STUDY BINDERS - Guidelines, table of contents and section detail

The Study Binder:

- Can be used for all study types (drug/device and non-drug/device research)
    - Grey sections = drug/device studies only
- Contains material relating to the conduct of the study
- Should be maintained centrally within Campus (if multiple departments within Campus are participating, each department should maintain core sections for staff reference).
- Must be kept in accordance with these guidelines (contain standard dividers)
    - A copy of this filing guideline is placed in each investigator file
- May be audited by Campus governance staff
- Must NOT contain participant identifying documentation (except for screening logs [initials])
- Has been formulated to meet the guidelines of the National Statement on Ethical Conduct of Research in Humans and Notes for Guidance on Good Clinical Practice (with TGA's annotated comments)

File Notes

- Place these in the section that they are relevant to.

Archiving

- While the study is open study documents are stored at the site where the study is conducted
- Once the study is closed documents are archived in accordance with ICH, FDA, Department of Human Services and RDE guidelines (may include off-site document storage and electronic archiving).

Templates

At the end of this document several useful templates are available for your adaptation and use.

Other files

Pharmacy Documentation

- The pharmacy department maintain their own files and records for clinical drug trials. Although the responsibility for investigational product accountability rests with the Principal Investigator, it is usually delegated to an appropriately qualified person. It is strongly recommended that the delegation be to RCH Pharmacy as clinical trials pharmacists have the knowledge and experience to manage all aspects to the required regulatory and good clinical practice standards. The requirements cover areas such as detailed recording of:
    - Product delivery to the trial site
    - Product inventory including dispensing to and returns by participants, product expiry, product disposal
    - Adherence to product storage requirements

Case Report Forms (CRF) and Participant/Guardian Information and Consent Forms (and other participant documentation)

- CRFs and signed PGICF/PICFs as well as any other participant documents (e.g. completed questionnaires) are stored separately by study staff in individual participant files.

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FOR DRUG & DEVICE TRIALS ONLY

20.0	**Regulatory Documents**
20.1	COPY OF NOTIFICATION TO REGULATORY AUTHORITIES (CTN/CTX) (fully signed by all parties)
20.2	ADDITIONAL REQUIREMENTS WHERE MCRI/RCH IS THE SPONSOR - Initial Notification: PI to retain record of submission to TGA (e.g. cover letter, Express Post record) - Notification of Completion: PI must notify the TGA when the final Australian trial site has been closed (e.g. a Clinical Trial Completion Advice form for trials under the CTN scheme).
21.0	**Investigator Brochure**
22.0	**Investigational Product**

DEFINITION AND REQUIREMENTS OF EACH SECTION

1. Contact list

Contact list (usually a table) listing all study related personnel and services that the study staff may need to contact during the course of the study.

Include contact details for those of the following (where applicable):

- All members of study staff
- Pharmacy personnel
- Collaborators, such as statisticians
- Laboratory services
- Address for shipping of any samples
- Companies for ordering any supplies
- Randomisation services
- Any emergency contact details

Suggested additional detail - notes on availability

2. Study Start-up Checklist

Certain steps must be taken before a research team is ready to start recruiting participants into a new study. It is recommended that a checklist is completed and filed to document that all the necessary steps were fulfilled prior to initiating the study.

Other documentation related to the commencement of the study should be filed in this section, such as minutes from a study team initiation meeting (if one is conducted) to confirm the preparedness of all study staff and to formalise the start of the study.

3. Protocol

All versions as provided to and as approved by ethics, including signed protocol signatory ('acknowledgement') page, should also be in this section

3.1. Current HREC approved study protocol

A copy of the most updated, currently approved protocol must be on file and easy to find for all study staff that may need to refer to it.

3.2. Superseded study protocol

To document revisions of the protocol that takes effect during the study.

4. Participant Information

Master documents that can be copied and provided to potential participants (and/or their parents) should be kept in here.

4.1. Current HREC approved PGICF & PICF

A blank copy of the currently approved information statement and consent form(s).

4.2. Current HREC approved other information for participants (advertisements, diaries etc)

A blank copy of the currently approved document(s).

4.3. Superseded PGICF & PICF

Blank copies of all previously approved PGICF/PICFs must be included here, include tracked versions.

