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Trial Set-up, Conduct and TMF of SOPs

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This page details the version history and the main changes made for each new version.

Version Log		
Version number and date	**Author**	**Details of significant changes**
Version 1, 23.06.11	J H Pacynko	Original SOP approved by R&D Committee on 23.06.11.
Version 2, 02.02.15	J H Pacynko	All links up-dated. Page 9 – R&D Monitor to set-up TMF on behalf of the PI Page 11 - R&D monitor will ensure that pharmacy receives a copy of the up-dated Delegation Log after monitoring visits. Appendix1 consent form & Appendix 2 GP letter up-dated
Version 3, 02.05.19	J H Pacynko	Randomisation instructions added to Section 4.5, page 6
Version 4, 19.09.19	S Moffat	Change of Trust name from Hull and East Yorkshire Hospitals NHS Trust (HEY) to Hull University Teaching Hospitals NHS Trust (HUTH). Hyperlinks removed. Reformatting of document. Removal of Appendices. Name changes of GCP documents. Page 15 - Additional wording in section 5 to include the Pharmacy Working File. Page 12 - Removal of section 4.15 Trial Master File from Investigator Responsibilities to section 6.1 Sponsor Responsibilities. Page 16 - Addition of section 6.2 For multi-centre studies where the TMF is set up and maintained by a CTU on behalf of the sponsor. Page 16 - Re-wording of section 6.3 Sponsor Trial File
Version 5, 02.03.22	S Moffat	Page 4, Section 2.3 – Changed from CI/PI to R&D QA responsible for the TMF. Page 7, Section 4.10 - Changes to include the new Combined Review for REC, MHRA and HRA submission via the IRAS system. Page 7, Section 4.11 - Addition of R&D C&C. Page 12, Section 6.1 – Changes made to reflect the use of an eTMF rather than a paper TMF.
Version 6, 21.12.22	S Moffat	Name of SOPs have been reformatted to R&D GCP SOP [number] [Title] throughout the document.

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		Section 4.8 Informed Consent Form, page 7, paragraph 5 - Trial Master File has been changed to Investigator Site File. <u>Section 6 Sponsor Responsibilities</u>: ● Page 12, paragraph 2 - to change location of eTMF to EDGE rather than the Y Drive. "The R&D Monitor or QA Manager will set up an electronic TMF (eTMF) on EDGE (a Clinical Research Management System used by all research departments within HHP) using the eTMF folder template which is available on on the Y Drive: \\hri_data3\clinicalgov\Research\GCP SOPs & forms\Contents lists of trial files\New Process eTMF." ● Page 13, addition of "The eTMF will have restricted access to R&D QA staff only." ● Page 13, addition of "Pharmacy Clinical Trials will have read only access to the eTMF. ● Page 13, addition of "All documents requiring signatures will be sent to the relevant research staff and R&D QA staff via Docusign. The signed documents will then be filed in the relevant folder of the eTMF." ● Page 13, paragraph 7, addition of "For EDGE security information please go to https://edgeclinical.com/security"
Version 7, 19.04.2023	L Cox	Changes made to remove EDGE for the use as an eTMF as this is not an acceptable system, confirmed by the EDGE providers via email on 01.03.2023. All previous changes made in Version 6, 21.12.2022 in relation to using EDGE as an eTMF have been removed from this SOP. Although folders were set up on EDGE to be used as an eTMF they were never activated for use in open studies. ● Page 14, paragraph 2 - to change location of eTMF to back to the Y Drive rather than EDGE. "The R&D Monitor or QA Manager will set up an electronic TMF (eTMF) on the Y Drive using the eTMF folder template which is available on: \\hri_data3\clinicalgov\Research\GCP SOPs & forms\R&D QA\5. Trial document templates\5.8 eTMF Template ● Page 14, deletion of "Pharmacy Clinical Trials will have read only access to the eTMF. ● Page 14, paragraph 7, deletion of "For EDGE security information please go to https://edgeclinical.com/security"
Version 8	L Cox	Alignment with ICH E6(R3) across the SOP, including explicit incorporation of *quality-by-design*, *risk-proportionate approaches*, and *critical-to-quality factors*. Strengthened Sponsor oversight requirements, including enhanced expectations for monitoring, vendor oversight, digital system validation, and documentation of Sponsor review. Modernisation of digital system requirements: validation, audit trails, access controls, secure storage, and data

