UNIVERSITY OF LEEDS / NHS The Leeds Teaching Hospitals NHS Trust Standard Operating Procedure	Title	A Researchers Guide to Trial Documentation				
	Scope	Information for researchers on Trial Master File set up and maintenance for Clinical Trials of an Investigational Medicinal Product				
	Version	4.0	Date	27/06/2019	SOP ID	LTU_QM24

Details:

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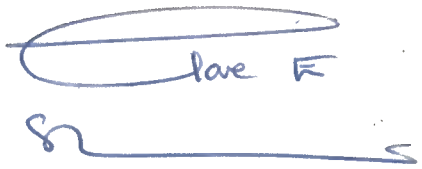
Version no. of replaced SOP:	3.0
Effective date of replaced SOP:	06/08/2018

Approval:

Version no. of SOP	Name of person approving this SOP	Date	Signature of the person approving this SOP
4.0	Clare Skinner Head of Research Integrity and Governance Secretariat / Faculty of Medicine and Health University of Leeds	13/09/2019	
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Distribution & Storage:

Distribution to:

Investigators and all members of research teams conducting or assisting with a CTIMP trial sponsored by the University of Leeds or Leeds Teaching Hospital NHS Trust.

Location of document:

Paper: QA Department, Room 5, Research and Innovation Centre, St James' University Hospital

Electronic: http://www.leedsth.nhs.uk/research/information-for-researchers/key-documents
http://lthweb.leedsth.nhs.uk/sites/research-and-development/resources/Sponsored%20CTIMPs%20%28Quality%20Assurance%29

Contents

Please note: *This SOP should be used and followed in conjunction with other UoL / LTHT SOPs developed for researchers to support study set up and management. These can be found on the LTHT website or by contacting R&I / QA directly. For clinical trials where Leeds is not the trial Sponsor, please refer to any Sponsor SOPs for further information.*

Section A: Introduction

1.1 This Standard Operating Procedure (SOP) acts as a guide for researchers to aid research teams with Trial Master File (TMF) set up and maintenance when conducting a Clinical Trial of an Investigational Medicinal Product (CTIMP) Sponsored by the Leeds Teaching Hospitals NHS Trust (LTHT) or the University of Leeds (UoL).

1.2 This SOP aims to support standardisation and continuity between research teams and increase awareness as to how to maintain trial documents in accordance with Good Clinical Practice (GCP) and local procedure.

1.3 For LTHT and UoL Sponsored non-CTRU / Clinical Research Organisation (CRO) managed CTIMPs, it is the responsibility of the Chief Investigator (CI) / delegated staff member to ensure the file is actively maintained and updated until trial closure.

1.4 ICH GCP section 8.1 states that the essential documents to be filed are those "which individually and collectively permit the evaluation and conduct of a trial and the quality of the data produced. These documents serve to demonstrate compliance of the Investigator, Sponsor and Monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements."

1.5 A TMF should be established at the beginning of a trial and maintained throughout the trial's lifetime to ensure it contains all essential documents.

1.6 Every trial is different therefore the content of each TMF may vary. This SOP is designed to support researchers with decisions related to the set up and maintenance of an individual trial.

1.7 This SOP will provide additional detail to compliment the template TMF index available from the Quality Assurance (QA) department and R&I website; highlighting further information that may be relevant.

Section B: Applicability

1.1 This SOP is applicable to all members of staff working on non-CTRU / CRO managed CTIMPs sponsored by the UoL or LTHT. *(Note - A separate process is in place for CTRU managed trials, please liaise directly with your CTRU contact for further information).*

1.2 The Chief Investigator has ultimate responsibility for ensuring that all applicable site staff adhere to this SOP.

Section C: A Researchers Guide to Trial Documentation

1.0 Setting up your Trial Master File (TMF):

1.1 The initial approvals, forms, correspondence and supporting documentation submitted as part of the trial set up process must be retained and stored for future reference. It is therefore recommended you set up your TMF at this time point.

1.1 The file must contain **all essential documents** pertaining to the trial. A minimum list of documents which must be maintained and filed can be located in section 8 of the ICH GCP E6 document (http://ichgcp.net/8-essential-documents-for-the-conduct-of-a-clinical-trial). This may be used as a checklist, **however this is not a definitive list**.

