

Standard Operating Procedure

Trial Files

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1. ABBREVIATION

ASST- PG23: Azienda Socio-Sanitaria Territoriale - Papa Giovanni XXIII

CRA: Clinical Research Associate

DM: Data Manager

FROM: Fondazione per la Ricerca Ospedale di Bergamo

ISF: Investigator Site File

PI: Principal Investigator

PM: Project Manager

QAM: Quality Assurance Manager

SOP: Standard Operating Procedure

TMF: Trial Master File

2. SCOPE

The aim of this Standard Operating Procedure (SOP) is to define the set-up and maintenance of Trial Master File (TMF) and Investigator Site File (ISF). This SOP describes also the approach for a correct temporary and permanent archiving of trial documents.

3. FIELD OF APPLICATION

This SOP applies to all clinical trial sponsored by FROM or by ASST-PG23.

4. RESPONSIBILITIES

Project Manager (PM) /Data Manager (DM)

- sets-up the Trial Master File (TMF) at trial start and ensures the completeness during the course of the trial;
- organizes the Investigator Site File (ISF) to be delivered to each site participating in a clinical trial;
- ensures that all trial documents are duly filed in TMF before the trial closure;
- ensures the transfer of the TMF of a closed and reported trial to a long-term archive.

Clinical Research Associate (CRA)

- checks the ISF during the monitoring visits for completeness and accuracy;
- collects the relevant documentation produced at the investigational sites;
- hands over the collected documents to the PM in charge of filing them in the TMF;
- ensures that all trial documents are filed in ISF before the close-out visit.

Principal Investigator (PI)

- ensures that the site staff maintains the ISF with complete, accurate and updated documents;
- ensures an adequate storage of trial documentation during the conduct and after the trial end at least for the period requested by regulation;
- grants access to CRAs, auditors and Inspectors to the trial documentation, including source documents.

5. PROCEDURES

Essential documents, individually and collectively, are the main tool to evaluate the conduct of a clinical trial and the integrity of clinical data. These documents serve to demonstrate the compliance of all parties involved with the standards of Good Clinical Practice and with all applicable regulatory requirements.

These documents are described in the International Conference on Harmonization Guideline for GCP - Section 8: "Essential Documents for the Conduct of a Clinical Trial". They are archived in the TMF and ISF.

In addition to Essential Documents, the files must also include documents required by applicable regulations or other documents used by FROM to describe or document specific activities.

A TMF and ISF are required for all clinical trials. They should be set up at the beginning of the trial. The TMF remains at FROM/ASST-PG23, while ISF is sent to investigators/sites at the time of the Site Initiation Visit.

The TMF and ISF should be available in case of audit by FROM and/or inspection by the regulatory authorities.

5.1. TMF and ISF set-up

TMF and ISF contain documents relevant to a clinical trial, filed into standardized sections and subsections. Sequence and numbering of each TMF section and sub-section are reported in **Trial Master File Index (T.CLI06.01/2)**. Sequence and numbering of each ISF section and sub-section are reported in **Investigator Site File Index (T.CLI06.02/2)**.

Complete indexes are included in the first binder of the TMF/ISF, while a binder-specific index is included at the beginning of each binder. Each section is progressively numbered according to the index. When a specific section is not applicable this should be reported on the index.

Documents are filed in the corresponding sections following the checklist order, so that each individual document or batch of documents can be easily identified.

Usually several binders are set-up depending on the quantity of the documentation.

The documents are archived in the TMF as General Documents, Country Documents and Center Specific Documents. The *General Documents* are the ones related to the overall organization and conduct of the trial and are not specific to any investigational site. The *Country Documents* are those common to a specific country (usually centralized trial approval by a central authority) and the *Site Documents* are those related to the organization and conduct of the trial at each Investigational Site.

The following information are reported on a label attached to the back of each binder of the TMF:

- Sponsor Name

- Trial code
- Investigational Product code/name
- TMF
- *<General Documentation> or <Country Documentation> or <Site No. > / <PI name>*
- Binder No. xx/yy.

The following information are reported on a label attached to the back of each binder of the ISF:

- Sponsor
- Trial code
- Investigational Product code/name
- ISF
- *<Site No. > / <P.I.name>*
- Binder No. xx/yy.

5.2. TMF and ISF Maintenance

The TMF must be kept up to date by the PM/DM throughout the course of the trial by filing the trial documentation collected. Before filing the documents have to be carefully revised by the PM/DM regarding to the content, dates and consistency with other related documents.

Throughout the course of the trial the CRA verifies the content of the ISF during the monitoring visits. If the file is not maintained correctly (e.g. inadequate or missing documents), the CRA should take the appropriate actions. Any deviation has to be reported in the monitoring reports, discussed with the Investigator/site staff, and additional instructions or training should be given to the staff.

The documents collected at the investigational site by the CRA are delivered to the PM/DM along with a cover letter listing all shipped documents (i.e. type of document, version and date).

If needed, a **Note to File (T.CLI06.03/2)** should be issued and filed in the relevant section of the TMF by the PM or in the relevant section of the ISF by the site staff. The Note to File is a short note to describe a minor deviation, the reason for the deviation and the action taken (if applicable). A Note to File can also be used to clarify or specify some issues. If needed, the QAM is consulted to draft the content of the Note to File.

5.3. Archive

The TMF/ISF contains confidential documents and the access should be limited to the PM or the delegated site staff, respectively. The TMF/ISF should be kept in a secure location and reasonable precautions should be taken to prevent binders' loss or damage.

Access to documentation is granted also to auditors in case of sponsor audit and to inspectors in case of regulatory inspection.

At the end of the trial the whole content of the TMF is checked by the PM/DM. This activity is documented in a report summarizing activities performed (i.e. quality control) and the outcomes. If some issues emerge, all effort should be made to solve the problem before filing the TMF in the long-term archive.

With regards to a site, the trial close-out can be performed when the CRA has verified the completeness of the ISF, numbered each binder progressively and confirmed in the monitoring report that all documents are duly archived and ready to be filed in a long-term archive.

The PI informs the CRA about the location of the ISF during the agreed archive period (i.e. as per local regulation or for a longer period, if requested by FROM/ASST-PG23). The PI is responsible to notify FROM/ASST-PG23 should he/she leave the institution prior to the end of the agreed archiving period.

The documentation is destroyed at the Investigator's site only upon FROM/ASST-PG23 approval.

6. REFERENCES

- Guideline for good clinical practice E6(R2) (CPMP/ICH/135/95).
- Decreto Legislativo 6 novembre 2007, n. 200 - Attuazione della direttiva 2005/28/CE recante principi e linee guida dettagliate per la buona pratica clinica relativa ai medicinali in fase di sperimentazione a uso umano, nonché requisiti per l'autorizzazione alla fabbricazione o importazione di tali medicinali".
- Decree 21st December 2007 - Directions for submitting the request for authorization of a clinical trial on a medicinal product for human use to the Competent Authority, for communicating substantial amendments, for declaring the end of the trial and for the request of an opinion to the Ethics Committee.
- Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic) EMA/INS/GCP/856758/2018.

7. TEMPLATES

T.CLI06.01/2 Trial Master File Index

T.CLI06.02/2 Investigator Site File Index

T.CLI06.03/2 Note to File

8. VERSION HISTORY

Version	Date	Reason for revision
1	30 Sept 2016	Starting document.
2	15 Jan 2020	General review of the document with minor and limited corrections.