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		integrity expectations along with finalised data sets before analysis for eCRFs, eConsent, electronic delegation logs, and electronic TMF components. Updated TMF requirements to emphasise contemporaneous maintenance, version control, audit trails, and periodic quality checks for both paper and electronic documents. Expanded protocol development requirements to include identification of critical data/processes, independent scientific/statistical review, and validation of electronic randomisation/data-capture systems. New risk-based controls for IMP management, pharmacy processes, sample handling, chain-of-custody, and temperature monitoring. Updated training requirements to mandate competency-based training, role-proportionate refreshers, and documentation of training in line with system or procedural changes. Strengthened feasibility (C&C) expectations, including assessment of staffing resilience, digital readiness, and vendor dependencies. Updated CRF, ISF, and patient list requirements to include electronic audit trails, secure access, and data integrity controls along with record location index and use of certified copies only. For electronic sponsor systems, user access roles to match delegation logs and revised routinely. General modernisation of terminology, processes, and expectations to reflect current MHRA guidance and contemporary trial management practices. Trust name changed from Hull University Teaching Hospitals NHS Trust (HUTH) to Humber Health Partnership (HHP- Hull University Teaching Hospitals NHS Trust and Northern Lincolnshire and Goole NHS Foundation Trust).

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Please note for definitions of acronyms refer to Appendix 2 of Management of SOPs.
Refer to Appendix 3 of Management of SOPs for the standards to which clinical trials that investigate the safety and/or efficacy of a medicinal product are conducted.

All the R&D GCP SOPs are available at:
https://www.HHP.nhs.uk/research/researchers/gcp-sops-for-HHP-sponsored-ctimps/

1 Purpose

1.1 This SOP describes the procedures for set up and conduct of HHP (HHP & NLaG) sponsored CTIMPs in accordance with ICH GCP, the UK Clinical Trials Regulations, and applicable guidance. The procedures outlined incorporate quality-by-design principles, proportionate risk-based approaches, and a focus on critical-to-quality factors to ensure participant safety, data integrity, and regulatory compliance.

1.2 As part of the set-up process a Trial Master File (TMF) is required which contains the essential trial documents (ICH GCP section 8 and UK CT regulation 31A). This SOP describes what is required for the TMF.

2 Introduction

2.1 It is a legal requirement for clinical trials with investigational medicinal products (CTIMPs) to be set up and conducted in accordance with ICH GCP and the UK CT Regulations.

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2.2 The TMF constitutes the complete and contemporaneous record of trial conduct and oversight. The TMF must be maintained throughout the trial lifecycle, ensuring traceability, version control, auditability, and secure management of both paper and electronic essential documents. During MHRA inspections, the TMF is closely inspected.

2.3 For single centre HHP-sponsored CTIMPs, the R&D QA Team is responsible for maintaining the TMF. It is important to note that the TMF also includes the Investigator Site File (ISF kept by the Principal Investigator), Case Report Forms (CRFs) and the Pharmacy Trial File (PSF kept at pharmacy). The CRFs, PSF and ISF are also inspected by the MHRA.

2.4 For multi-centre HHP-sponsored CTIMPs, the TMF is comprised of the CRFs, PSF, Sponsor Study File (SSF kept by R&D QA) and Investigator Site Files (ISFs). Each participating site keeps an ISF. If the trial is chosen for inspection by the MHRA all these files will be inspected.

3 Who should use this SOP

3.1 This SOP should be used by:

- All research staff involved with HHP-sponsored CTIMPs – chief/principal investigator, co-investigators, research nurses, project managers, clinical trial co-ordinators, data managers, administrators etc.
- Clinical trials pharmacy staff – technicians and pharmacists.
- All HHP R&D staff.
- Research staff involved with clinical trials sponsored by an external organisation where the sponsor has no SOP for trial set-up or the Trial Master File. HHP R&D SOPs are defaulted to in this case.
- Research staff involved with HHP-sponsored non-CTIMPs may find this SOP a useful guide for the set up of studies, although the SOP will need to be adapted for the non-CTIMP trial.