1.2 The TMF should be labelled with the trial title, R&I number and any other trial identifiers. You should label each file / box / binder with the volume number and sections contained e.g. TMF, Vol 1 of 2, Sections 1-7.

1.3 Each file should contain a contents page for easy navigation. It is also recommended that dividers are used to clearly identify sub sections.

1.4 The TMF should be located in a locked storage facility with access restricted to research staff.

1.5 Prior to commencing the trial please plan how much storage space will be required, taking into account the volume of paperwork likely to be generated (e.g. volume of CRFs, on-going correspondence etc.).

2.0 Filing and updating documentation throughout your trial:

Key TMF sections have been outlined below, with guidance as to what documentation must be filed:

2.1 Personnel and Key Contacts:

2.1.2 This section should list the main contact details for the trial including (where appropriate): the CI / PI, Sponsor, Trial Coordinator / Assistant, Data Manager, Lead Pharmacist.

2.1.3 This list **must be updated** when any changes to the contacts occur.

2.2 Protocol (final and amendments):

2.2.1 The initial protocol and any amendments must be reviewed and agreed by the trial Sponsor **prior** to submission to the Research Ethics Committee (REC) / Health Research Authority

(HRA) / Medicines and Healthcare products Regulatory Agency (MHRA). All approved versions should be filed within this section of the TMF.

2.2.2 All draft versions of the protocol must also be filed in the TMF for audit trail purposes.

2.2.3 As per GCP requirements (E6 section 8.2.6), the trial protocol must be signed to document Investigator and Sponsor agreement to the protocol and any subsequent amendments. Evidence of this must be filed in the TMF.

2.2.4 All formal trial documents should be appropriately version controlled using the document footer. Please refer to ***'QCRES_05_Researchers Guide to Version Control for Trial Documentation'*** for further information on version control.

2.2.5 Superseded documents should always be marked as such to avoid accidental misuse by striking a line through the front of the document and annotating as "superseded". These must be filed in descending date order behind the current protocol or in a separate section of the TMF if required.

2.2.6 For guidance on protocol contents/format please see the template protocol on the HRA website.

2.3 Blank Patient Information Sheet (PIS), Informed Consent Form (ICF) and GP letter (final and amendments)

2.3.1 Copies of all template versions of the PIS / ICF and GP letter used throughout the trial must be stored in the TMF (with all previous versions marked as superseded).

2.3.2 All information provided to the patient must be localised with the appropriate LTHT headers before use.

2.3.3 The PIS, ICF and GP letter must be appropriately version controlled - please see ***'QCRES_05_ Researchers Guide to Version Control for Trial Documentation'*** for further information.

2.3.4 For information on how to construct a PIS and ICF and what information should be included, please see the template versions located on the R&I / REC / HRA website.

2.4 Other Patient Related Documentation

2.4.1 Any other patient facing documentation used by the trial (e.g. patient ID card, diary card, adverts, posters, questionnaires) must also be filed in the TMF.

2.4.2 Template versions of these documents should be stored in the TMF as master copies and must be appropriately version controlled and ethically approved prior to use.

2.5 Original Signed Consent Forms

2.5.1 Within LTHT it is usual practice that original signed consent forms are stored in the TMF with a copy provided to the patient and a copy filed within the patients' medical notes (along with copies of the PIS and GP letter). However, as requirements may vary between trials, **please consult the trial protocol prior to obtaining consent.**

2.5.2 Any member of staff obtaining consent for a CTIMP must:

- Have completed NIHR GCP Training
- Be delegated to obtain consent by the CI / PI **prior to undertaking the task**
- Be appropriately qualified and permitted to undertake the task (e.g. research nurses are only permitted to obtain consent if this is clearly stated in the trial protocol and REC application).

2.5.3 Whilst obtaining consent and / or filing signed consent forms please check that:

- All fields are complete and refer to the correct ethically approved PIS in use.
- Both the Investigator and patient have signed the form on the same date (a patient must **personally sign and date** their part of the form).
- The member of staff obtaining consent is on the staff delegation log.
- All boxes are initialled by the patient (none left blank or ticked rather than initialled).

