Documentation and Archiving

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13.2.2020

Presentation Outline

- Trial Master File
- Essential Documents
- Archiving
- Retention of Records

All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification

Trial Master File

Trial Master File (TMF)

- The collection of essential documents
- For the management of the trail - used by sponsors, Contract Research Organizations (CROs) and investigators/institutions
- to review, verify and evaluate - the sponsor and the investigators/institutions have conducted the trial in line with the applicable regulatory requirements and the standards of GCP
- key role in the successful management of a trial

Trial Master File (TMF) (contd.)

Composed of Sponsor and Investigator TMF (investigator site file (ISF))

- Segregate some documents – E.g subject identification code list in investigator TMF only and master randomization list in sponsor RMF only
- Role based permissions for access to documents

(randomization codes and unblinded adverse event data)

Trial Master File (TMF) (contd.)

- Sponsor may choose to outsource its duties and functions to CRO (Contract Research Organization) - eTMF
- Multiple CROs involve – Sponsor should clearly define management, exchange, remote access and retention of documentation amongst CROs
- Access to the TMF should be based on a role and permission description defined by Sponsor/investigator/institution
- Sponsor remains responsible for the trial, need to maintain oversight

Quality of TMF

- **all essential documents generated available in the TMF**
- **documents filed in the appropriate locations**
- **documents added to the TMF in a timely manner**
- **documents correctly indexed**
- **documents only accessible according to the assigned roles and permissions**
- **review of the audit trail (for eTMF)**

Essential Documents

"ESSENTIAL" DOCUMENTATION

Documentation, Record Keeping, and Retention

- Components of the TMF
- Permits evaluation of the conduct of a study
- Permits evaluation of data collected
- Demonstrates GCP and compliance with applicable regulatory requirements
- Facilitates study management and oversight
- Allows for monitoring and evaluation of practices

Essential Documents (Regulatory Binder)

- organized documents are referred to as the **REGULATORY BINDER**
- The binder must be kept at the Investigator's clinical site

TIP: Synonyms: Investigator Binder = Regulatory Binder = Investigational Site File (ISF) = Study Binder = Master Trial File (MTF)

Regulatory Binder

Binder Check List

The following 'Essential Documents' should be collected and filed in the regulatory binder,

if applicable,

for each clinical study per

regulatory ICH and GCP.

***Required for both observational and interventional clinical research studies*

Essential Study Documents in Regulatory Binder

- Study Protocol – signed, dated by all entities (PI, sponsor)
- Study Protocol Amendments
- Informed Consent
- IRB Approval(s)
- Delegate of Authority and Log of Responsibilities
- Curriculum Vitae (CV's) current
- Financial Disclosures
- Protocol Training Documentation
- Training Documentation to conduct research, study-related duties or functions
- Adverse Events and/or unanticipated events
- Study Protocol Deviations
- Note to File (NTF)
- Standard Operating Procedures(SOPs); Manual of Procedures (MOPs) and or Appendixes
- All communications between entities (PI, research team, CRO, sponsors, governing boards)

Essential Study Documents in Regulatory Binder (contd.)

Protocol & Amendments

- IRB-approved Protocol (original and amendments)
- Signed principal investigator (PI) signature pages (PI address/ signature/date)
- IRB-approved Case Report Forms (CRF's)
- IRB-approved advertisements, brochures, letters
- IRB-approved Participant Information Sheets
- IRB-approved Protocol Amendments and (PI) signature page
- Store in reverse chronological order - current approved version first
- Log of protocol changes

GCP Documents FILING

- Before the Clinical Phase of the Trial commences
- During the clinical conduct of the trial
- After completion or termination of the trial

GCP Documents Filing: Before the Clinical Phase of the Trial Commences

Title of Document	Purpose	Located in Files of	
		PI/ Institution	Sponsor
INVESTIGATOR'S BROCHURE	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
INFORMATION GIVEN TO TRIAL SUBJECT – INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent	X	X
– ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
– ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
INSURANCE STATEMENT (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
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	 X X X	 X X (where required) X X

GCP Documents Filing: Before the Clinical Phase of the Trial Commences (contd.)

Title of Document	Purpose	Located in Files of	
		PI/ Institution	Sponsor
DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING: – protocol and any amendments – CRF (if applicable) – informed consent form(s) – any other written information to be provided to the subject(s) – advertisement for subject recruitment (if used) – subject compensation (if any) – any other documents given approval/ favourable opinion	To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s)	X	X
INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL (where required)	To document appropriate authorisation/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X

GCP Documents Filing: Before the Clinical Phase of the Trial Commences (contd.)

Title of Document	Purpose	Located in Files of	
		PI/ Institution	Sponsor
NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and/or ranges of the tests	X	X
MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS – 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	X (where required)	X
SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X
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	X	X

GCP Documents Filing: Before the Clinical Phase of the Trial Commences (contd.)