4 Investigator responsibilities

4.1 Funding

- Financial management processes must be proportionate to trial risk and must ensure transparency, traceability, and timely reporting to the Sponsor.
- The Chief/Principal Investigator (CI/PI) must secure and administer financial resources to finance the trial.
- If the trial is grant funded, the CI/PI must ensure a service level agreement is in place to confirm financial flow and oversight between the holder (recipient) of the grant and the sponsor (HHP R&D on behalf of HHP Trust) prior to the start of the trial.
- If grant funded, the CI/PI must ensure that finance up-date reports are sent to the sponsor in a timely fashion as agreed in the service level agreement.

4.2 Insurance/indemnity

- The CI/PI must ensure that adequate insurance or indemnity arrangements are in place to cover liabilities.
- Humber Health Partnership has indemnity to cover claims arising from negligent harm. HHP will only provide NHS indemnity cover for negligent harm to its substantive employees or researchers with honorary contracts who have had their clinical trial approved by the R&D Department.

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- If the CI/PI is employed by the University of Hull, the University has clinical trials insurance that covers non-negligent harm. It is important to contact the Insurance Officer at the University of Hull to notify the University of your Clinical Trial and obtain details of insurance cover.
- Insurance and indemnity arrangements must be reviewed periodically to ensure they remain appropriate for the duration of the trial.

4.3 Sponsorship

- The definition of Sponsor is an individual, company, institution or organisation, which takes responsibility, for the initiation, management and financing (or arranging the financing) of the trial (ICH GCP 1.53 and UK CT regulation 3).
- If you are developing a research project which you are hoping to be sponsored by Humber Health Partnership then the CI/PI must approach the R&D Manager to request sponsorship as early as possible. A sponsorship risk assessment is done and if sponsorship is agreed then R&D can advise what to include in the protocol and how to set up the clinical trial. The sponsorship risk assessment will identify critical-to-quality factors and proportionate controls.
- The CI/PI will be expected to sign an Investigator/Sponsor Formal Agreement which sets out the duties delegated by the sponsor (HHP R&D) to the CI/PI to ensure the set-up and conduct of the trial to ICH GCP and the UK CT regulations.

4.4 SOPs for HHP-sponsored CTIMPs

- You will need to use the GCP Standard Operating Procedures (SOPs) and the protocol template available from the R&D QA manager or monitor. GCP documents are available from the R&D QA manager or monitor. The SOPs are instructions on how to set up and conduct HHP-sponsored CTIMPs. The GCP documents required for the Investigator Site File are described in 4.15 below.

  GCP SOPs for HHP-sponsored CTIMPs
  http://www.hey.nhs.uk/rd (HHP R&D internet site)

4.5 Protocol

- The CI/PI must write the protocol using the Protocol guide for HHP sponsored CTIMPs available from R&D QA or at the following link https://www.hra.nhs.uk/planning-and-improving-research/research-planning/protocol/. This guide can be used as a protocol template and is the expected standard for HHP R&D approval. The guide is frequently being up-dated to be in line with the regulations and MHRA requirements, so always use the most recent version from R&D or on the HRA website using the link above.
- The CI/PI must ensure that the protocol has been developed using quality-by-design principles, identifying critical data and processes essential to participant safety and trial reliability.
- The CI/PI must ensure that the protocol has undergone independent scientific and statistical review and is compliant with the relevant regulations/guidelines. The CI/PI and research team must conduct the trial in compliance with the protocol approved by the MHRA, Research Ethics Committee (REC), Health Research Authority (HRA) and HHP R&D.
- The CI/PI and research team must not deviate from or change the protocol without agreement from HHP R&D and subsequent approvals from the MHRA, REC, HRA and HHP R&D (see R&D GCP SOP 08 Amendments).
- The CI/PI and research team must notify HHP R&D promptly of any major protocol deviations and serious breaches (see R&D GCP SOP 17 Serious Breach)
- The CI/PI must take into account all protocol deviations and any serious breaches in the final trial analysis and publication.

