Standard Operating Procedure for the Preparation and Maintenance of the Trial Master File (TMF) / 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, **http://www.ucl.ac.uk/jro/ standingoperatingprocedures/document-library** **SOP eDocument kept:** S:_SLMS\RSC_ALL_STAFF\CLINICAL_TRIALS\SOPs\EFFECTIVE_SOPs_Guides\Investigator SOP\INV_S02_Investigator Site File\INV_S02_SOP for the preparation and maintenance of the TMF-ISF_V06 Final.doc	

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

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

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 all clinical trials that fall under the UK Medicines for Human Use (Clinical Trials) Regulations 2004 SI/1031, and subsequent amendments.

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 2005/20/EC (in the UK, these Directives were transposed into UK law by SI 2004/1031, SI 2006/1928) and subsequent amendments and when applicable Regulation 536/2014 and subsequent relevant SIs. Where applicable it incorporates elements of ICH GCP tripartite guidelines (E6)".

A TMF should be established at the beginning of the trial both at the Investigator Site and Sponsor's office in accordance with the requirements of EU Directives 2001/20/EC 2005/28/EC and supporting guidance. The TMF shall consist of essential documents, which enable both the conduct of a clinical trial and the quality of the data produced to be evaluated according to Article 16 of Directive 2005/28/EC

The essential documents should be filed in an organised way that will facilitate management of the clinical trial, audit and inspection (Sponsor Trial Master File and Investigator and other trial Site Files).

In accordance with European guidance "Recommendation on the content of the Trial Master File and Archiving" July 2006, all parties involved in clinical trials should read and take into account the community guideline Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) (ICHE6)

DEFINITIONS

3.1 **Trial Master File (TMF)** – As per JRO procedures, the **preparation and maintenance of the TMF is delegated by the Sponsor to the Chief Investigator (CI).** The TMF is located at the CI's office.

3.2 **Investigator Site File (ISF)** – As per JRO procedures the **preparation and maintenance of the ISF resides with the Site Investigator.** The ISF will be

located at the relevant Site. *Note: For single centre studies the TMF and ISF may be combined.*

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

4. ACRONYMS

CI	Chief Investigator
CF	Consent Form
GCP	Good Clinical Practice
GP	General Practitioner.
IB	Investigator's Brochure
ISF	Investigator Site File
JRO	Joint Research Office http://www.ucl.ac.uk/joint-rd-unit
MHRA	Medicines and Healthcare products Regulatory Agency
MREC	Main Research Ethics Committee
PI	Principal Investigator
PIS	Patient Information Sheet
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TMF	Trial Master File

5. SCOPE OF THIS SOP

This SOP refers to the essential documentation and the creation of the TMF and 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.

6 RESPONSIBLE PERSONNEL

6.1 The CI is responsible for set-up and maintenance of all essential documentation related to his/her trial, and is responsible for providing the Sponsor with any updated documents as requested throughout the trial until trial closure.

6.2 This SOP must be read by all members of the team who are likely to file documents in the TMF and ISF. If any questions arise they should ask the Sponsor Regulatory Advisor or Compliance Oversight Advisor at the JRO for advice.

7. PROCEDURES

7.1 Before the trial commences

7.1.1 Each TMF / ISF will contain an index at the beginning of the file that indicates the sections where essential documents are filed. The minimum essential documents required are outlined in the EU Guidance on "Recommendation on the content of the Trial Master File and Archiving" July 2006. The Sponsor will provide relevant TMF/ISF indexes for the files. Each trial may require additional essential documents to be retained depending upon the nature of the trial, therefore requirements/indexes may differ from trial to trial.

7.1.2 For multi-centre trials, each PI site should set up an ISF containing all essential documents applicable to the conduct of the study at the site.

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

7.1.4 The Sponsor may perform a review of the TMF / ISF on site, or remotely, once confirmation of all necessary approvals and other trial documentation are in place.

7.2 During conduct of the trial

7.2.1 The Investigator must ensure that the TMF and ISF(s) are maintained regularly as the trial progresses. It is the CI's responsibility to notify all participating sites with the latest study documentation. The PI at the site is responsible for distributing the study documents to all staff members participating in the research activity / study at the site. The PI at the site should localise the appropriate study documentation (PIS, CF, and GP letter) and get local approvals before the study information is used locally.

7.2.2 Superseded documents must be retained in the TMF/ISF but scored through by placing a line to indicate that the document is no longer in use. Applicable signing and dating should be legible. Superseded documents must not be destroyed. If documents are held separately to the TMF/ISF, a file note should document the location of the documents and be filed in the TMF/ISF.

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

7.2.4 It is important to ensure that the TMF/ ISF is kept up to date and all documents are maintained accordingly. Any documents identified as missing must be obtained by the Investigator or the person to whom this task has been delegated.

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

7.2.6 The PI should archive all study documents once the study finishes. It is necessary to retain a hardcopy of essential documents. The CI should archive the study TMF once the study finishes.

7.3 Storage of Essential Documents

7.3.1 The TMF/ISF must be retained within a secure place, with appropriate environmental protections. Access should be restricted to authorised personnel only.

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

7.3.3 Any change in the location of the stored documentation should be recorded in order to allow tracking.

7.3.4 Upon request of the monitor, auditor, Ethics Committee, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records according to Community and national legislation.

7.4 After completion or termination of the trial

7.4.1 The Investigator shall notify the Sponsor of the declaration of trial end as defined in the protocol. Refer to SOP07-End of Trial Notification for further information.

7.4.2 Archiving of essential documents should occur after the trial has undergone the final close out visit and the close out report has been issued by the JRO.

7.4.3 Directive 2005/28/EC Article 17 and 18 sets out the requirements for retention of the essential documents and medical files (5 years following the conclusion of the study). On implementation Clinical Trial Regulation EU no 536/ 2014 article 58 retention for 25 years following the conclusion of the study will apply. For trials involving Advanced Therapies, paediatric studies or where clinical trials are submitted in support of a marketing authorisation, the retention period is longer.

7.4.4 Retention timesfor sponsors' records also apply to the records retained by contract research organisations (CROs) or other agents of the Sponsor, unless arrangements have been made to transfer the documents to the Sponsor.

7.4.5 Any transfer of ownership should be documented.

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8. REFERENCES

1. 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
2. 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
3. ICH Harmonised Tripartite Guideline for Good Clinical Practice, Step 4, May 1996.
4. UK Statutory Instrument 2006, No 1928. The Medicines for Human Use (Clinical Trials) Amendment Regulations.

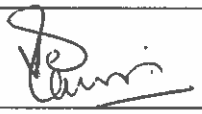
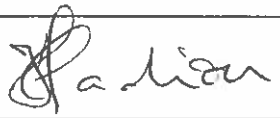
9. TEMPLATES/LOGS ASSOCIATED TO THIS SOP:

1	Appendix1 Trial Master File Index
	Appendix1b Trial Master File Review Template
2	Appendix 2 Investigator Site File Index
	Appendix 2b Investigator Site File Review Template
3	Appendix 3 Pharmacy Site File Index
	Appendix 3b Pharmacy Site File Review Template

10. SOP DISSEMINATION & TRAINING

This SOP will be provided to the 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 PI 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:	Shriram Velamuri, Sponsor Regulatory Advisor
Signature(s):	
Date:	05/10/2017
Authorised by: Name and Job Title	Helen Cadiou, QA Manager
Signature:	
Date:	05/10/2017

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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	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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