UTS IMPACCT Trials Coordination Centre

Standard Operating Procedure

6.12 Ethical Approval, Review and Reporting

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Introduction / Background

Good Clinical Practice requires that clinical study investigators are aware of their responsibilities regarding communication and compliance with Human Research Ethics Committees (HREC) through all stages of the study, and that the clinical study is properly conducted, and human participants are adequately protected.

The International Conference on Harmonisation of Good Clinical Practice (ICH GCP) guidelines and the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research describe in detail the process of obtaining review and approval by institutional review boards (IRB) and/or independent ethics committee (IEC). These principles and requirements apply to all studies conducted by the IMPACCT Trials Coordination Centre (ITCC) and are underpinned by the suite of ITCC Standard Operating Procedures (SOPs).

Objective

This SOP describes how sites communicate with the HREC to comply with regulations, to protect the safety of participants, and operationalises the national and international requirements by describing:

- the process of human research ethics submission, review, and approval at a lead site or single site level by HRECs in Australia;
- the process of human research ethics submission, review, and approval at an individual site level by Research Governance Office (RGO) in Australia;
- the process of documenting all studies undertaken or auspiced by the ITCC, where the suite of ITCC SOPs form the guiding procedural framework.

This SOP combines the ICH GCP sections of 5.11 (sponsor responsibilities for HREC submissions and approvals) and 6.12 (ethics), and does not replace other requirements from the ICH GCP, NHMRC and Human Resource Ethics Committee (HREC) documents.

Scope

This SOP applies to all staff involved in clinical studies conducted by ITCC irrespective of individual organisational employment, role, or position.

Ownership and Responsibility

The Coordinating Principal Investigator (CPI) of the protocol and/or Lead Site Principal Investigator (PI) if different to the CPI and ITCC.

Responsibilities of the Coordinating Principal Investigator (CPI) and/or Lead Site PI

- To ensure all essential documents are prepared, in date and provided for the Lead HREC, site RGO and UTS HREC ratification applications. Note that master documents are required at the Lead HREC level, and site-personalised documents for RGO level (*refer ICH GCP section 8.2*).
- To access the Lead HREC / RGO / UTS HREC (ResearchMaster) portal to review and sign off on submission application. Should the Lead PI not have UTS affiliation with access to ResearchMaster, the CPI (if different) or a sub-investigator with UTS affiliation will be required to complete this task.

The CPI and/or Lead Site PI may delegate the duties for the document preparation, upload, and portal application preparation (e.g. Site Study Coordinator, study nurse, ITCC staff etc.) and this should be recorded in the Staff Signature and Delegation Log (*refer* SOP 4.2.4 Delegation of Duties), however it is the responsibility of the respective site PI to ensure that all sections of the HREC / RGO application are complete and correct, including the required essential documents attached to the submission.

Responsibilities of ITCC

- To assist the respective PI and/or delegated site personnel with the essential document preparation and HREC/ RGO/ UTS HREC portal application if requested
- To file all communication, submission, and approval documentation within the Trial Master File (TMF) (*refer Template 20*)

Procedure

1. General

- Each study protocol is developed in line with SOP 6.0 Protocol Development and SOP 4.0 Investigator Roles and Responsibilities.
- Each PaCCSC/CST/ITCC study protocol is registered with the agreed study registry and has an allocated Randomised Controlled Trial Register Number.
- Australia has a single ethical review process where one central HREC provides approval for human research projects conducted in publicly funded health services across participating jurisdictions. This is known as the National Mutual Acceptance (NMA) system. During the protocol fiinalisation process, the appropriate HREC and a Lead Site are selected. The HREC is constituted and operates in accordance with the *NHMRC National Statement on Ethical Conduct in Human Research (2007)* (updated March 2014).
    - The Australian Capital Territory, New South Wales, Northern Territory, Victoria, Queensland, Tasmania, Western Australia and South Australia are all participating in the NMA system and have all agreed on a process of single ethical review by a nominated Lead Site HREC. This lead approval covers all subsequent sites across participating states and requires further submission to local RGOs for assessment of local implementation issues such as budget, staff, resources etc. This secondary local approval process ensures that the individual organisation can consider whether the project is suitable for the site, including whether it has the capacity to conduct the research at that site.
- Private sites (such as private hospitals) or sites that are not part of the participating jurisdictions or use private HRECs (such as Bellberry) require separate, single applications as they are not covered under the lead HREC application through the NMA system.
- Steps 2 – 5 below outline shared processes and procedures for single-site and multi-site studies at each level of ethics review described in step 2 (collectively termed “ethics application”), with guidance being general in nature. Individual HRECs and RGOs, including private sites and committees, use their own online portals with specific requirements. Therefore, it is strongly recommended that:
    - The respective PI or delegated representative responsible in the process outlined below, familiarise themselves with specific research office requirements (at either an HREC, RGO or UTS HREC level). This guidance is often located in the research office website for that organisation and includes the meeting schedule and deadline for ethics application submissions.
    - Communication between ITCC and site and/or research office is established early to ensure fewer delays and errors in submission requirements. This includes consultation or inclusion with the process outlined below to ensure that relevant ITCC SOPs are considered.
    - Communication is established between ITCC/ site staff and head of department (HoD) for the upcoming ethics application. This is to mitigate internal site delays,