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- If the trial is randomised the CI/PI must use an electronic randomization system. This system must have a log-in for those staff involved in recruitment. The randomization process must be documented using Working Instruction 28, approved and signed off by the CI/PI and statistician. There must be a 3rd party agreement in place for any external randomization organisation used as described in section 4.12 below. All third party providers will be subject to a Trust vendor assessment in order to assess suitability prior to the signing of contracts. Any electronic randomisation or data-capture systems must be validated, secure, and compliant with audit trail requirements.

4.6 Pharmacy

- When the protocol is in final draft, send to pharmacy for review of the trial medication and pharmacy sections. Pharmacy often request amendments to the protocol, therefore it is important to involve pharmacy in the review of the protocol at this early stage to prevent delays later on.
- Pharmacy may need to create the label for the IMP for the IRAS MHRA application (see 4.10 below). Involving pharmacy at this stage prevents delays with submission of the MHRA application.
- Pharmacy will also consider arrangements for handling, preparation, storage, dispensing and temperature monitoring of IMP and will advise if these arrangements need to be specified in the covering letter to the MHRA which is sent with the application.
- Pharmacy procedures must incorporate risk-based controls for IMP accountability, temperature management, and chain-of-custody documentation.

4.7 Patient Information Sheet

- The HRA website has useful guidance and headings with example text, for the design of your patient information sheet (PIS), at the following link: http://www.hra.nhs.uk/resources/before-you-apply/consent-and-participation/consent-and-participant-information/
- The PIS must be written using plain-language principles and, where feasible, assessed for participant comprehension.
- RECs closely review the patient information sheet and informed consent form and frequently request changes to be made before favourable opinion is given, so using the HRA template for the PIS should minimize these requests.

4.8 Informed Consent Form

- Use the template in WI 18 Informed consent form. Add in or delete the optional points on page 2 as applicable but make sure that the last point is 'I agree to take part in the above trial'.
- Ensure that the R&D GCP SOP 06 Informed Consent is adhered to.
- Investigators must ensure that the consent form is signed by the patient before any trial procedure is performed (including screening, quality of life questionnaires, blood tests etc).
- Ensure that only the CI/PI, co-investigator or delegated person listed on the *trial delegation and signature log* (see 4.18) take consent.
- Please note that a copy of the signed consent form must be given to the patient, a copy must be filed in the patient's casenotes and the original signed form must be filed in the Investigator Site File.
- Always ensure that the *latest REC and R&D approved versions* of the consent form, patient information sheet and GP letter are used when recruiting patients.

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- File one copy of the signed consent form in the patient's case notes/medical records together with a copy of the patient information sheet and the GP letter.
- Electronic consent (eConsent) may be used where appropriate, provided systems meet regulatory expectations for identity verification, audit trails, and secure storage.

4.9 GP letter

- Use the template in WI 32 GP Letter to design your GP letter.
- GP letter templates must be version-controlled and aligned with the approved consent materials .
- For multi-centre trials, where participating sites are GP centres then adapt the letter so that the Hospital Consultant looking after the patient is made aware that their patient is participating in the trial.
- The GP letter must be sent out on the day of consent or shortly after.

4.10 IRAS application

- Once you have your definitive trial documents, you will need to apply for REC, MHRA and HRA approvals. This is done for CTIMP applications via Combined Review and must be submitted using a new part of the Integrated Research Application System (IRAS). This is a separate login from the one used to access IRAS at www.myresearchproject.org.uk. You will need to set up an Identity Gateway account by using the following link: IRAS Website link
- Further information on Combined Review is available at https://www.hra.nhs.uk/combined-review
- All submissions must be tracked within the TMF with documented version control and evidence of Sponsor review.

4.11 Capacity and Capability

Confirmation of NHS trust Capacity and Capability (C&C) is the local feasibility procedure undertaken by an NHS Organisation to assess and evaluate site-level critical-to-quality factors, staffing resilience, digital system readiness, and vendor dependencies**.**

When REC, MHRA and HRA approval has been given you will need to receive HHP R&D confirmation of C&C (R&D approval).

4.12 Case Report Forms (CRFs)

- CRFs (patient data collection forms) must be designed in accordance with the protocol.
- CRFs may be designed using the R&D CRF template available from the R&D QA manager or monitor.
- CRFs must be designed with:
  - Clear indication of patient ID (initials and trial number, not patient's full name), visit numbers and dates.
  - Any patient demographic details required.
  - An inclusion and exclusion criteria checklist to indicate clearly that you have checked patient eligibility. The checklist must be signed and dated by the trial doctor (on *Training and Delegation Log* - see 4.17) assessing eligibility.
  - Clear details of concomitant diseases and medication, and space to document any changes at subsequent trial visits.
  - An adverse event (AE) report form.
  - A trial medication compliance form.

