol.

Pharmacy shall ensure that it informs any drug alerts and drug recalls from the MHRA immediately to the CI and/or study team and the R&D Office. The impact of this on the trial should also be provided to all parties. If the study is a multicentre study, the participating sites shall also be informed of the alert.

Pharmacy shall ensure that any dispensing errors such as the use of commercial stock instead of the clinical trial supply should be notified to the R&D Office, CI and also notified to the Trust Risk Management team as a Serious Untoward Incident as this will have cost implications for the Trust.

5.4 Nuclear Medicine (Radiopharmaceutical studies only)

A designated member in Nuclear Medicine shall ensure that all new clinical trial protocols and CTA applications are reviewed prior to study approval.

Nuclear Medicine shall ensure all sponsored Radiopharmaceutical clinical trials have a study file setup and maintained.

Before the commencement of a clinical trial nuclear medicine must ensure that the trial has regulatory (MHRA) approval and Trust R&D confirmation of C&C. The trial must also have been given a favourable opinion by the appropriate REC and ARSAC, where applicable.

Nuclear Medicine will carry out risk assessments for each clinical trial and put procedures in place to minimise the predictable risks from the radionuclide to patients and staff.

The Nuclear Medicine Department shall perform all the duties as delegated by the investigator above. A written agreement, detailing these delegated duties and any agreed fees (where applicable) should be in place for each clinical trial.

The Nuclear Medicine Department shall ensure all Clinical Trials Agreements (where applicable) are reviewed and approved by nuclear medicine.

Nuclear Medicine shall keep in regular contact with the R&D Department during the trial progress and ensure that the R&D Office is notified immediately of any issues regarding trial status change, radionuclide supply and management.

Nuclear Medicine shall ensure that prior to dispensing, the protocols on the Trust intranet are checked to ensure they are working to the current version.

5.5 Recording of Delegated Trial Activities

5.5.1 The CI shall ensure that appropriate trial functions have been delegated to suitably qualified and trained individuals. CVs of all trial staff as well as certificates (if applicable) should be filed in the Trial Master File (TMF) (see SOP-06) and/or training files (see SOP-07). Unless there is a record of what functions have been delegated, the CI is responsible for carrying out all sponsorship functions.

5.5.2 The CI shall ensure that all trial duties are recorded on a delegation/responsibilities log and maintained up-to-date. A template delegation log is given in Appendix 2. It is important for the Chief Investigator to periodically review the delegation/responsibilities log to ensure it is up-to-date and all staff involved in the trials are delegated with appropriate trial function and where necessary delegation details are updated.

6.0 RELATED DOCUMENTS

- SOP-06 - TMF
- SOP-07 - Research Staff Training
- SOP-17 - Archiving Essential Documents

- SOP-18 - Initiation
- SOP-21 - Trial Closure

7.0 APPENDICES

Appendix 1 - Definitions
Appendix 2 - Delegation Log Template

8.0 VERSION HISTORY

Revision Chronology:		
Version Number	**Effective Date**	**Reason for Change**
SOP-08-05	**October 2021**	1. Change from general Standard Operating Procedures (gSOP) to SOP 2. Removal of the '10.0 Agreement' from the template - all agreement signatures will be collated on a new 'SOP Signature Sheet Document' 3. Other minor amendments and clarification of terms following review including addition of transparency requirements
gSOP-08-04	**October 2017**	Minor amendments following review
gSOP-08-03	**01/10/2015**	Minor amendments following dissolution of consortium
gSOP-08-02	**07/05/2014**	Minor amendments following review
gSOP-08-01		SOP implemented at WHHT

9.0 AUTHORSHIP & APPROVAL

Author

Signature  **Date** 28/10/2021

R & D Steering Group Approval

Signature  **Date** 28/10/2021

Appendix 1: Definitions

Archive
The material storage area, including its operation, necessary for the secure retention and maintenance of material

Chief Investigator (CI)
The investigator with overall responsibility for the research. In a multi-site study, the CI has co-ordinating responsibility for research at all sites. All applications for ethical review should be submitted by the CI. For Trust sponsored trials, the CI had been delegated the pharmacovigilance responsibility for identification, recording and reporting of safety events, including submission of Development Safety Update Reports (DSURs) to the MHRA and REC.

Clinical Trial
A clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions. A Study Type

Clinical Trials Agreement (CTA)
Contract between the legal Sponsor and the hosting research sites.