as departmental approval is often required before it reaches the HREC/ RGO level.

- Step 6 specifically outlines the delegation of duties between CPI, site (including Site PI) and ITCC (also explained in Figure 1)

2. Human Research Ethics Committees (HREC), Research Governance Offices (RGO) and UTS HREC

- The Lead Site obtains and files documentation that lists the constitution of the HREC that has provided ethical oversight of the study, the HREC membership, the HREC NHMRC Number, and confirms the committee's compliance with the national requirements.
- Each site covered by the Lead HREC is required to submit separate applications to their local RGO once Lead HREC approval has been received. They are required to provide HREC approval documentation including associated documents, as well as site-personalised material (such as advertising material with site contact information).
- Additionally, all studies undertaken through ITCC require ratification through UTS HREC. This is submitted through the UTS ResearchMaster portal.

3. Initial submission

3.1. Preparation of essential documents:

The respective PI or delegated representative is responsible for ensuring all essential documents are present for an ethics application. These documents include, but are not limited to, those listed below (*refer* ICH GCP section 8.2):

- Institutional application form, and payment for industry sponsored studies
- Protocol and any protocol amendments including version numbers
- Investigator's brochure if required or Product Information
- Master Participant Information and Consent Forms (*refer* SOP 4.8.2 Participant Information and Consent Form)
- Other documents being provided to potential participants as master versions such as questionnaires
- Any other supporting documentation to be considered (for e.g., Scientific Assessment Reviews and Declaration of Prior Review form)
- Indemnity certification from the appropriate authority for that site
- Completed or draft Clinical Trial Notification forms where applicable
- Recruitment and marketing materials
- Supporting documents providing jurisdiction-specific information (e.g. Victorian Specific Module)
- Other documents as requested by the HREC
- One copy of the submission documents is to be kept in the Lead Site files, with an additional copy provided to the ITCC.

3.2. Completion of Human Research Ethics Application (HREA)/ Site Specific Assessment (SSA)/ UTS HREC ratification through online portals

The respective PI or delegated representative is responsible for completing the HREA/ SSA/ UTS HREC ratification within the respective portals, ensuring all sections are completed with as much information as required, avoiding jargon where possible. Ethics applications address the following areas (*refer* NHMRC National Statement on Ethical Conduct in Human Research):

- Risk and benefit: Ethics application portals provide a series of questions to determine the risk level of the proposed study. These can be A) Negligible, B) Low risk, or C) High risk as determined by the information below:
  - Vulnerability of the patient population (including age, dependence, and socioeconomic status), recruitment, privacy, and consent procedures
  - Sample and data collection and storage
  - Risk/ harm assessment of the proposed intervention
- Site list
- Investigator list (including information regarding responsibilities, experience and positions held)
- Funding information
- Project information (including a lay summary, trial design, intervention information, predicted study length)
- Data collection, use, storage, and archive
- Previous endorsements/ independent reviews
- Attachment of associated documents as prepared in Step 3.1 above.

3.3. CPI or site PI review and submission of ethics application

After the completion of Step 3.2, the respective PI is responsible for ensuring all sections have been completed with sufficient information and documentation. Following their review, they, or a delegated representative (if permitted within the portal) are responsible for submitting the ethics application. If required, it is recommended that the HoD is notified of this submission, as per the above guidance. This should ensure the timely review by the HREC/ RGO/ UTS HREC.

4. During the approval process

- All questions and requests for change arising from the HREC deliberations are copied to the:
  - Lead Site PI or Site PI
  - CPI (of the protocol)
  - ITCC
- All correspondence between the Lead Site and the HREC/ RGO/ UTS HREC is copied to the ITCC.

5. Communications

- Following approval of the protocol, any protocol amendment that requires a change in research activity is submitted to the Lead HREC, RGOs and UTS HREC. Administrative amendments are addressed in the submission of a revised protocol at

the completion of the study. Identification of the protocol and amendments is in line with SOP 6.10 Version Tracking.

