UNIVERSITY OF LIVERPOOL

Clinical Directorate Clinical Research Governance Team

Standard Operating Procedure

Maintaining a Trial Master File for CTIMPs

SOP015

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1. Introduction

A Trial Master File (TMF) is a standard filing system which allows the effective storage and location of essential documents required for Clinical Trials of Investigational Medicinal Products (CTIMPs). The filing system can be in the form of a single project file or a number of files / filing cabinets, depending on what is deemed most appropriate for the particular study. The regulatory and approvals documents within the TMF should be maintained alongside case report forms and source documentation.

The requirement to maintain a set of essential documents within a TMF comes from the International Conference on Harmonisation Good Clinical Practice (ICH GCP), an internationally recognised standard for the initiation, conduct, recording and reporting of clinical research involving human participants, particularly drug trials, the principles of which were adopted into UK law in the Medicines for Human Use (Clinical Trials) Regulations 2004 (the Regulations). As a consequence, it is a legal requirement to maintain a TMF for all Clinical Trials of Investigational Medicinal Products (CTIMPs) within the scope of the Regulations.

ICH GCP describes Essential Documents as:

"Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a clinical trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of Good Clinical Practice and with all the applicable regulatory requirements."

Although the Regulations do not indicate that all detailed aspects of ICH GCP must be followed, it is widely recognised that essential documentation is the primary quality system for validating the safe and appropriate initiation and conduct of CTIMPs. Furthermore, whilst demonstrating compliance with ICH GCP, the filing of regulatory and approvals documents in an orderly manner greatly assists the smooth running of a project and any such research evaluation and/or audit by a sponsor or regulatory authority (such as the MHRA).

A list of essential documents required for a TMF can be found in Section 8 of the ICH GCP Guidelines[1].

2. Scope of Procedure

The purpose of this SOP is to describe the essential documentation that should be maintained within a TMF, as required under the ICH GCP guidelines.

3. Who

This SOP is aimed at Chief Investigators (CIs), Trial Co-ordinators or study team members who have been delegated the responsibility for creating and maintaining a TMF of University of Liverpool (the University) (co)-sponsored CTIMPs. Documentation of the individual responsible for TMF

[1] https://ichgcp.net/8-essential-documents-for-the-conduct-of-a-clinical-trial

maintenance for a given trial/study will be recorded in the signature and delegation log held within the Trial Master File (see SOP006[2]).

4. When

The TMF should be established as soon as possible after funding is confirmed and before the first patient is recruited, and should be maintained and updated throughout the study.

5. Essential Documents and TMF Initiation and Maintenance

Individuals with responsibility for creating and maintaining a CTIMP TMF are directed to Section 8 of the ICH GCP Guidelines[3] Additional documents are identified in Appendix 1 (Table 1) which are recommended by the University for inclusion in the TMF. An example TMF checklist is available via the Clinical Research Governance Team (TEM023[4]).

As documents may need to be updated during a project it is important that amendment chronologies are kept, indicating the changes and the dates they are implemented. Old documents should be retained in the TMF alongside the amended version(s). Please remember that any substantial amendments to documents, such as the protocol or informed consent forms, should be approved by the relevant authorities (the research Sponsors, RECs, MHRA etc.) as appropriate, prior to implementing any changes to the trial.

For the purposes of audit and inspection any essential documents that have been stored electronically should be made available in paper format during the inspection. The creation of an electronic TMF must be discussed with the Sponsor before the trial opens.

It is noted that some documents are intended to be viewed electronically such as emails and Excel Spreadsheet trackers.

Care should be taken when compiling these documents for the TMF, and consideration should be given to the best format to present these for audit and inspection. Some recommendations are below;

Printed email correspondence;

- Ensure accompanying attachments are also printed and held either with the printed email or with a statement of location file note describing where the documents can be found
- Ensure emails that include comments typed in colour are printed in colour so the comments can be identified
- Ensure the printed email contains the date of the original email, rather than the date of printing

Electronic signatures

[2] Roles and Responsibilities for University of Liverpool Sponsored Research
[3] https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf
[4] Example Checklist for the Trial Master File Contents

Ensure the audit trail is provided with any signatures provided electronically. If signatures were collated using DocuSign™, BoxSign, Adobe Acrobat Sign or another validated e-signature platform then the certificate or summary of completion should be printed and filed.

If the signature was provided by an email approval the email should contain the following information;

- "Please accept this email as my electronic signature for approval of the following document:"
- Document title
- Document version and date
- Document reference number (if applicable)
- Date of approval
- Name
- Job title

Excel Spreadsheets

Where an Excel Spreadsheet it utilised as a live tracker for amendments, safety reporting, site opening etc., it is not expected these are printed and held in the paper TMF. Spreadsheets often contain a number of columns and they cannot be easily printed to be viewed on paper. Printing also removes the ability to search or filter the data and version control and page numbers are often lost. Where an Excel Spreadsheet is in use, there should be a Statement of Location in the relevant section of the TMF, and auditor/inspector access should be arranged. Storage of Paper TMFs

As some of the documents within a TMF will be originals and/or contain confidential data, it is important that they are retained within a secure place, with restricted access. It is recognised as best practice to store documents within a locked cupboard within a locked room. Documents should be maintained in a legible condition, with prompt retrieval possible. It is desirable to store all sections of the TMF in the same locations, however on the occasion that this is not possible the TMF index must adequately identify where sections are held to ensure prompt retrieval.

