Standard Operating Procedure for the Preparation and Maintenance of the Trial Master File (TMF) and Investigator Site File (ISF) for CTIMPs Sponsored by UCL

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Please check the JRO website to ensure that this version of the SOP is the current version, **https://www.ucl.ac.uk/joint-research-office/resources-and-templates**	

Revision Chronology:			
SOP ID Number:	**Effective Date:**	**Reason for Change:**	**Author:**
BRD/06/INT/S07/00	30/06/2006	N/A	Vicky Cooper
JRO/07/S03/00	18/06/2007	Administrative changes to include updating Biomedicines R&D Unit to Joint UCL/UCLH Biomedical Research Unit (JRO) and to implement the new numbering system. It was the original version for the new Unit.	Adeeba Ashgar
JRO/INV/S02/01	01/09/2009	To update the existing SOP for setting up the Investigator Site File. To implement new JRO formatting and numbering system as reflected in SOP on SOPs (JRO/SPON/S01/02).	Alison Evans and Ann Cochrane
JRO/INV/S02/02	22/01/2010	Format the SOP to the new UCL SOP template. Review the Investigator Site File Index	Ann Cochrane and Gurjinder Kahlon
JRO/INV/S02/03	01/02/2010	Error of previous omission from V02 regarding the “open to recruitment letter”	Ann Cochrane and Gurjinder Kahlon
JRO/INV/S02/04	17/10/11	Clarify who is maintaining the TMF and simplifying the SOP	Shruti Aggarwal and Gurjinder Kahlon
JRO/INV/S02/05	10/10/14	Chronological relay (arrangement in order of occurrence) of procedural instructions. Update of templates and associated logs to the SOP (including addition of TMF and ISF indexes and review templates	Tendai Nelson
JRO/INV/S02/06	15/09/17	Updated document list and other minor changes to the procedures.	Shriram Velamuri
JRO/INV/S02/07	01/08/2021	Updated regulations in line with post-Brexit arrangements. Updated wording for clarification and to include reference to the IMP/ Pharmacy Site File.	Catherine Maidens

ACRONYMS

CI	Chief Investigator
COA	Compliance Oversight Advisor
CTIMP	Clinical Trial of Investigational Medicinal
GCP	Good Clinical Practice
GP	General Practitioner.
IB	Investigator's Brochure
ICF	Informed Consent Form
ISF	Investigator Site File
IMP	Investigational Medicinal Product
JRO	Joint Research Office (https://www.ucl.ac.uk/joint-research-office/)
MHRA	Medicines and Healthcare products Regulatory Agency
MREC	Main Research Ethics Committee
RM (ATMP)	Regulatory Manager for Advanced Therapy Medicinal Products
PI	Principal Investigator
PIS	Patient Information Sheet
SpF	Sponsor File
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SRA	Sponsor Regulatory Advisor
TMF	Trial Master File

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1. PURPOSE

This Standard Operating Procedure (SOP) describes the requirements for the establishment of a Trial Master File (TMF) and Investigator Site File (ISF) for Clinical Trials of an Investigational Medicinal Product (CTIMP).

2. SPONSOR'S POLICY ON SOPs

All JRO SOPs will be produced, reviewed and approved in accordance with the JRO SOP on SOPs.

The UCL/UCLH Joint Research Office (JRO) is the representative of the Sponsor. The Sponsor will also be referred to as JRO in this SOP.

3. BACKGROUND

All SOPs are written in accordance with applicable GCP requirements as outlined in Directives 2001/20/EC and 2005/28/EC (these Directives were transposed into UK law by SI 2004/1031, SI 2006/1928) and subsequent amendments. Where applicable it incorporates elements of ICH GCP tripartite guidelines (E6).

In addition, for trials with EU and Northern Ireland sites the SOPs will have to be compliant with EU Clinical Trials Regulation No. 536/2014 if/when applicable. For convenience, this document will use the term 'Regulations' to cover the requirements of the UK SI legislation.

Under The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006/1928, Regulation 18 states 'the Sponsor shall keep a **trial master file** for a clinical trial which at all times contain the essential documents relating to that trial'. When UCL acts as Sponsor for a CTIMP, the Sponsor responsibilities are managed by the JRO. Responsibilities for creating and maintaining the TMF are **delegated to the Chief Investigator (CI), Clinical Trial Unit (CTU) or Clinical Research Organisation (CRO) (depending on the trial management set-up and agreement.)**

A TMF must be established at the beginning of the trial in accordance with the requirements of the regulations and supporting documents "Guideline for good clinical practice E6" and the "EMA Guidance on the content, management and archiving of the clinical trial master file (paper and/or electronic)".

The essential documents should be filed in an organised way that will facilitate management of the clinical trial and enable the trial team, as well as monitors, auditors and inspectors to evaluate compliance with the protocol, the trial's conduct and the quality of the data obtained.