2.5.4 Errors in consent should be rectified if possible and explained via a file note if necessary. Deviations to the consent process must be reported to QA in accordance with ***'QCRES_02_ Researchers Guide to Protocol Deviations, Violations and Potential GCP Breaches'***.

2.6 Contracts and Financial Agreements:

2.6.1 Contracts (signed copies) must be held in the TMF to document any agreements between the investigator/institution, Sponsor and third party subcontractors.

2.6.2 The Sponsor QA office **must review and approve** all third party agreements, including any changes to previously signed versions. The sign off and associated correspondence must be stored within the TMF as evidence of Sponsor oversight.

2.7 Sponsor Correspondence and Local Approvals:

2.7.1 All relevant Sponsor correspondence and documentation must be stored in the TMF. Examples include, **but are not restricted to:**

- "Confirmation of Sponsorship" letter
- QA Review Form(s)
- Risk Assessment Forms
- Initiation Visit Report

2.7.2 The LTHT Conformation of Capacity and Capability (CCC) (previously R&D Approval Letter for trials set up prior to April 2016) must be filed for audit trail purposes.

2.7.3 Local approvals (e.g., Pharmacy "Able to Support" letter, evidence of approval from all applicable support departments) must also be filed in the TMF when received.

2.7.4 All relevant correspondence between the research team / R&I and Sponsor must be filed with additional documentation / correspondence added throughout the life of the trial.

2.8 MHRA, REC and HRA Approvals and Correspondence:

2.8.1 **All documentation and correspondence** relating to MHRA, REC and HRA approvals must be filed in the TMF for confirmation and audit trail purposes.

2.8.2 Examples of documents that must be filed include:

- MHRA Clinical Trials Application
- IRAS Application
- Statement of Activities
- Schedule of Events
- Cover letters
- MHRA Grounds for non-acceptance / REC Provisional Opinion and the research team's subsequent response
- Approval letters

2.8.3 All trial-specific files held by support departments (e.g. pharmacy, laboratories) must function as a standalone file and include all approval documentation and associated correspondence.

2.10 Amendment Documentation and Correspondence

2.1.1 All relevant documentation and associated correspondence for **all amendments** to the trial must be filed in the TMF for audit trail purposes. Please see ***'QCRES_03_Researchers Guide to Notification of Amendments for UoL / LTHT Sponsored CTIMPs'*** for a definitive list of documents to be filed.

2.1.2 All relevant amendment documentation and associated correspondence must also be filed in any trial-specific filed held by support departments (e.g. pharmacy, laboratories).

2.11 General Correspondence

2.11.1 Relevant communication **must** be filed to document any agreements or significant discussions regarding the trial administration, protocol violations, potential serious breaches, trial conduct and adverse event reporting.

2.11.2 Any emails, letters and newsletters which contribute to the reconstruction of the trial must be filed.

2.11.3 The team should avoid duplication (e.g. chain emails) and file in date order with the most recent communication on top.

2.12 Staff Authorisation Log / Delegation Log and CVs / GCPs:

2.12.1 The staff delegation log allows the CI / PI to delegate specific trial tasks to members of the research team.

2.12.2 The tasks assigned must be appropriate to the skills, experience and qualifications of the member of staff. To evidence this, signed and dated CVs and GCP training certificates must be filed for every member of staff listed.

2.12.3 For further information please see ***'QCRES_04_Researchers Guide to Appropriate Delegation of Duties for UoL / LTHT Sponsored CTIMPs'***.

2.13 Screening Logs and Patient ID log:

2.13.1 A "Trial Screening Log" or "Pre-Screening Log" should be used to record patients who were approached / screened but not entered onto the trial (e.g. they later declined to participate or failed pre-screening).

2.13.2 Full names and identifiable information **must not** be recorded and stored in the TMF for any patient who **has not consented** to the trial (initials and date of birth are acceptable). **This log must be updated in real time.**

2.13.3 The reason why a patient was not consented / randomised should be captured on the log to identify recruitment patterns or problems with the trial design (e.g. if numerous patients fail the same inclusion / exclusion criteria a protocol amendment may be required).

2.13.4 A Patient Identification Log must also be maintained and filed confirming which patients entered the trial. Typical fields include: patient name, patient trial number, consent date and randomisation date. **This log must be updated in real time.**

2.13.5 Patient ID logs **must not** be sent off the NHS site (e.g. to the trial sponsor) so as not to breach patient confidentiality.

