Austin Health

OFFICE FOR RESEACH
PROCEDURE

The Study Site Master File and Essential Documents

1. Purpose:

To describe the procedures related to the maintenance of the Study Site Master File (ISF) and associated essential documents.

2. Scope:

All phases of clinical investigation for medicinal products, medical devices and diagnostics, inclusive of Industry Sponsored, Collaborative Group or Investigator Initiated trials.

3. Staff this document applies to:

Principal Investigator/ Investigator, Associate-Investigator(s), Clinical Research Coordinators and other staff involved in trial-related duties.

4. Procedure:

4.1 The Study Site Master File and Essential Documents

The Investigator(s) should:

- File essential documents at the site in a timely manner and in an organised way that will facilitate management of the clinical trial. All site-related materials should be made available for review by the sponsor's representatives (monitors and auditors) or regulatory authority(ies).
- Keep a minimum list of essential documents from the following stages of the trial (see Appendix 1).
  - Before the clinical phase of the trial
  - During the clinical conduct of the trial
  - After completion or termination of the trial.
- Study documentation should be maintained as specified in the Australian Code for Responsible Conduct of Research 2007 (Part A, Section 2.1)[4] as indicated below:
  - For short term research projects, that are for assessment purposes only (eg research projects completed by students), retention of research data for 12 months after completion of the project may be sufficient.
  - For clinical trials, data should be retained for a minimum of 15 years for adult studies or 25 years for paediatric studies.

- For areas such as gene therapy, research data must be retained permanently (eg patient records).
- If the work has community or heritage value, research data should be kept permanently, preferably within a national collection.

- For legal reasons, sites may consider indefinite archiving periods.
- The TGA position on document retention states: *"The TGA requires records to be retained by the sponsor for 15 years following the completion of a clinical trial. However, in Australia the overriding consideration for sponsors with respect to record retention is the issue of product liability and the potential need for sponsors of products to produce records at any time during, and possibly beyond, the life of a product in the event of a claim against the sponsor as a result of an adverse outcome associated with the use of the product."*

4.2 Documentation of Investigational Site Qualifications and Training Records

The investigator(s) should:

- Maintain evidence in the Study Site Master File of Investigational Site Qualifications and Training Records as per AH SOP01 <link>

4.3 The Site File

- The site file should contain all the essential documentation referred to in Appendix 1.
- The site file must be retained within a secure place, with appropriate environmental protections. Access should be restricted to authorised personnel only.
- For commercially sponsored studies, sponsoring companies will normally provide site file complete with tab separators for ease and consistency of filing, but departments may reorganise these site files to comply with their specific requirements as necessary.
- For Studies conducted on behalf of smaller companies or for investigator-initiated studies, the site file should be structured in accordance with the template provided in Appendix 3.
- Financial documentation such as the clinical trial agreement may be filed in a separate location to the Study Site Master File.
- The site pharmacy will usually keep investigational product shipping, receipt and accountability documents in the study Pharmacy Folder. The site itself does not have to replicate these documents. However, the records must be made available to sponsors monitors and auditors.

Glossary

Chronological Filing: Organizing and ordering documents and records in a dated sequence. This sequence can be according to their date of receipt, or date and time of their creation. The item youngest-by-date is usually in front of or on top of the previous items.

Clinical Research Coordinators: A research worker who works at a clinical research site under the immediate direction of a Principal Investigator, whose research activities are conducted under Good Clinical Practice guidelines. May also be called "Clinical Trial Coordinator" or "Research Coordinator". (ARCP Definition.)

Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced

Good Clinical Practice (GCP): From the International Conference on Harmonisation (ICH) guidance, GCP is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Human Research Ethics Committee (HREC): A body which reviews research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines. The National Statement requires that all research proposals involving human participants be reviewed and approved by an HREC and sets out the requirements for the composition of an HREC.

International Conference on Harmonisation (ICH)
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use is a joint initiative involving both regulators and research-based industry focusing on the technical requirements for medicinal products containing new drugs.

Study Site Master File (ISF): The file held by the site Principal Investigator containing the essential documents that demonstrate that the trial has been conducted in accordance with regulatory requirements and ICH GCP, enabling both the conduct of a clinical trial and the quality of the data produced to be evaluated. The preparation and maintenance of the ISF resides with the Site Investigator and set up at the start of a study and is archived at the end of the study.

Principal Investigator: An individual responsible for the conduct of a clinical trial at a trial site ensuring that it complies with GCP guidelines. If a trial is conducted by a team of individuals at

a trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator. In this instance they may delegate tasks to other team members.

Sponsor: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Associate Investigator: Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows).