Clinical Trial of Investigational Medicinal Product (CTIMP)
A clinical trial that is within the scope of the UK Medicines for Human Use (Clinical Trials) Regulations 2004. An investigation in human subjects, other than a non-interventional trial, intended: a) to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products, b) to identify any adverse reactions, or c) to study absorption, distribution, metabolism and excretion, with the object of ascertaining the safety and/or efficacy of those products.

End of Trial
When the study has been notified as closed to the MHRA and/or ethics committee by sending the End of Trial Notification Form. The end of trial definition should be detailed in the protocol, but where this is not the case the trial should be closed 30 days after the last patient has received their last treatment/visit including any patients at multicentre sites. The archiving period should be for minimum of five years from this date. Any change to the definition of 'End of Trial' in the protocol must be submitted as a substantial amendment.

Essential Documents
Essential documents are those documents which individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced. Essential documents include the Trial Master File (TMF), source documents, Case Report Forms (CRFs) and the pharmacy documentation relating to the trial which should have all accountability and destruction records for the study drugs.

Good Clinical Practice (GCP)
Good Clinical Practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.

Investigational Medicinal Products (IMP)
A pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a Clinical Trial, and includes a medicinal product which has a marketing

authorisation but is, for the purposes of the trial - a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation, b) used for an indication not included in the summary of product characteristics under the authorisation for that product, or c) used to gain further information about the form of that product as authorised under the authorisation.

MHRA Clinical Trial Authorisation (CTA)
This is the authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) to conduct a Clinical trial of an investigational medicinal product (CTIMP). No CTIMP can commence in the UK without both a CTA and a favourable ethical opinion. Applications to the MHRA and the Research Ethics Committee (REC) may be made in parallel.

Principal Investigator (PI)
The investigator responsible for the research site. There should be one PI for each research site. In the case of a single-site study, the chief investigator and the PI will normally be the same person.

Source Documents
Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

The Medicines & Healthcare products Regulatory Agency (MHRA)
The MHRA is the competent authority for the UK in relation to the Directive 2001/20/EC and the Clinical Trials Regulations, and for Medical Devices, the competent authority in relation to the Medical Devices Regulations 2002.

The Regulations
Medicines for Human Use (Clinical Trial) Regulations 2004 transposed the EU Clinical Trials Directive into UK legislation, as Statutory Instrument 2004 no 1031. This became effective on the 1st May 2004. An amendment to implement Directive 2005/28/EC was made to the Regulations as Statutory Instrument 2006 no 1928.

Trial Master File
The Trial Master File contains all essential documents held by the sponsor/Chief Investigator which individually and collectively permits the evaluation of the conduct of a trial and the quality of the data produced.

Appendix 2: Delegation Log Template

Trial Name/Title	Chief Investigator—Name
Trial– WHHT	Prof/Dr

Delegation of Trial Responsibilities

Name	Signature	Initials	Position	Delegated Responsibility Code(s)	Start Date	End Date	Chief Investigator Signature (as agreement of responsibilities)	Date
			Chief/Principal Investigator					
			Trial Coordinator/Data Manager					
			Clinical Trial Pharmacists					
			Research Nurse					

Responsibility Code

1. To have overall responsibility for the trial at the centre	8. To maintain logs of all patients/subjects, screened and/or enrolled	15. Review relevant test reports e.g. ECG, chest X-ray	22. Prescribe study drug
2. To provide trial coordination and maintain Investigator Site File	9. To record medical and surgical history	16. Sign off Lab Report	23. Receive, dispense and collect study medication and record in drug accountability book
3. To obtain ethical approval and any other necessary approval e.g. Trust approval	10. Perform physical examination/ performance status	17. CRF completion	24. Check study drug compliance
4. Data management	11. Perform protocol specific assessments e.g. Blood pressure, heart rate, ECG, height and weight measurements	18. CRF sign off	25. To maintain pharmacy file
5. To evaluate patient suitability	12. Process pathology/biopsy samples e.g. Blood, urine/tissue samples and ensure dispatch to designated laboratory, as per protocol	19. Record adverse events (AEs)	26. To meet with Trial Monitor when required and prepare for audit as per protocol
6. Explain trial to patient/subject	13. Obtain biopsy or operative specimen	20. Review all AEs and SAEs and assess and record causality for all adverse events according to the protocol	27. Provide and complete characterisation questionnaire as appropriate
7. Obtain informed consent	14. Perform tumour assessment—RECIST	21. Report SAEs according to the Sponsor's specifications	