2.14 Pharmacovigilance:

2.14.1 The trial protocol must include a safety reporting section explaining how both Adverse Events (AEs) and Serious Adverse Events (SAEs) are defined and reported. For further guidance please see ***QCRES_01_Pharmacovigilance for Researchers for UoL / LTHT Sponsored CTIMPs'***.

2.14.2 Blank Serious Adverse Event (SAE) Forms and reporting procedures should be filed in the TMF. Please ensure the most current versions of these are filed.

2.15 Protocol Deviations and Serious Breaches

2.15.1 All deviations / suspected serious breaches of GCP or the trial protocol must be reported to QA as per ***'QCRES_02_Researchers Guide to Protocol Deviations, Violations and Potential GCP Breaches'***.

2.15.2 Blank copies of the current ***CTT20*** deviation reporting form must be filed in the TMF.

2.15.3 Completed deviation / serious breach reporting forms alongside all correspondence must be filed in the TMF for audit trail purposes. Evidence of any corrective actions implemented as a result of the deviation must also be present for audit trail purposes.

2.16 Investigational Medicinal Product (IMP) – Accountability Logs, SPC and IBs

2.16.1 Pharmacy related documents (e.g. drug accountability log, shipping records, disposal logs, dispensing procedures, temperature logs) are usually maintained in a separate file held by the clinical trials pharmacy department. If these documents are to be held in pharmacy please add a file note to the TMF documenting their location.

2.16.2 Drug Accountability Logs must fully document what medication was received by the site, patient, when and where, as well as any medication returned or destroyed. The running total of medication held at pharmacy should also be recorded.

2.16.3 Pharmacy must maintain temperature records to confirm the IMP is stored within the correct parameters as instructed by the dispensing procedure, Investigator Brochure (IB) or Summary of Product Characteristics (SPC). If the IMP is to be stored with the research team, separate temperature records must be maintained. Please liaise with LTHT pharmacy for guidance.

2.16.4 Any equipment used (i.e. temperature probes and fridges) must be regularly serviced and calibrated for use. Please ensure all servicing and calibration records are filed.

2.16.5 If your department is responsible for storing or dispensing the IMP (e.g. IMP is stored in clinic or theatre for the duration of the trial), separate accountability records should be maintained to ensure the whole IMP pathway is documented.

216.6 IBs / SPCs for all IMPs used in the trial must be stored in the TMF and updated as required (please see ***'QCRES_09_Researchers Guide to Reference Safety Information (RSI)'***). Any other required documents such as Good Manufacturing Documents, Qualified Person Release, Certificate of Analysis, Manufacturing Authorisation and IMP License must also be filed.

2.17 Central Laboratory and Local Analysis of Biological Samples:

2.17.1 A laboratory agreement must be in place for all laboratories to be used during the trial (including internal UoL / LTHT labs). This should include details of any accreditations the facility has, the SOPs in use and staff training. This should be signed off by the head of department, Sponsor (where applicable) and investigator and filed in the TMF to document that the facility is capable of conducting the required testing to the appropriate standard.

2.17.2 If external laboratories / analysis are used, third party contracts must be established with the organisation and agreed with Sponsor QA. These must be filed in the TMF.

2.17.3 For any lab equipment used (e.g. freezers, centrifuges), please ensure all calibration records are stored in the TMF or record an alternate location via a file note.

2.17.4 Please store copies of the trial specific lab sample request forms in the TMF along with confirmation of sending / receipt.

2.17.5 Support departments must retain all documentation and trial specific results for the agreed time period (or until otherwise instructed). Where possible, all trial related documentation should be held together allowing it to be easily accessed for auditing / data verification purposes.

2.17.6 Researchers must be aware of the location of all support department documents as these form part of the overall TMF. Should the Sponsor or MHRA request to see support department documentation, this **MUST** be provided along with the main TMF.

2.18 Randomisation and Un-blinding

2.18.1 Where applicable, randomisation information, code break instructions, template un-blinding forms, out of hours contacts and registration numbers / confirmation of randomisation must be filed in the TMF.

