Imperial College London

Research Governance and Integrity Team

Imperial College Healthcare NHS Trust

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Essential Documentation and the Creation and Maintenance of Trial Master Files

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Version 1.0	03 Jul 2006	Annual Review
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Version 6.0	29 Nov 2012	Annual Review
Version 7.0	18 Feb 2015	Scheduled Review
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Version 9.0	19 Oct 2020	Scheduled Review Template removed and administrative changes to SOP. JRCO name change to RGIT.

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1. PURPOSE

This SOP describes the essential documentation that should be maintained within a Trial Master File (TMF), as required under the International Conference on Harmonisation Good Clinical Practice (ICH GCP).

The primary focus of the SOP is clinical trials of investigational medicinal products (CTIMPs) that fall under the remit of the Medicines for Human Use (Clinical Trials) Regulations 2004 (called "Clinical Trials Regulations"). However, it is also relevant for any project conducted within the NHS, which has to meet the UK Policy Framework for Health and Social Care Research, and other clinical investigations that may have an impact on the safety and well-being of human participants.

2. INTRODUCTION.

A TMF is a standard filing system which allows the effective storage and location of essential documents – the large volume of regulatory and approvals documents needed for clinical research. 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. 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 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 in UK law in the Medicine for Human Use (Clinical Trials) Regulations 2004. As a consequence, it is a legal requirement to maintain a TMF for all clinical trials of Investigational Medicinal Products (IMPs) within the scope of the Regulations.

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 clinical trials of IMPs. 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 research evaluation and/or audit by a sponsor or regulatory authority (such as the MHRA).

Importantly, although it is only a legal requirement to maintain a TMF for clinical trials of IMPs, the principles should still apply for the filing of study related documentation for ALL research projects within the NHS, which have to meet the UK Policy Framework for Health and Social Care Research, and any other clinical investigations which may have an impact on the safety and well-being of human participants.

Please note, however, that not all documents will be of relevance to every project - the content of the TMF will therefore differ according to the nature of the study. For example, for clinical trials of IMPs, most of the essential documents must legally be maintained whereas, for solely observational studies, certain documents will not be applicable. We have tried to indicate this wherever possible. You should therefore interpret the guide in the context of your own individual project.

If after reading the guide anything is unclear or you would like to discuss study documentation in greater detail, please contact a member of the Research Governance and Integrity Team.

3. PROCEDURE

3.1. Essential Documents and TMF Initiation and Maintenance

A TMF should be established as soon as possible after an outline protocol/proposal is available and/or first contact is made with a research sponsor. The Chief Investigator is responsible for setting up, maintaining, storing and archiving the Trial Master File. This duty may be delegated to another member of staff on the Delegation and Signature Log.

Appendix 1 (RGIT_TEMP_013) lists the essential documents that should be maintained within a TMF. As noted above, the specific documents filed will differ according to the nature of a study. The list is not exhaustive, and it is strongly recommended that any approvals and communication not listed here should also be retained. The TMF should be held at the lead investigation site, and copies of relevant documents should be kept at participating sites. There is an example checklist of essential documents in **Appendix 2 (RGIT_TEMP_014)** that you should include with each project file.

Document management

As documents may need to be amended during a project, it is important that amendment chronologies are kept, indicating changes and the dates they are implemented. 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 Sponsor, RECs, HRA, MHRA etc.), as appropriate, **prior** to implementing any changes to the project/trial. The original document is source data and must always be retained. Strikethough old versions of documents and mark as superseded to ensure they are not mistaken for current documents.

If any documents are filed separately from the TMF, a File Note should be kept in the TMF detailing where the document is filed, e.g. drugs details may be filed in the pharmacy.

3.2. Storage

As some documents within a TMF will be originals and/or contain confidential data, it is important that they are retained in a secure place, with restricted access. All members of the research team should have access to the TMF. It is recognised best practice to store documents in a locked cupboard within a locked room. Documents should be maintained in a legible condition, with prompt retrieval possible. For Imperial sponsored CTIMP studies and studies subject to MHRA inspections, e-TMFs are not permitted by the Sponsor and it is necessary to print and retain hard copies of all documents.

For non-CTIMP studies, e-TMFs may be considered, provided they are readily available (including to auditors and monitors) for the entire duration of the study and throughout the archiving period. They must contain accurate documents and ensure that all study information is recorded, handled and stored in a way that allows accurate reporting, interpretation and verification of all study data and meet the requirements and standards set out in this SOP.

3.3. Archiving

It may be necessary for the results of a clinical research project/trial to be examined and checked after it has finished so essential documents should be archived in an easily accessible way and readily available on request. For clinical trials of IMPs, archiving should occur after the trial has undergone a final closeout visit (this may be initiated by the Sponsor if they feel it is warranted) and the closeout report is issued.

All essential documents should be boxed and clearly labelled with the following information:

- Project/trial name
- Reference Number
- Site Number (if applicable)
- Chief Investigator
- Lead Site
- Date of Archive

The documents should be stored in a secure room, with appropriate environmental controls (and adequate protection from fire, without water sprinkler systems, water etc.), and access only by authorised personnel. It is recommended that all trial related documents should be centrally archived to prevent accidental damage, amendment, loss or destruction. Any change in the ownership and location of documentation should be documented in order to allow the tracking of the stored records. If archived documents are reviewed at a later date, it is good practice to record who, what documents were reviewed and the date they were accessed in an archive index/log and retain it with the TMF.

Legally for clinical trials of IMPs (CTIMPS), all trial-related documents should be kept for a minimum of 5 years (and at least one copy of trial data must be kept for the lifetime of any product whose licensure depends on this data). If a particular trial has been sponsored by a pharmaceutical company, the company should be contacted to check whether it is appropriate to destroy the records.

Although there are legally required retention times, the Imperial College London Retention Schedule states that primary research data should be retained for a minimum period of 10 years following completion of the study. This refers to all forms of research and not just clinical trials. For Imperial College Healthcare NHS Trust sponsored studies, the retention period is 5 years following completion of the study. Further details on archiving can be found in RGIT_SOP_019, Archiving Study Documents. Researchers must also be aware that for advanced therapy trials of IMPs ATIMPS all trial-related documents should be kept for a minimum of 30 years.

4. REFERENCES

ICH E6 (R2) Good clinical practice (cited 22 June 2020)

Medicines - The Medicines for Human Use (Clinical Trials) Regulations (cited 02 July 2020)

UK Policy Framework for Health and Social Care Research (cited 22 June 2020)

RGIT website:

RGIT - About Us (cited 08 October 2020)
RGIT_SOP_019 - Archiving
Imperial College London - Retention Schedule (cited 22 June 2020)

Clinical Trials Toolkit - TMF (cited 15 Sep 2020)
Clinical Trials Toolkit. Archiving (cited 15 Sep 2020)

Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic)(cited 22 June 2020)

5. APPENDICES

The following Appendices list the following Templates associated to this SOP which can be found on the SOP, Associated Documents & Templates page.

Appendix 1: Essential Documents to be maintained with a TMF – RGIT_TEMP_012
Appendix 2: Example Checklist for Inclusion with Research Project Files – RGIT_TEMP_013
Appendix 3: RGIT Contact Details – RGIT_TEMP_014