3.1. Definitions

Essential Documents – those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.

Trial Master File (TMF) – this should be set up at the beginning of the trial, and the essential documents that make up the file should be kept in a secure but accessible manner. As per JRO procedures, the **preparation and maintenance of the TMF is delegated by the Sponsor to the CI/ CTU/ CRO**.

Investigator Site File (ISF) – this should contain the essential documents necessary for the investigator and the research team at that trial site. As per JRO procedures the **preparation and maintenance of the ISF resides with the Site Investigator.** The ISF will be located at the relevant trial site.

Investigational Medicinal Product/ Pharmacy Site File – this contains a selection of essential documents regarding Investigational Medicinal Product (IMP) management at the Pharmacy of the trial site. The IMP/ Pharmacy Site File will sometimes be incorporated into the ISF instead of being a separate file held at Pharmacy.

Sponsor File (SpF) – this contains a selection of essential documents which confirms compliance with Sponsor SOPs and provide evidence of Sponsor oversight and management of the trials. The SpF is located at the sponsor's office.

Trial Site - is the location(s) where trial related activities are conducted.

4. SCOPE OF THIS SOP

This SOP refers to the essential documentation and the creation of the TMF and Investigator Site File (ISF) for Clinical Trials of Investigational Medicinal Products (CTIMPs).

The scope of this SOP is to give guidance to trial personnel to set up and maintain the TMF and ISF.

Where the maintenance of the TMF and ISF has been delegated to a CTU/ CRO the procedures may follow the CTU/ CRO SOPs, and as such are out of the scope of this SOP.

5. RESPONSIBLE PERSONNEL

The Chief Investigator (CI) is responsible for the set-up and maintenance of all essential documentation related to their trial in the TMF and is responsible for providing the Sponsor with any updated documents as requested throughout the trial until trial closure.

The JRO is responsible for the set-up and maintenance of a Sponsor File, where a selection of essential documents which confirms compliance with Sponsor SOPs and provides evidence of Sponsor oversight and management of the trial are filed. Details pertaining to the establishment of the Sponsor File are outlined in JRO/SPON/S11 SOP for the Preparation of the JRO Sponsor File.

This SOP must be read by all members of the team who are delegated to maintain and file documents in the TMF and ISF. If any questions arise, they should ask the Sponsor Regulatory

Advisor (SRA) / Regulatory Manager for Advanced Therapy Medicinal Products (RM (ATMP) or Compliance Oversight Advisor (COA) at the JRO for advice.

6. PROCEDURES

6.1. Before the trial commences

The Sponsor will provide the trial team with the **JRO Trial Master File (TMF) and Investigational Site File (ISF) Indexes** (associated templates) for the files. These indicate the sections and the essential documents that should be filed.

For **single site trials**, the CI must set up a TMF and a separate ISF according to the indexes provided by the Sponsor.

For **multi-centre trials**, each Principal Investigator (PI) must set up an ISF containing all essential documents applicable to the conduct of the trial at their site.

At the time of **trial set-up**, the CI should have a TMF containing all essential documents (i.e., pertinent to the conduct of the trial as a whole).

At the time of **site initiation**, the CI/PI should have an ISF containing all essential documents (i.e., pertinent to the conduct of the trial at their site).

The trial site may choose to set-up a separate **IMP/ Pharmacy Site File** with a selection of essential documents regarding Investigational Medicinal Product (IMP) management at the trial site. The JRO can provide a **JRO IMP/ Pharmacy Site File Index** (associated template) if required. The pharmacy file may be incorporated into the ISF instead of being a separate file.

The trial team will perform a review of the TMF and ISF (and IMP/ Pharmacy Site File, if applicable) on site, once confirmation of all necessary approvals and other trial documentation are in place.

6.2. During conduct of the trial

The CI or delegated trial personnel must ensure that the TMF is maintained and kept up to date as the trial progresses.

The CI/PI must ensure that the ISF is maintained at site as the trial progresses.

It is the CI's or delegated trial personnel's responsibility to notify all participating sites with the latest study documentation. The PI/ delegated trial personnel at the site are responsible for distributing the study documents to all staff members participating in the research trial at the site.

Documents should be filed in the appropriate sections as per the TMF / ISF Index in a timely manner.

All documents should be filed chronologically within each section to allow the most recent documents to be easily accessed.

Documents should be complete, accurate, legible and unambiguous and signed and dated where appropriate.

Any documents identified as missing must be obtained by the Investigator or the person to whom this task has been delegated.

Superseded documents (e.g., previous versions of Protocols, Investigator Brochures etc.) must be retained in the TMF and ISF but scored through by placing a line to indicate that the document is no longer in use and marked 'superseded'. The document should then be signed and dated by a member of the trial team. Evidence of implementation date of the new version of the document should also be filed where applicable.