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  - Record of samples taken.
  - Questionnaires/VAS/data collection forms (including lab report forms)
  - Patient status details at the end of each visit i.e. patient included, excluded (if so why), ongoing, withdrawn (if so why), completed and whether there have been any protocol deviations (if so specify).
  - Signature and date of investigator (CI/PI or other trial medic) at end of CRF to confirm the observations recorded.
- Investigators must ensure patient confidentiality is respected by referring to patient's initials and trial number only on CRFs.
- CRFs must be stored during the trial in a secure but accessible location e.g. locked filing cabinet in a locked room.
- If the trial is multi-centre, PIs must keep an original or certified copy of the CRF (paper or electronic) as part of the Investigator Site File at the participating sites for the duration of the trial and archive.
- Where electronic CRFs are used, systems must be validated, include audit trails, and ensure data integrity and data set to be finalised prior to the interim analysis or final analysis along with password protection.

4.13 Third Party Agreements

- The CI/PI must ensure that Agreements are in place with 3rd party organizations outside of the Trust providing services such as (but not limited to); IMP supply, laboratory work, statistics, randomization, IVRS, supply of equipment, project management, data management etc.
- Check with HHP R&D who has templates for some 3rd party agreements.
- All the appropriate contracts/agreements must be in place prior to the trial commencing and the sponsor (HHP R&D) must be a signatory to these contracts/agreements. The sponsor must be notified of any changes and agree to these in writing.
- The CI/PI must be kept informed of, and comply with, any indirect or direct obligations from any third party agreements/service level agreements.
- The CI/PI must ensure that all staff appointed to work on the trial and whom are not employees of the sponsor (contracted staff) have appropriate employment contracts and that clear agreements/job descriptions are in place that outline respective roles and responsibilities (i.e. statistical services, laboratory services and project management personnel).
- The CI/PI must ensure that all staff participating in the research on behalf of the sponsor hold substantial or honorary contracts/letters of access with this Trust.
- Vendor oversight plans must be documented, risk-proportionate, and include performance monitoring, system validation evidence, and escalation pathways.

4.14 Material Transfer Agreement

- The CI/PI must ensure that where required a Material Transfer Agreement is in place for the transfer and storage of human tissue prior to any patient being enrolled in the trial. Sample handling processes must incorporate chain-of-custody controls, temperature monitoring, and traceability.
- Contact HHP R&D for a template for the Material Transfer Agreement.
- The CI/PI must be aware of, and adhere to, all obligations placed on him/her as Chief/Principal Investigator and as custodian of the samples, with regards to ensuring all guidelines and regulations are adhered to for the storage and transfer of tissue and blood samples to and from HHP as part of the trial protocol.
- Any central labs used in the research must hold and evidence the necessary license/accreditation.

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- The CI/PI must obtain agreement from the HHP Pathology labs for any processing, storage and handling of tissue and bloods prior to recruiting the first patient.
- For multi-centre studies, the Chief Investigator must ensure that clear instructions are given to each participating site in a Lab Manual regarding the processing and secure transfer of samples to the lead HHP site.

4.15 Approvals

- The CI/PI must ensure that the following trial approvals have been obtained prior to any screening procedure for the trial and prior to the *first patient being consented* and entered into the trial:
  - MHRA clinical trial authorization
  - REC favourable opinion
  - HRA approval
  - R&D approval (confirmation of Capacity and Capability)
  - HHP R&D as sponsor representative will send a 'green light' email to the CI/PI and research team to confirm that the trial can start. The Sponsor's green-light process must confirm that all critical-to-quality factors are in place prior to first participant enrolment.

  In addition, for multi-centre studies each participating site requires a 'green light' letter issued by the sponsor (HHP R&D) as detailed in R&D GCP SOP 18 Site initiation of multi-centre trials .