Title of Document	Purpose	Located in Files of	
		PI/ Institution	Sponsor
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		X
DECODING PROCEDURES FOR BLINDED TRIALS	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)
MASTER RANDOMISATION LIST	To document method for randomisation of trial population		X (third party if applicable)
PRE-TRIAL MONITORING REPORT	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
TRIAL INITIATION MONITORING REPORT	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)	X	X

GCP Documents Filing: During the Clinical Conduct of the Trial

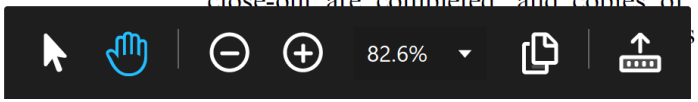
Title of Document	Purpose	Located in Files of	
		PI/ Institution	Sponsor
INVESTIGATOR'S BROCHURE UPDATES	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
ANY REVISION TO: – protocol/amendment(s) and CRF – informed consent form – any other written information provided to subjects – advertisement for subject recruitment (if used)	To document revisions of these trial related documents that take effect during trial	X	X
DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING: – protocol amendment(s) – revision(s) of: – informed consent form – any other written information to be provided to the subject – advertisement for subject recruitment (if used) – any other documents given approval/favourable opinion – continuing review of trial (where required)	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).	X	X
REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR: – protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X

GCP Documents Filing: After the Clinical Conduct of the Trial

8.4 After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in Sections 8.2 and 8.3 should be in the file together with the following

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.4.1	**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 subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION**	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3	**COMPLETED SUBJECT IDENTIFICATION CODE LIST**	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	**AUDIT CERTIFICATE** (if available)	To document that audit was performed		X
8.4.5	**FINAL TRIAL CLOSE-OUT MONITORING REPORT**	To document that all activities required for trial close-out are completed and copies of essential		X



GCP Documents Filing: After the Clinical Conduct of the Trial

Integrated Addendum to E6(R1): Guideline for Good Clinical Practice

8.4.6	TREATMENT ALLOCATION AND DECODING DOCUMENTATION	Returned to sponsor to document any decoding that may have occurred		X
	Title of Document	**Purpose**	**Located in Files of**	
			Investigator/ Institution	**Sponsor**
8.4.7	FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)	To document completion of the trial	X	
8.4.8	CLINICAL STUDY REPORT	To document results and interpretation of trial	X (if applicable)	X

Essential Documents Checklist

COMPONENTS:

SITE MASTER FILE | SMF
*Documents maintained **on-site***

TRIAL MASTER FILE | TMF
*Documents sent to the study **Sponsor***

DOCUMENT VERSION KEY
ORIGINAL COPY N/A

		SITE MASTER FILE	SPONSOR TMF
1	Protocol & Amendments		
2	Investigator Brochure | IB		
3	Signature Sheets | SS		
4	Statement of Investigator | FDA Form 1572		
5	Experience & Training		
6	Delegation & Signature Log		
7	Financial Disclosure Form | FDF		
8	Laboratory Accreditations, Certifications & Normal Values		
9	Investigational Product | IP		
10	IRB Membership & Federal Wide Assurance | FWA		
11	IRB Approvals & Correspondence		
12	Informed Consent Forms | ICF & HIPAA Authorizations		
13	Recruitment & Retention Materials		
14	Correspondence & Miscellaneous Documents		
15	Monitoring Log & Reports		
16	Serious Adverse Events | SAEs & Unanticipated Problems		

Archiving

Archiving

- Shall be archived in a way that ensure it is readily available and directly accessible upon request
- Access to documents and data is maintained for the entire archiving period
- Maintaining the system addressed by the organization by written procedures
- Transferring the data to new media as technology advances would need to be considered by the organization

Archiving of Sponsor TMFs

- For paper-based archived TMFs, an index/log should be use to track when TMFs is retrieved, accessed and returned
- For electronically archived TMFs, tracking can be ensured by the audit trail
- Sponsor TMF may be transferred to a CRO (external archive), ultimate responsibility resides with SPONSOR
- make available for direct access all requested trial-related records by monitor, auditor, IRB/IEC, or regulatory authority
- Responsibility of a sponsor – to inform the investigator/institution in writing, when trail documents no longer need to be retained

Archiving of Investigator/Institutional master file

- Should make the sponsor aware of the storage arrangements
- If investigator/institution unable (relocation, retirement, closure of institution) – in writing of this change and informed to whom the responsibility will be transferred
- It should be independent of the sponsor and should be free of any conflict of interest
- May be stored in the external archive, but the main responsibility will be on investigator/institution

- It is considered preferable that two copies of the data are held at different sites to ensure that neither copy is altered and that both copies are not destroyed in accidental circumstances.
- fireproof facility which does not have a sprinkler system
- The investigator should retain a copy of the patient log, and only the investigator should recall information from this archive

Retention of Records

Retention times of TMF

For all trials in which the clinical trial data are used to support a marketing authorization (including paediatric use), essential documents should be retained for

- at least 15 years after completion or discontinuation of the trial or
- at least two years after the granting of the last marketing authorisation in the European Union or
- at least two years after formal discontinuation of clinical development of the investigational product

References

1. Guideline on the content, management and archiving of clinical trail master file (paper and electronic) EMA/INS/GCP/856758/2018
2. E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) 2018
3. Storage and Retention of clinical records (No. DWD.POL-CL-006.02) 2016


THANK YOU