4.4. Superseded other information

Blank copies of all previously approved other documents must be included here, include tracked versions.

4.5. For translated documents:

- Retain forward- and back-translations and certification by translators.

5. Ethics & Governance

The purpose of this section is to document that the research, and any amendments and/or revisions have been subject to HREC and/or Governance review and given approval plus to identify the current version number and date of the study document(s).

5.1. Approval certificates

Ensure that this section contains letter/s documenting the ethics committee and governance approval of the following documents:

- Approval of the current protocol
- Approval of the current informed consent form
- Approval of the current version of any materials viewed by participants (such as recruitment advertising materials, participant letters, participant questionnaires or diary cards, if applicable)
- Approval of the prior versions of all of the above documents, if applicable
- Approval of the Annual Report submitted for Annual Review

All approval letters must document the version number and version date of the document being approved, as well as the date the approval is granted.

5.2. Submission documentation (initial and amendments)

The complete signed applications that were submitted to the ethics/governance office should be filed in this section, along with any pertinent correspondence between the study staff and the ethics/governance office, such as requests for changes to documents or responses to questions raised by the committee.

All subsequent submissions also need to be filed. This includes (but is not limited to) protocol amendments, revised PICF/PGICF or recruitment advertisements.

5.3. HREC membership list

To document that the HREC is constituted in agreement with Good Clinical Practice.
If the Principal Investigator is a member of HREC, check for a statement that he/she did not vote on the project.

5.4. Annual and final study reports

Annual report - Ethics approval is conditional on annual review of each ongoing project by the ethics committee.

Final report - It is an NHMRC requirement that all investigators undertaking research approved by an Institutional Ethics Committee submit a Final Report once the research has ceased. A copy of the submitted Final Research Report must be filed in this section, prior to archiving the contents of the study binder.

5.5. Other Correspondence

Include in this section any letters to and from the ethics/governance office that do not fall into one of the categories above. This will include (but is not limited to) protocol deviations and violations, change of investigator letters and date safety and monitoring board letters.

6. Participant Screening and Enrolment logs

The purpose of a **screening log** is to keep a record of all potential participants who were screened for inclusion in the study, tracking the outcome of the screening.

The log includes data on those that are screened but found to be ineligible, and those that refuse consent. The reason for screened participants being excluded from enrolment is recorded. This information can be valuable as it builds up over time to identify any selection bias. For studies with difficult recruitment, the screening log may also provide patterns of ineligibility which may be helpful to investigators.

The participant **enrolment log** is a list of all participants enrolled into the study, in chronological order of enrolment. The log documents the status of each enrolled participant; current study participants, number enrolled, number that have completed the study, and number of early withdrawals.

7. Study Procedures

A Study Procedures Manual (sometimes called a Manual of Operations or a Study Coordinator's Manual) is a reference document that clearly outlines the details of how to carry out the procedures detailed in protocol.

The following are examples of some sections that are commonly included in a study manual;

- Diagram of procedures to be conducted at each visit
  - A quick reference flow chart describing the procedures that are required at each subject visit, based on the protocol. This ensures no procedures are omitted and is a more practical reference than the protocol.
- Sample Handling Procedures
  - A reference or flow diagram of steps to follow when collecting blood, tissue or urine samples for the study, to ensure that they are processed, packaged, labelled, stored and transported correctly.
- Annotated Forms
  - Examples of correctly completed forms can be filed as useful references for study staff, such as a pathology request form completed for a 'dummy subject'.

- AE Grading Reference
  - If the criteria for grading the severity of adverse events are not detailed in the protocol, file an appropriate grading scheme in the Study Procedures Manual, such as the NCI's Common Terminology Criteria for Adverse Events (CTCAE) v4.0 available as PDF at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x8.pdf

This section also contains the current, approved version of any materials to be viewed by participants and/or their legally acceptable representatives (such as recruitment advertising materials, participant letters, updates, participant questionnaires or diary cards).

Superseded versions of previously approved participant materials should be filed behind the current version and clearly marked as 'superseded'.