4.16 Investigator Site File

- For single-centre HHP sponsored studies the R&D monitor will provide the CI/PI with an Investigator Site File for the Site Initiation Visit using the list of contents and forms.
- For multi-centre studies, the Chief Investigator at the lead HHP site is responsible for supplying the Principal Investigators at each participating site with an Investigator Site File and the appropriate essential documents for the file. For an example ISF list of contents contact the R&D QA Manager or Monitor.
- For multi-centre studies where a Clinical Trials Unit is managing the trial on behalf of HHP, the CTU is responsible for supplying the Principal Investigators at each site with an Investigator Site File and the appropriate essential documents for the file. A Sponsor review of the Investigator Site File will be made prior to its use.
- The PI (or delegated member of the research team) is responsible for maintaining and keeping the essential documents up-to-date within the ISF for the duration of the trial. In particular, the *Training and Delegation Log* and *Trial Patient List* must be kept up-to-date at all times.
- The PI must ensure that the ISF is kept in a secure place with restricted access for the duration of the trial and is archived in a secure location after trial completion according to the trial contract/agreement. See R&D GCP SOP 14 Archiving Procedure.
- The ISF must be maintained contemporaneously, with version control, audit trails for electronic files, and documented quality checks. ISF to include record-location index where essential records are held when split across TMF/ISF/PSF/SSF and external systems. In case a copy replaces an original essential record, it must meet 'certified copy' requirements and be filed accordingly.

4.17 Training

- The Chief/Principal Investigator must ensure that all research staff involved with the trial have been trained in the trial procedures, training must be competency-based,

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proportionate to role, and refreshed when significant modification or system changes occur and include but not limited to:

- The protocol and any amendments
- Case report form
- The informed consent procedure, consent form, patient information sheet and GP letter
- Serious and non-serious adverse event reporting
- Prescribing procedures
- Completion of source documents particularly patient's hospital or GP medical records/casenotes
- Breaking the randomization code for a patient for safety reasons if the trial is blind
- Responsibility to report serious breaches

- The CI/PI must keep a record of training to confirm that members of the research team were trained prior to their involvement in the trial using the Training and Delegation Log supplied by the R&D Monitor. This form will need to be adapted according to the trial. The monitor/QA manager will need to approve the form before use.
- The CI/PI must ensure all research staff are GCP trained prior to their involvement in the trial. GCP training must have been undertaken within the last two years. Contact the R&D office for advice on GCP training or go to the https://www.hey.nhs.uk/research/researchers/gcp-training/on the HHP website.
- The R&D QA manager and monitor must ensure that the TMF or a department training file contains up-to-date GCP certificates and CVs (signed and dated) for all research staff involved with the trial.
- For multi-centre studies, the Chief Investigator must ensure that all Principal Investigators are fully trained on the protocol and trial procedures prior to involvement in the trial and must keep records of training dates. Training may be given during pre-trial investigator meetings or during site initiation visits.
- For multi-centre studies where a Clinical Trials Unit is managing the trial on behalf of HHP, the CTU must ensure that all Principal Investigators are fully trained on the protocol and trial procedures prior to involvement in the trial and must keep records of training dates. Training may be given during pre-trial investigator meetings or during site initiation visits**.**

4.18 Training and Delegation Log

- The Chief/Principal investigator (CI/PI) is responsible for the completion of the *Training and Delegation Log* in the ISF prior to and during the trial to confirm all the research staff involved with the trial and their duties which have been delegated to them by the CI or PI. Delegation logs must be updated in real time. Electronic logs must include audit trails capturing the identity of the individual making changes and the date/time of the change. For the sponsor systems uses in eCRF, randomisation, eConsent, user access roles on software must aligns to the delegation log and reviewed routinely.

- All significant duties or tasks such as taking consent, assessing eligibility, prescribing or dispensing IMP, physical examinations etc can be delegated by the CI or PI to those who have the necessary education, training and experience. If the CI/PI delegates tasks to other team members it is important to note that the CI/PI still retains responsibility for the trial at site.

- The following duties can only be delegated on the *Training and Delegation Log* to a trial medic;
  - assess the eligibility of trial patients,

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- answer any final questions and then sign the consent form with the patient (unless delegation to another team member e.g. research nurse, has been approved by the Research Ethics Committee)
- perform physical/medical examinations
- sign off prescriptions
- assess how severe and serious adverse events are and whether SAEs are related to IMP.