If documents are held separately to the TMF or ISF, a file note should document the location of the documents and be filed in the TMF or ISF.

Relevant correspondence that is necessary for reconstruction of key trial conduct activities and decisions should be retained. Correspondence should be filed with the associated documents where appropriate. Only general correspondence not associated with a document should be filed in the 'correspondence' sections of the TMF and ISF.

No patient identifiable data should be filed in the TMF.

The trial team should perform a periodic review of the TMF and ISF (and IMP/ Pharmacy Site File, if applicable) to check it is being maintained and that all essential documents are appropriately filed. The Sponsor may also perform a periodic review of the TMF and ISF on site, or remotely. The reviews can be documented using the **JRO Trial Master File (TMF) / Investigational Site File (ISF) / IMP/ Pharmacy Site File Review Checklists** (associated template).

6.3. Storage of the TMF and ISF

The TMF and ISF must be retained within a secure place with appropriate environmental protections, to ensure completeness and to prevent accidental or premature loss, unauthorised alteration or destruction of documents. Access should be restricted to authorised personnel only.

Storage conditions should ensure that essential records are maintained in a legible condition and can be retrieved upon the request of a regulatory authority.

Upon request of the Sponsor, monitor, auditor, or Regulatory Authority, the Investigator/institution should make available for direct access all requested trial-related records according to local and national legislation.

6.4. After completion or termination of the trial

Archiving of the ISF should occur after all site close out procedures have been completed by the JRO (as per JRO/SPON/SOP21 SOP for Investigators and Sponsor for Site & Trial Close Out procedures). Prior to archiving a full review of the ISF should be carried out by the trial team to ensure all documents are filed and any missing documents are file noted.

Archiving of the TMF should occur after all trial close out procedures have been completed by the JRO (as per JRO/SPON/SOP21 SOP for Investigators and Sponsor for Site & Trial Close Out procedures). Prior to archiving a full review of the TMF should be carried out by the trial team to ensure all documents are filed and any missing documents are file noted.

The contents of the TMF and ISF should be archived in a way that ensures that it is readily available, and directly accessible, upon request by the Sponsor, Auditor or Regulatory Authority.

The TMF should be archived in accordance with JRO/SPON/S21 SOP for Archiving Essential Documentation relating to Clinical Trial of Investigational Medicinal Products (CTIMPs) once the study finishes. Retention periods are outlined in the UCL Records Retention Schedule.
Retention times for Sponsors' records also apply to the records retained by CTUs / CROs or other agents of the Sponsor, unless arrangements have been made to transfer the documents to the Sponsor.

The ISF should be archived as per local procedures, and in accordance with the Clinical Trial Site Agreement and current clinical trial regulations.

7. REFERENCES

1. The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031)
2. The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (SI 2006/1928)
3. Directive 2001/20/EC OF the European Parliament and of the Council of 4 April 2001on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
4. Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such product
5. UK Statutory Instrument 2006, No 1928. The Medicines for Human Use (Clinical Trials) Amendment Regulations.
6. Guideline for good clinical practice E6(R2), Dec 2016
7. EMA Guidance on the content, management and archiving of the clinical trial master file (paper and/or electronic), Dec 2018

8. APPENDICES

None

9. TEMPLATES/LOGS ASSOCIATED TO THIS SOP:

1	Trial Master File Index
2	Trial Master File Review Checklist
3	Investigator Site File Index
4	Investigator Site File Review Checklist
5	Investigational Medicinal Product/ Pharmacy Site File Index
6	Investigational Medicinal Product/ Pharmacy Site File Review Checklist

10. SOP DISSEMINATION & TRAINING

This SOP will be provided to the CI / PIs prior to, or at initiation at the latest. All staff trial team concerned by this SOP will sign the SOP training log (12. SOP TRAINING LOG) part of this SOP. In addition each trial team member should have an “Individual staff SOP and courses log” which will need to be updated once trained on this SOP. These documents should be filed in the ISF.

11. SIGNATURE PAGE

Author and Job Title:	Catherine Maidens, Pharmacovigilance Manager
Signature(s):	DocuSigned by: Catherine Maidens 6A859A9CF4EB497...
Date:	01/07/2021
Authorised by: Name and Job Title	Helen Cadiou, Head of QA
Signature:	DocuSigned by: Helen Cadiou 9FE319AE9B744D5...
Date:	01/07/2021

12. SOP TRAINING LOG:

	Name of Staff (Capital letters)**:**	**Job Title:** **Department:**	Training **Date**	**I confirm that I understand & agree to work to this SOP SIGNATURE**	**Name of Trainer** **(if applicable)**	**Signature**	**Date**
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