- The Lead Site/ Site PI in consultation with the CPI provides interim and/or annual reports and a final written report to the HREC. Copies are maintained in the investigator files in accordance with the SOP 8.0 Essential Documents, SOP 8.4.1 Archiving of Research/Project Materials, and SOP 5.5.1 Electronic Data Handling.
- In addition, the Lead HREC and each RGO require periodic renewal of ethical approval (usually annually). Notification for this is copied to the ITCC.
- Written approval from the Lead HREC and site RGO to implement the protocol must be received prior to the commencement of the study. Any documentation modified during the course of the study is submitted to the Lead HREC and each site RGO.
- The reporting of all adverse and serious adverse events of studies is in line with SOP 5.17 Adverse Event Reporting.
- In the event that a study is terminated or suspended prematurely, the Lead HREC and relevant RGO is immediately informed and followed up with a written explanation of the termination or suspension.

6. Delegation of procedures for multi-site study under review by a Lead HREC (see Figure 1)

The ITCC:

- Before Lead HREC submission:
  - Discusses and appoints a Lead Site for the study and determines the Lead HREC.
  - Supplies the:
    i. Current protocol.
    ii. Investigator's brochure or Product Information if required.
    iii. Master Participant Information and Consent Form (PICF).
    iv. Master versions of other study documents (e.g., recruitment and retention materials, questionnaires, guides and instructions etc.)
  - Draft the HREA.
  - For sites covered by the lead HREC but which are located in states that use a different portal to the lead HREC: The ITCC may assist with preparing the minimum data file required to complete the Site Specific Assessment (SSA) form and RGO review process after lead HREC approval is received.
- After Lead HREC/ RGO approval:
  - Arranges sponsor approval and submission of the online Clinical Trial Notification (CTN) and payment to the TGA.
  - Completes and submits UTS HREC ratification.
  - Sends confirmation of listing to individual sites once a recruitment start date has been confirmed. Recruitment must not commence at the site until all requirements are met and formal site activation notification is received (*refer* SOP 5.7 Site Initiation).

The Lead Site/ CPI (or delegated representative where possible):

- Completes and submits the HREA (see steps 3.1 – 3.3), sending a copy to ITCC.
- Responds to Lead HREC questions or requests for clarifications (see step 4).
- Receives and forwards approval letter to ITCC. The approval letter must state exactly:
    - The full site listing covered by that HREC
    - A full list of all documents, including version and date of each document, submitted to the HREC and subsequently approved
- Generates SSA forms for each site, and sends each site the approval letter, respective SSA form and documents listed in step 3a.
- Maintains the Lead HREC correspondence for all submissions and approvals (see Figure 2), including:
    - Correspondence with the Lead HREC;
    - Correspondence with each participating state site, including notification of new sites, change in investigators, protocol amendments, annual/progress reports and any subsequent approvals by the site; and
    - Supplies copies of all correspondence to ITCC

Site PIs (or delegated representative where possible)

- Creates site-personalised documents, including, but not limited to, site-specific PICF, and advertising material.
- Completes and submits the local application to the RGO (see steps 3.1 – 3.3) and sends a copy to ITCC.
- Receives and forwards local approval letter to ITCC listing the exact details of the documents reviewed and approved.
- Each study site maintains a file of correspondence including:
    - Correspondence with the Lead Site;
    - Correspondence with the RGO;

ITCC and all Sites:

All correspondence is filed including:

- Initial submission/ approvals;
- Amendments;
- New sites, changes to investigators;
- Annual and progress reports;
- Adverse and serious adverse reports;
- Any other correspondence.

Figure 1 details the tasks undertaken by each site (assuming ITCC as sponsor).