- The CI/PI must ensure that no staff member is added to the *Delegation Log* without appropriate training. Training must be recorded on the Training and Delegation Log for the trial. The R&D Office must be notified of any staffing issues that may prohibit the Trust from fulfilling its obligations during the course of the trial.
- Clinical trials pharmacy staff must also complete the *Training and Delegation Log* prior to the start of the trial.

- *The Training and Delegation Log* requires up-dating during the trial when new research staff become involved or research staff leave. The R&D monitor will ensure that pharmacy receives a copy of the up-dated Training and Delegation Log after site monitoring visits. This applies to both single-centre and multi-centre studies.
- The signature and initials of staff on the *Training and Delegation Log* ensure they can then be identified on forms, CRFs, casenotes, prescriptions etc. If any changes are made to documents then a single line is drawn through the wrong value and the correct value written alongside is initialed and dated so that it is clear who made the change and when.
- If the trial is chosen for MHRA inspection, the inspectors want to see evidence that research team members and pharmacy staff are qualified to carry out the duties that they have been delegated and have been trained in the appropriate trial procedures. They will also want to see a clear audit trail of any corrections made to documents.

4.19 Trial Patient List

- The Chief/Principal Investigator (or delegated person) is responsible for keeping a confidential list of names of all patients screened for the trial and those that were eligible to be recruited and allocated to trial numbers (ICH GCP 8.3.20 - 8.3.22). The *Trial Patient List* is used for this purpose and available from the R&D monitor. This is the only place in the Investigator Site File where the full name, case note/medical records number and contact details (optional) of trial patients are documented (the full name is also on the consent forms and prescriptions). This allows the investigator to reveal the identity of trial patients if necessary. Trial patients should only be referred to by the patient's initials and trial number on CRFs. This form must be kept up-to-date during the course of the trial.
- Where electronic systems are used, access must be restricted, encrypted, and auditable

4.20 Trial Equipment

- The Chief/Principal Investigator is responsible for the proper maintenance of all equipment used in the trial. This may include fridges, freezers, centrifuges, weighing scales and equipment used for medical procedures.
- Any equipment used for the trial should be listed in the Equipment File Note (WI 33 Trial Equipment File note) and filed in section 4 of the TMF. Equipment used for critical-to-quality data must have documented calibration, maintenance schedules, and validation where applicable.
- Check indemnity arrangements are in place for any equipment loaned to the Trust for use in the trial. Contact R&D for advice.

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4.21 Trial Meetings

- Regular team meetings should be held involving staff working on the trial. Meetings should be minuted or notes made of all significant decisions affecting critical-to-quality factors and record follow-up actions. Copies of minutes or notes must be kept in the ISF.
- It is recommended for large multi-centre or long-running trials that trial oversight committees are set up e.g. a Trial Management Group, Data Monitoring Committee (DMC) and Trial Steering Committee, in order to review trial data and oversee trial management at regular pre-defined intervals during the trial. See R&D GCP SOP 11 Trial Oversight Committee.

5 Pharmacy responsibilities

5.1 **Pharmacy Study File (PSF)**

- The R&D monitor (or QA manager) is responsible for setting up and maintaining the PSF using the PSF list of contents which can be found on the Y Drive: Research/GCP SOPs & forms/ Contents lists of trial files.
- Pharmacy documentation must include contemporaneous IMP accountability, temperature monitoring logs, and deviation management procedures.
- Where a CTU is managing the trial on behalf of the sponsor the above responsibility would be delegated by the sponsor to the CTU.

5.2 Pharmacy Working File (sections 3 and 4 of the PSF)

- The Principal Pharmacy Technician (or delegated person) is responsible for setting up and maintaining the Pharmacy Working File using the Working File list of contents**.** The Working File contains original and confidential documents and must be kept in a secure location with restricted access for the duration of the trial.
- The Principal Pharmacy Technician (or delegated person) is responsible for preparing the Dispensing Procedure prior to the first patient entering the trial.
- All clinical trials pharmacy staff involved with the trial must complete the *Training and Delegation Log* prior to the start of the trial.

