Introduction to Good Clinical Practice

Natalie Barber
Head, Research Governance and Platforms
Telethon Kids Institute

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Good Clinical Practice

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Introduction to Good Clinical Practice

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GCP Overview

- Standards and why we have them
- Study Set-up – responsibilities, approvals and essential documents
- Informed Consent
- Case Report Form, Source Data and Data Entry
- Safety Reporting

Standards and why we have them

- What is the significance of standards in clinical research?
  - Safeguard and protect research subjects
  - Risk Reduction
  - Quality data/outcomes
  - Excellent research, good science
What is GCP?

International ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

Standards and why we have them

- Nuremberg code 1947
- Declaration of Helsinki 1964
- Therapeutic Goods Act 1989
- International Conference on Harmonization (ICH) GCP 2016 (E6(R2))

Regulations

- Therapeutic Goods Administration (TGA)
  - Therapeutic Goods Act 1989
    - Responsible for regulating medicines and medical devices

- National Health and Medical Research Council (NHMRC)
  - NHMRC act 1992
    - Specifically required to issue guidelines for the conduct of medical research and ethical matters related to health.

In Australia, all research involving humans must comply with:

- National Statement on Ethical Conduct in Human Research 2007 – updated 2018 NHMRC (The Statement)
- Australian code for the responsible conduct of research
  - Developed jointly by the NHMRC, the Australian Research Council and Universities Australia (The Code)
  - State and territory guidelines.
Regulations

- Clinical trials of medicines and medical devices also must comply with:

  *Note for guidance on good clinical practice* (CMP/ICH/135/95) (Therapeutic Goods Administration)

Clinical trials of medical devices must also comply with ISO 14155:2011 Medical devices — Clinical investigation of medical devices for human subjects: Good clinical practice.

WA Health Research Governance Policy

All human research and experimentation conducted within WA Health:

- World Medical Association
- National Statement
- The Code

And:

- National Health and Medical Research Council “Values and Ethics: Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research” 2003;

- TGA “The Australian Clinical Trials Handbook” 2006, and “Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)” 2000; and

- Relevant Commonwealth or State legislation and guidelines including the Department of Health “Occupational Safety and Health Policy” 2005.

13 Principles of GCP

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory.

2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

13 Principles of GCP

5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
13 Principles of GCP
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.*
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented. *

Standards and why we have them
• Ever evolving in response to changing landscape
• No single document which provides the standards and laws by which you conduct clinical research.
• Ensure you are aware of and compliant with relevant laws, policies and codes of conduct
  – Additional information provided in handouts

Study Set-up
“In any successful project the important factor is your belief. Without belief there can be no successful outcome”
William James

GCP Guidelines
Responsibilities: Sponsor

- For securing the arrangements to initiate, manage and finance a study
- They can delegate any or all of their functions to third parties but they cannot delegate responsibility
- Where delegated there must be arrangements in place for oversight of the delegated activities
- Clinical Trial responsibilities with respect to GCP are extensive
- Detailed in item 5 of the Note for Guidance on GCP¹


Responsibilities: Principal Investigator

- Coordinating Principal Investigator
  - Overall responsibility for the research project
  - Submits the project for ethical and scientific review for multi-centre projects.
  - Ongoing communication with the Human Research Ethics Committee (HREC) and passing on any outcomes from this to the Principal Investigators. This includes annual progress reports and final report including outcomes to the HREC
  - Duties delegated by the Sponsor

- Responsibilities: Sponsor

  - Risk and Quality management
  - Medical expertise
  - Trial design analysis
  - Trial management and Data Handling and Record Keeping
  - Selection of appropriate investigator(s) and institution(s)
  - Insurance and indemnity
  - Approvals (HREC, TGA etc)
  - Manufacture, packaging, labelling/coding
  - Safety evaluation
  - Monitoring/Audit/Inspection
  - Clinical Study Report
Responsibilities: Everyone

- **Everyone’s Responsibilities**
  - Ensure the safety and wellbeing of the participant
  - Fulfil the duties delegated to you

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Approvals

- Do not start until:
  - Favourable opinion from a Human Research Ethics Committee
  - Authorisation to commence a project at site
  - For Clinical Trials
    - CTN or CTX
    - Registered on Clinical Trial Registry E.G. [http://www.anzctr.org.au/](http://www.anzctr.org.au/)

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Approvals

- **Clinical Trial Notification (CTN) Scheme**
  - Notification of intent to conduct a clinical trial to TGA
  - HREC responsible for scientific validity, safety efficacy and ethical acceptability and approval
  - TGA does not review any data relating to the clinical trial

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Approvals

- Once the Sponsor, PI, chairman of the HREC, and the person responsible from the Approving Authority have signed the CTN form it is submitted to the TGA along with the appropriate notification fee

- **CTN trials cannot commence until the trial has been notified to the TGA and the appropriate notification fee paid**
Approvals

• **Clinical Trial Exemption (CTX) Scheme**
  – Sponsor submits an application for evaluation and comment
  – TGA reviews summary of pre and clinical data, overseas status, proposed usage guidelines
  – **Cannot commence the trial until written advice received from the TGA AND approval obtained from an ethics committee and institution at which the trial will be conducted.**

Study Protocol

• Research approvals consider the protocol
• Sets out the specific procedures for conduct and data collection
• Must be followed to ensure consistency
• Document acceptance to follow protocol – signature page required

Feasibility

• Before agreeing to conduct the study, PI must consider;
  – Requirements of the Protocol
  – Participant population
  – Staff to conduct the study
  – Specific equipment
  – Support from other departments, e.g. pharmacy and imaging

Investigational Product

• PI must ensure appropriately trained person takes responsibility for IMP, usually Pharmacists
• **Both** responsible for ensuring systems are established, documented and people trained
• Covers all stages from receipt of IMP to return to Sponsor or destruction
Investigational Product

- Must ensure compliance with the protocol
- Records must be kept at each stage
- What been done, by whom, when
- Quantities
- Batch or Serial Numbers
- Expiration dates
- Unique codes relating to participant

And also......

