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HEALTH+MEDICAL RESEARCH

Investigator site file and essential documents

Standard Operating Procedure



NSW Health

100 Christie Street

St Leonards NSW 2065

(02) 9391 9228

www.health.nsw.gov.au

www.medicalresearch.nsw.gov.au

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1. Purpose

To describe the requirements for the establishment of an investigator site file (ISF) and the maintenance of essential documents for clinical trials with external sponsors. To ensure that sites conducting clinical trials take appropriate account of the Guidelines for Good Clinical Practice based on sponsor requirements¹.

2. Scope

All clinical trials (except Teletrials)² conducted at NSW Public Health Organisations.

3. Applicable to

The principal investigator (PI) and all site staff involved in a clinical trial.

All support departments storing essential documents.

4. Definitions

Refer to SOP-G-01: Glossary of terms.

5. Background

ICH GCP defines essential documents as '*documents which individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced*'.

An ISF should be established at the beginning of the trial so that essential documents can be filed in an organised way that will facilitate the conduct of the trial, audit, and inspection. Contents should enable the adequate reconstruction of trial conduct at the site along with any key trial decisions.

The sponsor normally provides a template for the ISF but where no template is provided, a suitable indexing system should be agreed with the sponsor to ensure that all documents are appropriately sorted and filed. Section 8 of ICH GCP contains guidance on ISF content, noting that ICH GCP permits this content to be supplemented or reduced 'based on the importance and relevance of the specific documents to the trial'.

The ISF contains identifiable data and proprietary information and should be stored securely with restricted access to authorised staff. It should be actively maintained as the trial progresses. All documentation filed should be complete, accurate and legible. If essential documents are stored separately from the ISF (e.g. staff training records, maintenance/calibration records for key equipment

used in the trial) a file note in the ISF should indicate their location. Superseded documents should be retained but scored through to indicate that the document is no longer in use. Direct access to all trial-related records stored in the ISF should be provided when requested by monitors, auditors, ethics committees or regulatory authorities.

Essentials documents stored in the ISF should be originals or certified copies of original documents; defined in ICH GCP as:

A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Essential documents include the correspondence generated during a trial. These documents (e.g. e-mails, telephone call reports, meeting minutes) are an important component in reconstructing the trial as they contain key decisions and discussions relating to the care of participants and the management of the trial.

Certified copies

ICH GCP requires copies of documents to be certified when they replace the original and that original is no longer available to either sponsor or site (e.g. paper documents in an ISF are transferred to a different media for archive and the originals are destroyed). Where copies of documents are made but the original is retained in the ISF, a certified copy is not required. The copy should, however, be of sufficient quality for the intended purpose.

When certified copies are made, they should be certified by the person making the copy who should also document the audit trail for the process (when and how and by whom the process took place). The copy should be checked for:

- Accuracy and completeness – the congruency of the information contained between original and certified copy is confirmed (e.g. page counts)
- Quality and legibility – e.g. an appropriate resolution
- No loss of metadata – e.g. accurate file name (marked as an updated version of an existing document), colour copies where colour is important for the interpretation of the document.

¹ All trials must comply with the principles of GCP (Section 2 of ICH GCP (E6 R2) or Clause 4 of ISO 14155) however sponsors submitting data to regulatory authorities will normally require full compliance with ICH GCP (E6 R2) or ISO 14155 GCP Guidelines.

² NSW Health have published an annotated version of these SOPs for sites utilising a Teletrials model.

Electronic ISF

Where all or part of the ISF is held electronically, the same controls should be in place for managing the e-ISF as would be possible for a paper-based ISF. This should include appropriate security and control over unauthorised edits and access and an audit trail for any documents that are amended (e.g. a dated file name).

Any process used to convert paper documents to electronic versions (e.g. scanning) should also be validated and used with appropriate quality control checks to ensure data and metadata are not lost.

Both paper and electronic ISFs should adequately identify the trial and where more than one file is created, each file should indicate a specific file/folder number and the total number of files/folders.

The use of file notes

File notes may be acceptable when an event, decision or situation requires explanation and there are no other study documents designed or suitable to capture this information. They should not be overused (e.g. the issue can be recorded in trial documentation that already exists such as part of a response to a sponsor's monitoring report). They should describe (or refer to) the corrective and preventive actions (CAPA) plans that were put in place to correct the problem and prevent a recurrence. They should not be overused (e.g. the issue can be documented in study documentation that already exists (e.g. as part of a response to a sponsor's monitoring report)). They should not be used inappropriately, for example, to track protocol deviations.

Pharmacy file

For investigational medicinal product (IMP) trials, the site pharmacy normally maintains a pharmacy file which constitutes part of the ISF, holding documents pertinent to the management of IMP(s). The PI should ensure that the role of maintaining the pharmacy file is delegated to a staff member qualified by education, training and experience.

6. Procedure

Principal Investigator (PI)

Ensure an ISF is established for each trial prior to the start of recruitment and actively maintained as the trial progresses and a named person(s) is responsible for the ISF (and the pharmacy file if relevant) throughout the trial.

Ensure an ISF is archived at site (or as otherwise agreed with the sponsor) for the period specified by

the sponsor and is retrievable in the event of an audit or regulatory inspection.

Ensure systems are in place for inspectors and sponsor representatives (e.g. monitors and auditors) to have access when requested and that access to electronic medical records is restricted to study participants.

At trial completion, review the ISF to confirm that it is complete.

Ensure the ISF is archived in accordance with site policies.

PI or delegate

Sign the delegation log.

Set up and maintain the ISF in accordance with sponsor requirements.

Ensure the ISF is kept securely.

Ensure access only to authorised individuals.

7. References

[ICH GCP \(E6 R2\): Good Clinical Practice Guidelines – Annotated by the TGA](#)

[EMA Guideline on the content, management and archiving of the clinical trial master file \(paper and/or electronic\)](#)

8. Associated documents

Source document location plan – available in the Standard Operating Procedures templates [zip file](#)

[TransCelerate delegation log](#)

File note template – available in the Standard Operating Procedures templates [zip file](#)