6. Use of electronic TMF

It is acceptable for a TMF to be either completely electronic, or a mixture of paper and electronic, provided this structure is sufficiently defined. Where an eTMF is used, the same controls must be available for managing the eTMF as for a paper TMF in terms of security, control over unauthorised edits and access, ease of retrieval of documents etc.

If an eTMF is to be utilised for a trial the Sponsor will complete FORM018 Electronic Trial Master File requirement checklist to ensure suitability of the system. This may be conducted as part of a Vendor Selection Audit, or on a trial by trial basis as appropriate.

Use of a shared departmental drive, or file sharing software (such as SharePoint) is not generally acceptable, and appropriate controls and security must be in place when using an eTMF.

It is recommended that an eTMF be a document management system containing stringent controls including approval of documents via a workflow system, password enabled electronic signatures, the system must have an audit trail in place to identify date/time/user details for creation, uploading, approval and changes to a document. It would also be recommended that a system for locking documents or the entire eTMF is considered to prevent changes to documents, such as when the eTMF is archived. Finally, all members of staff involved in the conduct of the trial must receive training in using the system and this should be documented.

The eTMF could contain digital documents in their original format, potentially with digital signatures, or records that have been converted from another format (such as paper documents that have been converted to digital images, which may contain wet-ink signatures). Records that only exist in a digital format are often only printed onto paper at the time of an inspection as they normally are accessed in their digital form. This can result in loss of any version control applied in the computer system (e.g. dated filename).

Unlike a paper TMF, documents loaded into the eTMF will require the addition of metadata to enable the document to be identified within the system. Metadata is that data that is associated with the document (but not the document itself) so typically would be identifying codes for the trial, site, protocol, product etc. The type of metadata is recommended to be formally defined to ensure consistency across all documents.

The eTMF will require validation to demonstrate that the functionality is fit for purpose, with formal procedures in place to manage this process and for change control. The validation of the system should follow previously published standards. The documentation for this process must be retained.

7. Roles and Responsibilities

It is the Sponsors' responsibility to ensure that that an appropriate TMF is in place.

Where the University is the Sponsor of a CTIMP managed via a CTU the function of creation and maintenance of the TMF will be formally delegated to the CTU via appropriate contracts detailed below;

- For Sole Sponsored studies being managed by Liverpool Clinical Trials Centre (LCTC) this will be via TEM033 LCTC Sole Sponsorship Internal Delegation Plan;
- For Sole Sponsored studies with an external CTU this will be via a Collaboration Agreement and TEM034 External CTU Communication plan and division of responsibilities and functions or a CTU document if all responsibilities are covered.

Where the University is the Sponsor of a CTIMP not being managed via a CTU the function of creation and maintenance of the TMF will be formally delegated to the CI via the Sponsorship Approval letter. The CI may then further delegate this to an appropriate member of their study team.

8. Abbreviations

CI	Chief Investigator
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
ICH GCP	International Conference on Harmonisation Good Clinical Practice
LCTC	Liverpool Clinical Trials Centre
MHRA	Medicines and Healthcare products Regulatory Agency
TMF	Trial Master File
The University	University of Liverpool

9. Associated Documents and References

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004 No. 1031)

ICH Good Clinical Practice guidance

SOP006 Roles and Responsibilities for University of Liverpool Sponsored Research

TEM023 Example Checklist for the Trial Master File Contents

TEM033 LCTC Sole Sponsorship Internal Delegation Plan

TEM034 External CTU Communication plan and division of responsibilities and functions

FORM018 Electronic Trial Master File requirement checklist

10. Training and Resources

CIs, students, trial coordinators and other members of University Staff involved in set-up, management and conduct of clinical research sponsored by the University of Liverpool should be aware of and familiar with this SOP. Training can be provided by the Clinical Research Governance Team upon request.

11. Monitoring and Audit

Compliance with this SOP will be audited periodically by the Clinical Research Governance Team as part of the annual audit plan.

12. Appendix 1 - Additional Documentation Recommended by the University to be retained in the Trial Master File

Title of Document Referenced by ICH/GCP	Purpose
Before the clinical phase of the trial commences. During this planning stage the following documents should be generated and should be on file before the trial formally starts	
Risk Assessment	Potential hazards should be identified for every clinical trial and the risk of harm assessed; All Clinical trials therefore need to undergo a risk assessment, which may then be used to plan the details of trial management and the approach to, and extent of, monitoring in the trial
Before and during the clinical conduct of the trial In addition to having on file the above documents, the following should be added to the files before during the trial as evidence that all new relevant information is documented as it becomes available	
Records of meetings of the Trial Management Group (TMG)	The Trial Management Group normally includes those individuals responsible for the day-to-day management of the trial, such as the chief investigator, statistician, trial manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.
Records of Meetings of Trial Independent Oversight Committees - Trial Steering Committee (including their agreed terms of reference)	The overriding remit of these committees is to safeguard the interests of trial participants. The role of the Trial Steering Committee (TSC) is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The TSC will have members who are independent of the investigators, in particular an independent chairperson. Recommendation decisions to the Sponsor about continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the Trial Steering Committee
- Data Monitoring Committee (including their agreed charter)	The role of a Data Monitoring Committee (DMC) is to review the accruing trial data and to assess whether there are any safety issues that should be brought to participants' attention or any reasons for the trial not to continue. The Data Monitoring Committee should be independent of both the investigators and the funder/sponsor and should be the only body that has access to unblinded data. It normally makes recommendations to the TSC.