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Category: Pre study procedures and Study conduct

Title: Establishing a Trial Master File (TMF)

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1. Purpose

This standard operating procedure (SOP) describes the procedures study personnel will use to fulfill the regulatory and ethical responsibilities for preparing and maintaining the Trial Master File (TMF) for sponsored/academic studies.

2. Scope

The SOP is limited to the preparation and maintenance of the TMF. This document provides guidance on the contents of TMF and the retention requirements for essential documents involved in the conduct of clinical trials.

3. Responsibilities

Principal Investigator (PI), Co-investigator (Co-I), Study Co-ordinator, or any other qualified member of staff in the team, as delegated by the Principal Investigator, will be responsible for preparing and maintaining the TMF.

4. Applicable rules, regulations and guidelines

- ICMR's Ethical Guidelines for Biomedical and Health research involving Human Participants,ICMR(2017)http://www.icmr.nic.in/guidelines/ICMR_Ethical_Guidelines_2017.pdf (last accessed 20 Dec 2024)
- New Drugs and Clinical Trials Rules, 2019 https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf (last accessed 20th Dec, 2024)
- Indian GCP Guidelines 2001 https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=MzM5NQ==(last accessed 20th Dec, 2024)
- International Conference on Harmonization, Guidance on Good Clinical Practice ICH GCP E6 (R3) https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf (Adopted on 06 January 2025)

5. Reference to other applicable SOPs

SOP No: D 18/09 Archiving documents

6. Detailed Instructions

- A trial master file (TMF) will be prepared by the Study Co-ordinator under the supervision of Principal Investigator.
- Maintenance of the TMF will be the responsibility of the Study Coordinator.
- The TMF will be labeled with study title and Institutional Ethics Committee protocol number including date of approval, name of sponsor and name/affiliation of the PI.
- The following should be on the first page of the TMF.
  1. Title of the study, Name of Study Team
  2. Institutional Ethics Committee Protocol number
  3. CTRI registration number
  4. Date of Licensing authority approval (if applicable)
  5. Name of the Principal Investigator
  6. Date of the initial protocol submission
  7. Date of the IEC approval
  8. Date of the Site Initiation Visit (SIV)
  9. Total sample size
  10. No. of participants approved for this site.
  11. Date on which the first participant was enrolled.
  12. Date of last participant's last follow up (updated accordingly)
  13. Date of submission of the annual study report
  14. Date of study close out visit by the sponsor (updated accordingly)
  15. Date of close out report submitted to the IEC (updated accordingly)
  16. Date of submission of Clinical Study Report (CSR) to IEC
  17. Date of archival of the documents
- TMF should be prepared and maintained in the Department before the site initiation.
- All study-related documents should be updated as soon as they are received in real time.

- TMF should be reviewed by the study team at least once a month and a meeting for the same should be set up by the study coordinator.

6.1 Checklist of the documents for a TMF

Before site initiation

SR. No.	Title of Document	Purpose
6.1.1	Signed protocol and amendments (if any) and sample case record form (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF
6.1.2	Information given to trial subject - informed consent document - assent document (if applicable) (including all applicable translations, back translations with translation certificates)	To document the informed consent
6.1.3	Subject diary card/ questionnaire (if applicable) (including all applicable translations, back translations with translation certificates)	To document study related events during follow up
6.1.4	Investigator's brochure	To document that relevant and current scientific information about the investigational product has been provided to the investigator

6.1.5	Advertisement for volunteer recruitment (if used)	To document that recruitment measures are appropriate and not coercive
6.1.6	Financial aspects of the trial (if any)	To document the financial agreement between the investigator/institution and the sponsor for the trial
6.1.7	Insurance policy/ certificate (where required)	To document that compensation to participant(s) for trial-related injury will be available
6.1.8	Signed agreement between involved parties, e.g.: - investigator/institution and sponsor - investigator/institution and CRO - sponsor and CRO - investigator / institution and authority(ies) (where required)	To document agreements
6.1.9	Final approval letter (letter of permission) from respective IEC	To document that the trial has been subjected to IEC review and given approval/favorable opinion. To identify the version number and date of the document(s)
6.1.10	Regulatory authority Approval/ notification of protocol (where required)	To document appropriate authorization/ approval/ notification by the regulatory authority has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)
6.1.11	CTRI registration	To ensure transparency, accountability, and internal validity of the study
6.1.12	-Administrative approval letter -Administrative sanction for sending	To ensure whether administrative sanction has been taken a-priori

	blood samples outside the institution (if applicable)	
6.1.13	Curriculum vitae, medical registration certificate and GCP certificate of study team members	To document qualifications and eligibility to conduct trial and/or provide medical supervision of participants
6.1.14	Duty delegation log	To ensure the study related work is performed by the delegated team member
6.1.15	Copy of annexures of initial submission	To ensure whether required documents are submitted for initial IEC review
6.1.16	Letter(s) of communication from IEC	To ensure whether all study related events are reported to IEC
6.1.17	Letter(s) of communication from sponsor (if applicable)	To ensure whether all relevant communications from sponsor are documented
6.1.18	Normal value(s)/ range(s) for medical/ laboratory/ technical procedure(s) and/or test(s) included in the protocol (if applicable)	To document normal values and/or ranges of the tests
6.1.19	Medical/laboratory/technical procedures/ tests (if applicable) - certification or accreditation or established quality control and/or external quality assessment or other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results
6.1.20	Instructions for handling of	To document instructions needed to ensure

	investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure)	proper storage, packaging, dispensing and disposition of investigational products and trial-related materials
6.1.21	Shipping records for investigational product(s) and trial-related materials	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability
6.1.22	Certificate(s) of analysis of investigational product(s) shipped	To document identity, purity, and strength of investigational product(s) to be used in the trial
6.1.23	Master randomization list	To document method for randomization of trial population
6.1.24	Decoding procedures for blinded trials [if not mentioned in the protocol]	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining participants' treatment
6.1.25	Site feasibility report (if applicable)	To document that the site is suitable for the trial
6.1.26	Site initiation visit report (if applicable)	To document that trial procedures were reviewed with the investigator and the investigator's trial staff
6.1.27	Ethics committee registration number	