Appendices:

Appendix 1: List of documents to be generated during the conduct of a clinical trial from initiation to close-out

Appendix 2: Study Site Master File Index and Contents Template

Legislation/References/Supporting Documents:

1. Based on, and with permission of the Victorian Managed Insurance Authority – VMIA GCP SOP No.002 Version:1.0 Dated 17 September 2007
2. Note for guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments DSEB, July 2000.
3. The Australian Clinical Trial Handbook, March 2006
4. Australian Code for the Responsible Conduct of Research, (2007). https://www.nhmrc.gov.au/guidelines-publications/r39
5. National Statement on Ethical Conduct in Human Research, (2007).
6. NHMRC Human Research Ethics Portal https://hrep.nhmrc.gov.au/national-approach/glossary
7. QH GCP SOP 2: The Study Site Master File and Essential Documents, 2010.

8. APPENDICES:

Appendix 1: List of documents to be generated before and kept during and after completion/termination of the trial (ADAPTED from ICH-GCP)

Appendix 2: Study Site Master File Index and Contents (Template)

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TBC

APPENDIX 1: LIST OF DOCUMENTS TO BE GENERATED BEFORE AND KEPT DURING AND AFTER COMPLETION/TERMINATION OF THE TRIAL (ADAPTED FROM ICH-GCP)

Before the Clinical Phase of the Trial Commences During this planning stage the following documents should be generated and should be on file before the trial formally starts:	
Title of Document	**Purpose**
Investigator's Brochure (or Product Information document for a marketed product- see SOP004 section 4.4)	To document that relevant and current scientific information about the investigational product has been provided to the investigator.
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.
Information given to trial Subject: • Informed Consent Form (including all applicable translations) • Any other written information • Advertising for Subject recruitment (if used)	To document the informed consent. To document that Subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent. To document that recruitment measures are appropriate and not coercive.
Financial aspects of the trial • Study contract including study budget • Financial Disclosure Forms • Form FDA 1572 (where applicable)	To document the financial agreement between the investigator/institution and the sponsor for the trial.
Insurance statement (where required)	To document that compensation to Subject(s) for trial-related injury will be available.
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.
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).
All other correspondence between the investigator and the IRB.	To document all correspondence between the investigator and the IRB.

Before the Clinical Phase of the Trial Commences During this planning stage the following documents should be generated and should be on file before the trial formally starts:	
Title of Document	**Purpose**
Institution Review Board/Independent Ethics Committee Composition	To document that the IRB/IEC is constituted in agreement with GCP.
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).
Curriculum Vitae and/or other relevant documents evidencing qualifications of investigator(s) and Associate-investigator(s)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of Subjects.
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.
Medical/laboratory/technical procedures/tests: • Certification; or • Accreditation; or • Established quality control and/or external quality assessment; or • Other validation (where required) • Laboratory Manual (where required)	To document competence of facility to perform required test(s) and support reliability of results.
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.
Shipping records for investigational products 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.
Decoding procedures for blinded trials (where applicable)	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.
Trial initiation monitoring report	To document that trial procedures were reviewed with the investigator and the investigator's trial staff.
Dated, documented authorisation from Institutional Research Governance Officer of the following: Site Specific Application Form (SSA); Site Specific Participant Information Sheets and Consent Forms, any other site specific documents including advertisements, additional clearances and approvals as required.	To document that authorisation to conduct the research project at that site have been granted and all approvals for research procedures have been obtained.

During the Clinical Conduct of the Trial In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available:	
Title of Document	**Purpose**
Investigator's Brochure Updates	To document that investigator is informed in a timely manner of relevant information as its becomes available.
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 the trial.

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).

Regulatory authority(ies) authorisations/ approvals/notifications where required for: • Protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements.
All other correspondence between the investigator and the IRB	To document all correspondence between the investigator and the IRB.
Curriculum vitae for new investigator(s) and/or Associate-investigator(s)	To document qualifications and eligibility to conduct research project and/or provide medical supervision of participants (where required).
TransCelerate mutually recognised GCP certificate for all research personnel (Investigators and Coordinators) performing trial related duties	To provide documented evidence of understanding of the principles of Good Clinical Practice in the conduct of clinical trials
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.
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 tests remain adequate throughout the trial period.
Documentation of investigational product(s) and trial-related materials shipment	

Relevant communications other than site visits such as: 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.
During the Clinical Conduct of the Trial In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available:	
Title of Document	**Purpose**
Signed informed consent forms	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each Subject in trial. Also to document direct access permission.
Source documents	To document the existence of the Subject and Substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of Subject.
Signed, dated and completed case report forms (CRF)	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded.
Documentation of CRF corrections	To document all changes/additions or corrections made to CRF after initial data were recorded.
Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports.
Notification by sponsor and/or investigator, where applicable to regulatory authority(ies) and IRB(s)/IEC(s) of unexpected serious adverse drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions and other safety information.
Notification by sponsor to investigator of safety information	Notification by sponsor to investigators of safety information.
Interim or annual reports to IRB/IEC and authority(ies)	Interim or annual reports provided to IRB/IEC and to authority(ies).
Subject screening log	To document identification of Subjects who entered pre-trial screening.
Subject identification code list	To document that investigator/institution keeps a confidential list of names of all Subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any Subject.
Subject enrolment log	To document chronological enrolment of Subjects by trial number.
Investigational products accountability at the site	To document that investigational product(s) have been used according to the protocol.
Signature sheet	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs.
Record of retained body fluids/tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated.
After the Conduct of the Clinical Trial After completion or termination of the trial, all of the documents identified above should be in the file together with the following	