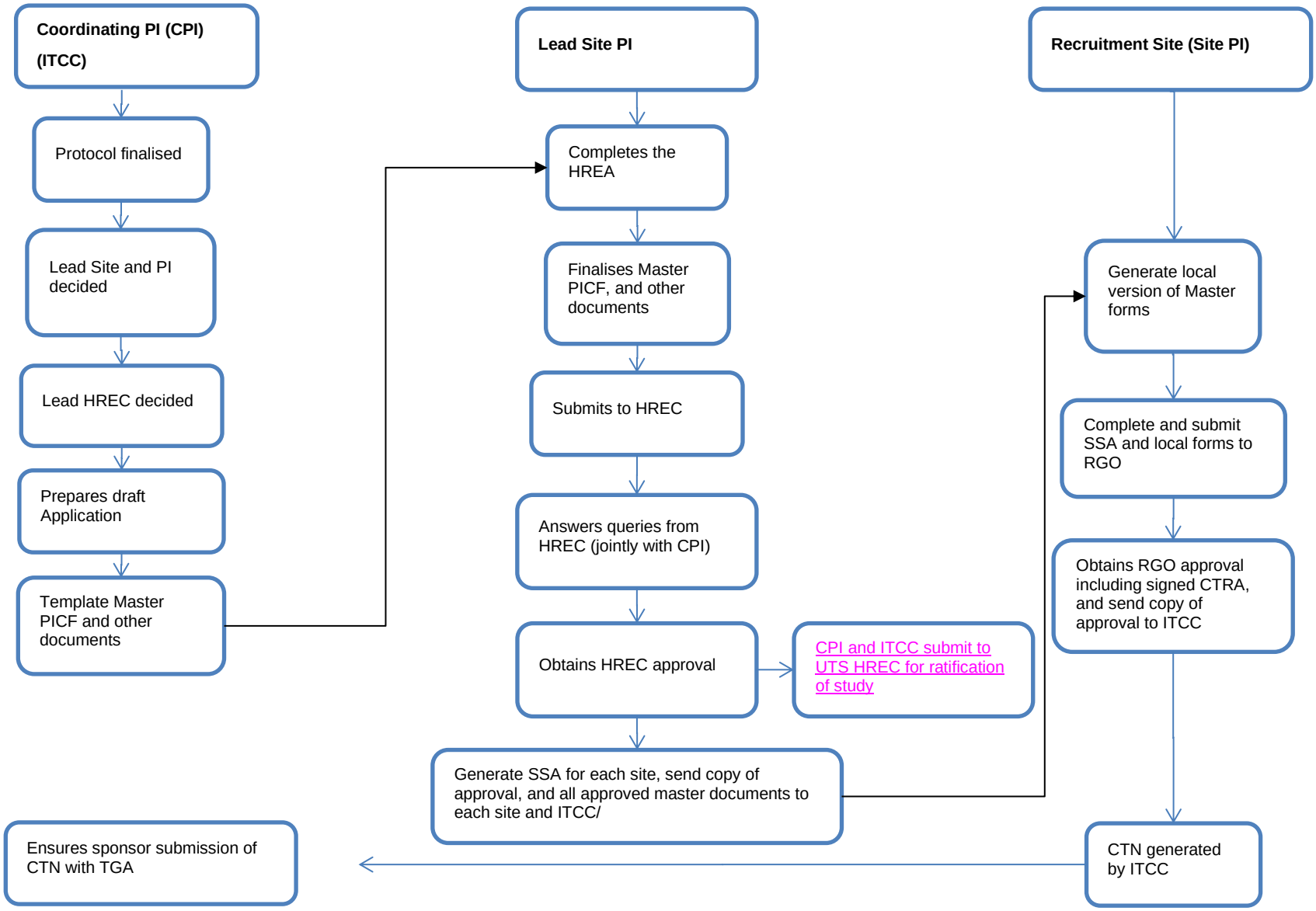

Figure 1 Flow of tasks for each site (assuming ITCC as sponsor)