	[mentioned in IEC communication documents]	
6.1.28	Undertaking from the sponsor [If Applicable]	
6.1.29	IEC approval letter copies of other sites (if applicable)	

6.2. During the conduct of the Trial

SR. NO.	**Title of Document**	**Purpose**
6.2.1	Investigator's brochure updates [If any]	To document that investigator is informed in a timely manner of relevant information as it becomes available
6.2.2	Any revision to: - protocol/amendment(s) and CRF - informed consent form - any other written information provided to participants - advertisement for participant recruitment (if used)	To document revisions of these trial related documents that take effect during trial
6.2.3	Dated, documented approval/favorable opinion of institutional ethics committee (IEC) of the following: - protocol amendment(s) - revision(s) of: - Informed consent form - Any other written information to	To document that the amendment(s) and/or revision(s) have been participant to IRB/IEC review and were given approval/favorable opinion. To identify the version number and date of the document(s).

	be provided to the participant - Advertisement for participant recruitment (if used) - Any other documents given approval/favorable opinion - Continuing review of trial (where required) Letter of communication from IEC	
6.2.4	Regulatory authority approvals/ notifications where required for: - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements
6.2.5	Curriculum vitae for newly added investigator(s) and/ or sub-investigator(s)	
6.2.6	Updated duty delegation log	To ensure the study related work is performed by the delegated team members
6.2.7	Updates to normal value(s)/ range(s) for medical/ laboratory/ technical procedure(s)/ test(s) included in the protocol	To document normal values and ranges that are revised during the trial
6.2.8	Updates of medical/laboratory/ technical procedures/tests - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document that the quality of tests remain adequate throughout the trial period
6.2.9	Documentation of investigational product(s) and trial-related materials shipment	
6.2.10	Certificate(s) of analysis for new batches of investigational products	

6.2.11	Relevant communication from sponsor (if applicable)	To ensure whether all relevant communications from sponsor are documented
6.2.12	Monitoring visit reports	To document site visits by, and findings of, the monitor
6.2.13	Relevant communications other than site visits - letters - meeting notes - notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting
6.2.14	Notification by investigator to sponsor of serious adverse events and related reports	Notification by investigator to sponsor of serious adverse events and related reports
6.2.15	Notification by sponsor and/or investigator, where applicable, to regulatory authority and IEC of unexpected serious adverse drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IEC of unexpected serious adverse drug reactions
6.2.16	Notification by sponsor to investigators of safety information	Notification by sponsor to investigators of safety information
6.2.17	Data safety monitoring board reports (if applicable)	
6.2.18	Interim report [if available] and annual reports to IEC and authority	Interim or annual reports provided to IEC and to authority

6.2.19	Participant screening log	To document identification of participants who entered pre-trial screening
6.2.20	Participant identification code list	To document that investigator/institution keeps a confidential list of names of all participants allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any participant
6.2.21	Participant enrolment log	To document chronological enrolment of participants by trial number
6.2.22	Investigational products accountability at the site	To document that investigational product(s) have been used according to the protocol
6.2.23	Signature sheet	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs
6.2.24	Record of retained body fluids/ tissue samples (if applicable)	To document location and identification of retained samples if assays need to be repeated

6.3. <u>After Completion or Termination of the Trial</u>

Sr. No.	Title of Document	Purpose
6.3.1	Investigational product(s) accountability at site	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to participants, returned by the participants, and returned to sponsor

6.3.2	Documentation of investigational product destruction (if applicable)	To document destruction of unused investigational products by sponsor or at site
6.3.3	Completed participant identification code list	To permit identification of all participants enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time
6.3.4	Audit certificate (if applicable)	To document that audit was performed
6.3.5	Final trial close-out monitoring report	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files
6.3.6	Treatment allocation and Decoding documentation (if applicable)	Returned to sponsor to document any decoding that may have occurred
6.3.7	Final report by investigator to IEC, and where applicable, to the regulatory authority	To document completion of the trial
6.3.8	Clinical study report	To document results and interpretation of trial

7. Storage conditions

- PI should ensure that the TMFs are maintained in a legible condition and can be retrieved upon the request of a regulatory authority and/or IEC.
- Any change in the location of the stored documentation should be recorded in order to allow tracking. Adequate, safe, and suitable space should be provided for the secure storage of TMFs of completed studies. **Please refer to SOP No. D 18/09 (Archiving of documents)**

8. Duration of retention of TMF

- All the essential documents shall be retained for at least for 5 years after the trial is completed or as per the instructions from sponsors/IEC. **Please refer to SOP No. D 18/09 (Archiving of documents)**

9. Abbreviations:

i.	AE	: Adverse Event
ii.	Co-I	: Co-Investigator
iii.	CRF	: Case Record Form
iv.	CRO	: Contract Research Organization
v.	CSR	: Clinical Study Report
vi.	CTRI	: Clinical Trials Registry – India
vii.	GCP	: Good Clinical Practice
viii.	ICH	: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ix.	ICMR	: Indian Council of Medical Research
x.	IEC	: Institutional Ethics Committee
xi.	IRB	: Institutional Review Board
xii.	PI	: Principal investigator
xiii.	SIV	: Site Initiation Visit
xiv.	SOP	: Standard Operating Procedure
xv.	TMF	: Trial Master File

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