Title of Document	Purpose
Complete and unused set of CRF's	To indicate the CRF documents used to collect study data at the site. To be archived with all study documents.
All pharmacy and drug compliance and monitoring documents (where applicable)	To indicate correct storage and monitoring of Investigational Product. To indicate compliance with protocol procedures regarding storage, return and/or disposal of Investigational product.
Documentation of Investigational Product destruction (where applicable)	To document destruction of unused investigational products by sponsor or at site
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.
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.
Clinical Study Report (if applicable)	To document results and interpretation of trial
Study closure notification to IRB/IEC and Subsequent acknowledgement	To document notification and acknowledgement of trial closure.

APPENDIX 2: STUDY SITE MASTER FILE INDEX AND CONTENTS TEMPLATE

File Section	Documentation	Done
Contact List	Contact list table for study related personnel	☐
Correspondence	General correspondence with sponsor, CRO, teleconference and meeting notes	☐
Agreements	Clinical trial agreement location, site indemnities, confidentiality agreement(s) location, letters of intent	☐
Finance	Financial disclosure forms for any person listed on the FDA Form 1572 (IND study only)	☐
Ethics committee 5.1. Ethics Committee Approvals/Acknowledgements 5.2. Ethics Committee Composition 5.3. Ethics Committee Correspondence	All ethics correspondence and documentation including all versions of the informed consent form, ethics committee composition, statement of committee compliance to NH&MRC National Statement, approval letters, reports to ethics committee, correspondence as applicable to commercial sponsorship, Submission package(s), sample informed consent form, approved advertising materials/wording, other information provided to study Subjects and approved by ethics, tracked changes to protocol and summary tables, insurance certificate	☐
Investigator's Brochure and safety updates	All versions as provided to ethics, safety updates from sponsor	☐
Protocol	All versions as provided to and as approved by ethics, signed protocol signatory page should also be in this section	☐
Regulatory documents	Australian CTX or CTN form (fully executed), IND form 1572, other regulatory agency forms, all correspondence to the regulatory agencies	☐
Sample CRF	Approved version of sample CRF (a blank set that can be duplicated)	☐
Serious Adverse Events	Documentation tracking the incidence and reporting of SAEs, reports to ethics, reports to the applicable agency (interim and final)	☐
Monitoring	All general monitoring correspondence unless specifically belonging in another file section, pre-trial monitoring report, feasibility assessments, monitoring visit reports and follow-up letters, monitor-site correspondence, close-out visit reports	☐
Audit	Auditor correspondence, audit reports (if available) and auditor follow-up letters	☐
Laboratory	Clinical laboratory certification (NATA, CLIA), laboratory normal values for medical/laboratory/technical procedures and/or tests included in the protocol, all laboratory related correspondence	☐

File Section	Documentation	Done
Curriculum vita	Signed and dated copies of *curriculum vita* for all medical staff, principal investigator, Associate-investigators updated to include current positions. CVs should be present for all those listed on the delegation log	☐
Signature log	Site personnel signature sheet with a list of signatures and initials of all persons authorised to make entries and/or corrections on the CRFs and certain delegated tasks	☐
CRF completion guidelines	Any correspondence, presentations and/or CRF completion guidelines provided by the Sponsor	☐
Shipping records	Shipment records, date of shipment, batch numbers, method, shipment receipt records, certificate of analysis for investigational product, storage conditions. Shipping details of other study related documentation or materials should also be recorded.	☐
Accountability records	Investigational product accountability correspondence and/or records	☐
Decoding and Unblinding	Any correspondence relating to decoding and unblinding. Documents how identity of blinded investigational product can be revealed in case of emergency.	☐
Subject screening logs	Screening logs including participant identification logs (site only for identification in case of emergency), participant registration/screening logs containing a chronological listing of screening/enrolment of Subjects	☐
Subject identification code list	A confidential list of names of all Subjects allocated to trial numbers on enrolment in the trial. Allows investigator/institution to reveal Subject identity	☐
Subject enrolment logs	Chronological enrolment of Subjects by Subject number	☐
Visit log	Records for all site visits, monitoring visits, sponsor visits, auditor visits, agency audits	☐
Data query tracking	Data query tracking, monitors site queries and correspondence	☐
Clinical study report	Final clinical study report (signed copy) if provided	☐
Signed Informed Consent Forms	Informed Consent forms should be fully signed with all signatories dating their own signature. In addition, time of consent should be recorded in order to establish that consent was obtained prior to any trial procedures. Where informed consent is placed in the medical record, a file note stating this must be added to this section of the file	☐
Other-study specific	Other documents not included in the previous sections	☐