8. Data – Forms & Procedures

Case Report Forms (CRFs) are the official data-recording documents used in a study. Relevant data is transcribed from the patient record (and other sources) onto the CRF pages in a specific format, in accordance with the protocol. This allows for efficient and complete data processing, analysis and reporting. The CRF is designed according to the protocol: all data specified in the protocol *must* be collected on the CRF, and data that will not be analysed **should not** appear on the CRF.

A blank copy of all other data collection tools, such as surveys, eligibility forms, templates for the participant study visit data, should also be filed in this section.

8.1. Blank Sample CRF

Approved version of sample CRF (a blank set that can be duplicated)

8.2. Superseded CRF

Any versions of the CRF that have been superseded (clearly marked as so) so that this section forms a complete record of any changes in data collection throughout the study (this is relevant only if your site is responsible for CRF design).

8.3. CRF completion guidelines

It is advisable to create a document describing the rules for completing CRFs to ensure consistency in the data. For example, the guidelines may specify how to complete fields if some data was not collected or unknown, how to correct errors made on the CRF, etc.

8.4. Data queries

Include details in this section regarding how queries will be generated from completed CRFs and the resolution process and timelines. Include Data query tracking, monitors site queries and correspondence.

8.5. Decoding and unblinding

Include information regarding how, in case of an emergency, the identity of blinded investigational product can be revealed for a participant (ensure that the blind is not broken for the remaining participants).

9. Adverse Events

9.1. Internal SAEs (Serious Adverse Events) and SUSARs (Suspected Unexpected Serious Adverse Reactions)

A condition of ethics committee approval for each study is that Serious Adverse Events (SAEs) are reported to the ethics committee to enable their ongoing review of the ethical acceptability of the study. The participant should be referred to in the report by their study ID, not their name, so that this documentation does not compromise participant confidentiality. Any supporting documentation submitted to the ethics committee (such as death certificates) should be de-identified.

A copy of the submitted documentation for every SAE reported to the ethics office can be filed in this section or in the specific participant's study file. HREC acknowledgement of the submitted report should also be filed in this section.

9.2. External SUSARs (Suspected Unexpected Serious Adverse Reactions

SUSARs (individual or periodic line listings) occurring at other sites and requiring submission to the ethics committee should be filed here, along with HREC acknowledgement of the submitted report.

10. Data and Safety Monitoring

All studies should prepare and work to a documented plan for monitoring study data. For intervention studies, a plan for monitoring safety should also be developed and adhered to. All monitoring plans should be filed in this section.

Where separate groups (e.g. data monitoring group or an external, independent Data and Safety Monitoring Board [DSMB]) are utilised to oversee the study, all reports and correspondence should be filed in this section. DSMB (if applicable) terms of reference and membership should also be filed in this section (if your site is undertaking overall conduct of the study).

11. Monitoring/Audit

If your study is audited by a member of the Ethics Office or an external monitor, letters and reports documenting the auditor's visit and findings should be filed here. All general monitoring correspondence (unless specifically belonging in another file section), pre-study monitoring report, feasibility assessments, monitoring visit reports and follow-up letters, monitor-site correspondence, close-out visit reports should be included here.

12. Site Documentation

This section must include details of any supporting departments to be used during the study to document competence of the facilities to perform the required test(s) and support the reliability of test results. For example:

- laboratory certification (NATA, CLIA)
- laboratory normal values for medical/laboratory/technical procedures and/or tests included in the protocol
- log of tissue samples retained at site

- refrigerator and/or freezer temperature logs.

13. Study team documentation

13.1. Delegation and signature log

The delegation logs are to document signatures and initials of all persons authorised to make entries and/or corrections on CRFs, sign consent forms and undertake procedures as detailed in the protocol.

The delegation log is a record of the study tasks that have been delegated to each staff member by the Principal Investigator (PI). The delegation log provides a quick reference of who is authorised to do what on the study; staff must only perform tasks for which they have been delegated.

The delegation log also captures the signature and initials of all staff members prior to start on the study which, for example, helps to authenticate CRF entries and prescriptions.

13.2. Qualifications (CV) and Training

The Principal Investigator is responsible for ensuring that all research staff are qualified by education, training and experience to adequately perform their delegated study tasks and, if applicable, to provide medical supervision of research participants.