2.19 Case Report Form:

2.19.1 A blank template of the current CRF should be stored in the site file alongside any previous versions (must be marked as superseded for audit trail purposes).

2.19.2 Only information requested on the CRF should be recorded, and it **should not contain any patient identifiable information**.

2.19.3 The CRF should directly match the protocol and only record information which is specifically required.

2.20 Quality Assurance / Audit / Inspections and Monitoring:

2.20.1 A record of any monitoring visit or audit reports must be kept within the TMF.

2.20.2 All monitoring documentation and correspondence (e.g. Notification of Monitoring Visit, Monitoring Action Reports, QA Follow Up Report) must be filed in the TMF.

2.20.3 A full audit trail of completed responses showing any corrective actions that were implemented must also be filed in the TMF for confirmation purposes.

2.21 TSC / DMC Correspondence

2.21.1 Trial Steering Committees (TSC) must be held in accordance with the protocol with all meeting minutes and documentation of any significant discussions stored in the TMF. Please see ***'QCRES_10_Researchers Guide to Trial Steering Committees and Data Monitoring Committees'*** for further guidance.

2.22 Database and Data Record Logs

2.22.1 A blank copy of any trial database and any associated documentation (e.g. work instructions) and correspondence must be stored within this section. Evidence of any database validation and QC checks must also be filed.

2.23 Statistical Analysis Plan

2.23.1 A copy of the statistical analysis plan or relevant section of the protocol describing the statistical considerations of the trial should be filed in the TMF.

2.24 Safety Reporting:

2.24.1 Copies of Development Safety Update Reports (DSUR) sent to the MHRA and Annual Progress Report sent to the REC must be filed alongside evidence of submission.

2.24.2 For guidance on reviewing and updating a trial's Reference Safety Information (RSI) in line with the DSUR reporting timelines, please see ***'QCRES_09_Researchers Guide to Reference Safety Information (RSI)'***.

3.0 Documentation to be stored following trial closure:

3.1 Trial Closure

3.1.1 Please complete and file the declaration of end of trial form once the end of trial definition outlined in the protocol is met. **A copy of this form must be sent to the Sponsor QA office for confirmation purposes**.

3.1.2 The Sponsor Close-out Monitoring Visit will ensure the TMF is complete and ready for archiving. A copy of the Close-out Monitoring Report must be filed.

3.1.3 Within one year of the declaration of end of trial, a final study report must be submitted to the MHRA and Sponsor QA office.

3.1.4 For further information, please see ***'QCRES_08_Researchers Guide to End of Trial Procedures'***.

3.2 Publications

3.2.1 Once data from the trial has been published any relevant documentation must be filed within the TMF and a copy forwarded to Sponsor QA for their records.

3.3 Archiving

3.3.1 Please refer to the archiving section of your trial protocol or the separate archiving SOP available from QA / R&I website.

Section D: References

MHRA Good Clinical Practice Guide 2012
E6 Guideline for Good Clinical Practice version 2.1 August 2011
QCRES_01 Researchers Pharmacovigilance
QCRES_02 Researchers Guide to Protocol Deviations Violations and Potential GCP Breaches
QCRES_03 Researchers Guide to Notification of Amendments for UoL/LTHT Sponsored CTIMPs
QCRES_04 Researchers Guide to appropriate Delegation of Duties for UoL LTHT Sponsored CTIMPs
QCRES_05 Researchers guide to Version Control for Trial Documentation
QCRES_08 Researchers Guide to End of Trial Procedures
QCRES_09 Researchers Guide to Reference Safety Information (RSI)
QCRES_10 Researchers Guide to Trial Steering Committees and Data Monitoring Committees

Section E: Acronyms

CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
IB	Investigator Brochure
ICF	Informed Consent Form
LTHT	Leeds Teaching Hospitals NHS Trust
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
PIS	Patient Information Sheet
QA	Quality Assurance
R&I	Research and Innovation
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operation Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TSC	Trial Steering Committee
UoL	University of Leeds

Section F: Previous versions of Document

Version no.	Valid from	Approved by	Date approved
1.0	21/10/2013	Stephen Smye & Clare Skinner	17/01/2014 & 20/01/2014
2.0	28/09/2016	Clare Skinner & Louise Brook	28/09/2016