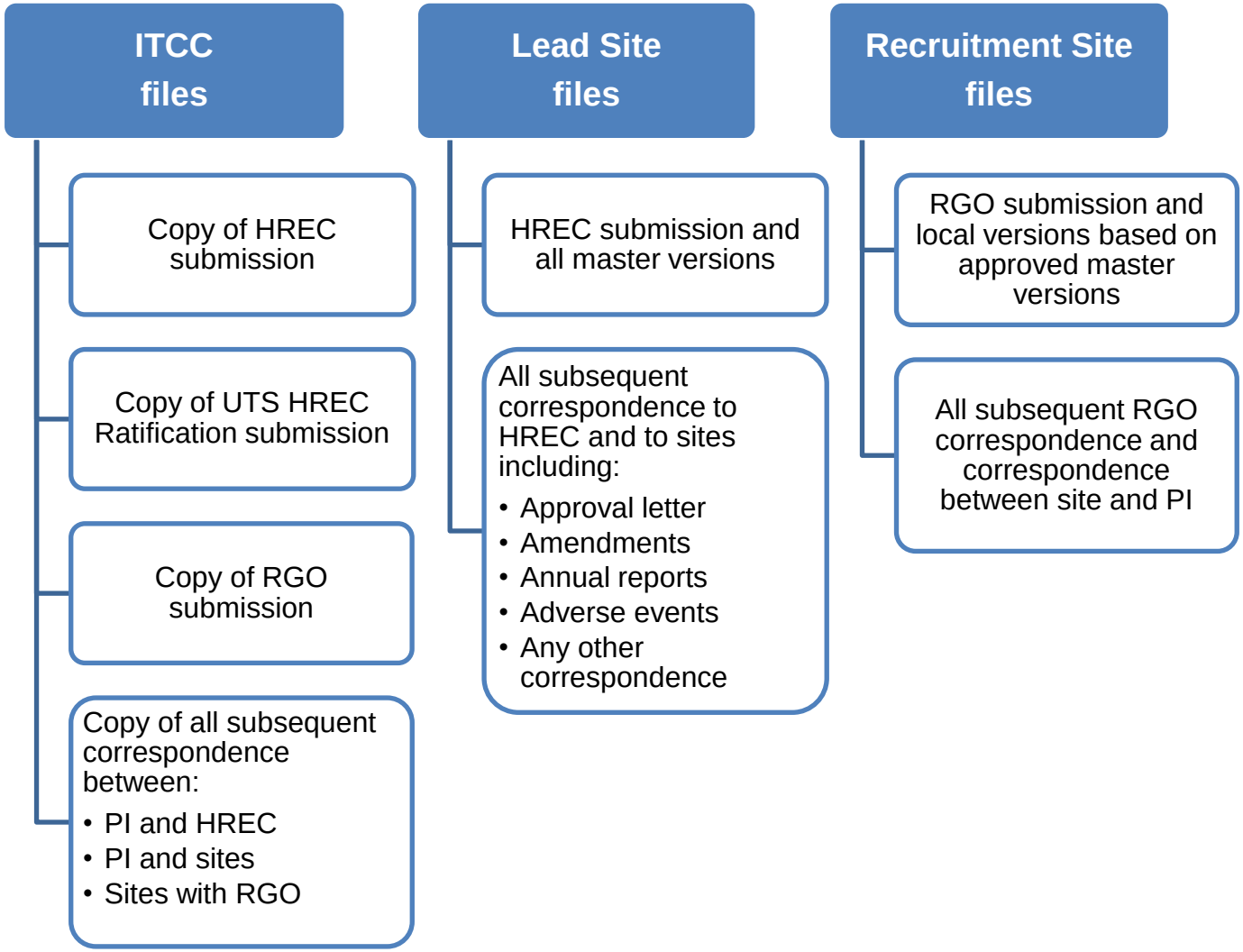

Figure 2 Outline of filing HREC documentation for each site (assuming ITCC as sponsor)

Related SOPs

4.0 Investigator Roles and Responsibilities

4.2.4 Delegation of Duties

4.8.2 Participant Information and Consent Form

5.17 Adverse Event Reporting

5.5.1 Electronic Data Handling

5.7 Site Initiation

6.0 Protocol Development

6.10 Version Tracking

8.0 Essential documents

8.4.1 Archiving of Research/Project Materials

Related Templates

20 Trial Master File Index

References

COSA Standard Operating Procedures for Investigational Sites. March 2006. A publication of the Centre for Clinical Research Practice, Inc.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). November 2016 (accessed 06/01/2022)

https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf ISRCTN International Standard Randomised Controlled Trial Number Register (accessed 26/02/2020) https://www.isrctn.com/

National Statement on Ethical Conduct in Human Research (2007) - Updated March 2018 - (accessed 06/01/22) http://www.nhmrc.gov.au/guidelines-publications/e72

Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Annotated with TGA comments 2000 (accessed 17/01/22)

https://www.tga.gov.au/sites/default/files/ich13595an.pdf

History			
Version	Date	Author	Reason
1.1	10/01/2006	Contributing authors	New procedure
1.2	25/02/2007	S Whicker	Administrative update
1.3	18/07/2007	B Fazekas	Update prior to MAB review
1.4	16/10/2007	B Fazekas	Update after David Currow review
1.5	30/06/2010	B Fazekas	Periodic review
2.0	3/02/2011	B Fazekas	Changes ratified by MAB
2.1	7/03/2014	B Fazekas	Periodic review
2.2	3/06/2015	C Hope	Periodic review
2.3	28/02/2018	B Fazekas, S Kochovska	Periodic review Publication of the ICH GCP E6 (R2)
2.4	26/02/2020	V Yenson S Kent	Periodic review IMPACCT Trials Coordination Centre
2.5	11/02/2022	V Yenson	Periodic review Combining PI and Sponsor responsibilities

Approval		
Version	Approval Name	Approval Signature
2.5	Meera Agar