In this section file documentation evidencing the appropriate qualification of all study staff listed on the delegation log. Such documentation may include:

- copies of signed and dated CVs (check CV is current and lists current institution and role)
- training certificates (e.g. ICH-GCP, hazardous substances, IATA)
- licences (e.g. a licence to give injections, a medical license).
- Study-specific training (protocol, protocol amendments etc)

Any study specific training materials generated for training study staff should also be filed in this section.

14. Supplies/Shipping records

For accountability, in this section file documentation relating to study supply provision (excluding investigational drugs/devices – see section 23).

15. Legal Documentation

In this section file:

- Original Financial Agreement/Budget Details (including grant application and conditions of award) – original and any revisions (if applicable) - clearly indicate the most recent version.
- Any other agreements that are made in relation to the study should be filed in this section, such as the agreement of a collaborating statistician to provide a certain number of hours of support, a publication agreement made with collaborators or an agreement with the pharmacy that clarifies their role in the study. If agreements are revised during the course of

the study, revised documents should be filed in the section, marking the prior versions 'superseded'.

The following documents should also be filed in this section:

- Confidentiality agreements
- Correspondence with hospital insurers or lawyers
- Indemnity (if applicable)
- Insurance Certificate (if applicable)

16. Finance Documentation

In this section file:

- FDA 1582 forms and any financial disclosure forms for any person listed on the FDA Form 1582 (IND study only).
- Any records related to participant reimbursements (if applicable and approved by the ethics committee).
- All other finance documentation.

17. Correspondence

Keep pertinent correspondences detailing any agreements or significant decisions or discussions regarding study conduct. The correspondence may take the form of emails, letters, meeting notes/minutes and/or notes of telephone calls.

17.1. Sponsor/Funding body

Any pertinent correspondence between the study team and the sponsor or the funding body of the study.

17.2. General

Any correspondence that doesn't fall in the above sections, include three-way communications.

17.3. Newsletters

Any newsletters from the sponsor of the study regarding the project, or any newsletters generated by the study team for distribution

17.4. General

Include in this section any other correspondence.

18. Study reports/publications

This section can be used to file the publications related to the study and the study interim report, if applicable.

19. Other

Include here any documents that do not fall into any of the above sections.

********** FOR DRUG/DEVICE TRIALS ONLY **********

20. Regulatory documents

This section must include copies of

- For all clinical trials
  - Initial notification/submission – a copy of the fully executed document (signed by all parties) Australian CTX or CTN form, other regulatory agency form (where applicable) and all correspondence to the regulatory agencies (e.g. TGA).
- For trials where MCRI/RCH is the Sponsor:
  - Initial notification – PI should retain documentation of submission to TGA (e.g. cover letter, Express Post record) or other regulatory agencies (where applicable).
  - Notification of Completion: PI must notify the TGA when the final Australian trial site has been closed (e.g. for trials under the CTN scheme a Clinical Trial Completion Advice form must be completed).

21. Investigational product information – Investigator Brochure (IB)

The IB documents that relevant and current scientific information about the investigational product has been provided to the investigator. Include the current HREC approved/acknowledged IB here.

Note that information on investigational products that are already registered in Australia can be found on the TGA website http://www.tga.gov.au/about/ebs-picmi.htm#.UwWYl63xuUk in the form of:

- Consumer Medicine Information (CMI) – this is a plain language leaflet about the safe and effective use of a medicine.
- A Product Information document (PI) provides health professionals with a summary of the scientific information relevant to the safe and effective use of a prescription or pharmacist-only medicine. The information has been written by the pharmaceutical company responsible for the medicine and has been approved by the TGA.

21.1. Superseded IB/PI/CMI

This can be the front page of the document only (to conserve space)

22. Investigational product accountability

Responsibility for investigational product accountability rests with the Principal Investigator; it is usually delegated by the Principal Investigator to an appropriately qualified person. It is strongly recommended that this be delegated to RCH Pharmacy as clinical trials pharmacists have the knowledge and experience to manage all aspects to the required regulatory and good clinical practice standards. The requirements cover areas such as detailed recording of:

- Product delivery to the trial site
- Product inventory including dispensing to and returns by participants, product expiry, product disposal
- Adherence to product storage requirements