6 Sponsor responsibilities

6.1 Trial Master File (TMF) for single-centre and multi-centre trials managed by the HHP R&D

- The R&D monitor or QA manager is responsible for setting up and maintaining the Trial Master File for both Trust sponsored single-centre and multi-centre trials. The eTMF must be validated, with documented user access controls, audit trails, and periodic quality checks.
- The R&D Monitor or QA Manager will set up an electronic TMF (eTMF) on the Y Drive
- This template follows the TMF List of Contents which has been compiled from ICH GCP Section 8 and contains the essential documents for the set-up and conduct of a clinical trial.
- All documents/forms set up for the trial should be filed in the eTMF in the relevant folder.
- The eTMF will have restricted access to R&D QA staff only.

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- All documents requiring signatures will be sent to the relevant research staff and R&D QA staff via Docusign. The signed documents will then be filed in the relevant folder of the eTMF.
- The R&D QA manager and monitor should be responsible for maintaining and keeping the essential documents up-to-date within the eTMF for the duration of the trial. During the trial, the eTMF should be kept secure ensuring that the same IT requirements are followed as stipulated in the R&D GCP SOP 13 Data Management for the trial database e.g. restricted access to authorized personnel only, audit trail of changes, regular back-ups, clear consistent naming of documents and folders, audits done to check documents are named correctly etc.
- After trial completion, the R&D Monitor and Archivist organizes central archiving for the eTMF, ISF, CRFs, PSF and eSSF for HHP-sponsored CTIMPs as set out in the R&D GCP SOP 14 Archiving Procedure.
- For all other trials that are hosted by HHP, the archiving arrangements should be specified in the trial contract/agreement signed prior to the trial commencing at this site.
- If trial documents are amended e.g. the protocol, patient information sheet etc, it is important that old versions are filed in a “Previous” folder and new versions are filed in the “Current” folder within the relevant section of the eTMF. The Study Tracking Log should be updated to reflect the version changes. This ensures a version history is kept of documents used during the trial. Refer to R&D GCP SOP 08 Amendments for procedures regarding trial amendments and R&D GCP SOP 01 Version control of Trial Documents.
- File Notes (a template will be produced by the R&D monitor) are very useful for explaining if any trial documents are missing or located elsewhere or if any protocol deviations have occurred. It is useful to explain events in chronological order in the file note and to note who, what, where, when, why, how and to include corrective and preventative actions. The inspectors often quote ‘if it isn’t documented then it didn’t happen’.

6.2 **For multi-centre trials where the TMF (paper or electronic) is set up and maintained by a CTU on behalf of the Sponsor**.

The Sponsor must be able to demonstrate risk-proportionate oversight activities by the following methods (not exhaustive):

- Review of evidence of system validation of the TMF (electronic) including the audit trail.
- Review of the CTU’s TMF set up and maintenance SOP(s).
- Review of training manuals.
- Review of the structure and indexing of the TMF.
- Monitoring of the TMF throughout the duration of the trial (QC).
- Arranging independent audit of the TMF (QA).
- Have “read only” access to the TMF (electronic).
- Request key documents for the Sponsor Trial File.
- Review the CTUs process of consolidation and reconciliation of the TMF and SSF at the end of the trial (there must be evidence of the records the sponsor held over the duration of the trial).
- Review of the CTU’s archiving SOP.
- Review and approval of the Sponsor Oversight Report.

6.3 Sponsor Study File (SSF)

For multi-centre trials where the TMF is set up and maintained by a CTU on behalf of the Sponsor, the R&D monitor or QA manager is responsible for setting up and maintaining an SSF in electronic format using the list of contents and forms available from the Y Drive: Research/GCP SOPs & forms/ Contents lists of trial files.

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For the eSSF ensure that the same IT requirements are followed as stipulated in the R&D GCP SOP 13 Data Management for the trial database e.g. restricted access to authorized personnel only, audit trail of changes, regular back-ups, clear consistent naming of documents and folders, audits done to check documents are named correctly etc.
The SSF must demonstrate evidence of ongoing Sponsor oversight, including monitoring reports, quality checks, and vendor oversight documentation.

7 Implementation

Implementation of this SOP requires training, version control, and periodic review to ensure continued alignment with ICH GCP and evolving regulatory expectations.