- Establish Systems and processes
  - Documented, SOPs, compliance, trained
- Calibration of Equipment
- Randomisation
- Blinding
  - Everyone must know how to unblind in an emergency

Essential Documents

- “Essential documents are those documents which individually or collectively permit the evaluation of the conduct of a trial and quality of the data produced.” ICH GCP 8.1

- Demonstrate the compliance of the Investigator, Sponsor and Monitor with the standards of Good Clinical Practice and all applicable regulatory requirements.
**Essential Documents**

- So how do we organise this mass of documents?

**Site File**

- The Sponsor and Principal Investigator must keep a Trial Master File (TMF) for each study
  - ICH GCP refers to a TMF for all studies, not only clinical trials
  - PI copy sometimes known as a Site File
  - TMF normally held at CI office or study coordinating centre

**Site File**

- A collection of documents which ‘tell the story’ of the study which has a beginning, middle and end
- Not a single file, but a filing system
- Contains every piece of information you receive at site relating to a specific study (including emails/letters/conversations between Investigators and team)

**Examples of Essential Documents**

- An easy way to remember all essential documents is to put them into two simple categories
  - Non-participant specific
  - Participant Specific
Non-participant Specific

- Protocol including amendments
- Letters of invitation to send to potential participants
- Participant Information Sheet
- Consent/Assent Form (unused)
- Regulatory applications and responses/approvals
- Delegation log/CVs/GCP certificates
- Correspondence/newsletters
- Safety reports

Participant Specific

- Case Report Form (data collection tool)
- Signed consent forms/assent forms
- Data queries
- Patient notes
- Search lists identifying potentially eligible participants

Essential Documents should be

- Filed in a designated file(s)
- Kept in a designated place
- Maintained by a designated person(s)
- Archived for recommended time

Storage of Essential Documents

- Safe secure storage is vital
- The physical integrity of the Site File must be maintained
- The Site File must have protection from the environment (damp, mould, fire, pests etc.)
- Space to store essential documents is often underestimated
Storage of Essential Documents

- Although the Sponsor will hold almost identical TMF, only the local Site File (Principal Investigator’s) will contain the subject identification list.

No participant identifiable data should be provided to the Sponsor
(unless agreed by Research Ethics Committee)

Delegation of Duties Logs

Probably the most important ‘essential’ document as it is the only one which identifies the individuals to whom the PI has delegated study specific tasks.

Delegation of Duties Logs

- The PI must review and sign the Delegation of Duties Log for each study and
  - Must be satisfied as to the competence of the individuals to whom they are delegating
  - Ensure that all individuals are informed of their involvement and the duties required of them
- CVs, GCP certificates (and job descriptions) must be available for everyone on the Delegation of Duties Log

Remember

If it is not documented it did not happen!
Informed Consent

“A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate. Informed consent is documented by means of a written signed and dated Informed Consent Forms.”

ICH GCP 1.28

Informed Consent Children and Young People

- The Statement Chapter 4.2 Children and Young People addresses principles that apply specifically in research

- WA Health Research Governance Procedures section 3.6.1 Recruitment of Minor (aged less than 18 years of age) in Research

Consent Process

- Process is not a single act

- Introduce study idea, give verbal/written information to the participant
  - Participant Information Sheets, consent and assent forms as approved by the HREC
  - Refer to 4.8.10 of Note for Guidance on Good Clinical Practice for comprehensive breakdown of what to discuss regarding consent (a-t)
Consent Process

- Time to think
- Ask/answer questions
- Agreement to proceed from parent/guardian (and child)
- Initial each box
- Sign and date Consent form
  - Parent/guardian must sign and date the forms themselves, the date should not be added by any member of the team
- Completed assent forms, where appropriate
- Re-confirm willingness to continue at every visit

Case Report Form, Source Data and Data Entry

Case Report Form (CRF)

“A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial”

ICH GCP 1.11

Case Report Form, Source Data and Data Entry

Source Data/Documents

“Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial)”

ICH GCP 1.52
Case Report Form, Source Data and Data Entry

- The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site’s trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

ICH GCP 4.9.0

Case Report Form, Source Data and Data Entry

Responsibilities

- Investigator responsibilities refer to section 4.9 of ICH GCP

- Sponsor responsibilities refer to section 5.5 of ICH GCP

Source Data Verification = SDV

- Monitors verify the data collected in the CRF is correct and transcribed accurately from the source

- Every piece of information entered into a CRF or eCRF must be documented in the source data

- Every piece of information should be recorded twice
  - Source is the original entry
  - Transcribed onto the Sponsor’s data collection tool
Golden rules of data entry

- All fields must be complete
- Not Known (NK) only when all avenues are exhausted
- If Not Done (ND) why?
- It is not enough simply to write NK or ND – need to give an explanation why in the Site File/CRF
- Make sure your writing is legible
- Always write in black

- Put a single line through any mistake
- Make the amendment clear
- Never occlude the original entry
- Initial and date any alteration even if completing blank fields retrospectively
- Never, ever use White-out or POST-IT notes

Protocol Deviations

- Minor or Administrative departures from protocol
- Do not affect the scientific soundness of the research or the rights, safety, or welfare of research participants
  - Examples:
    - Follow-up visits outside of protocolled time frame due to participants schedule
    - Blood samples obtained close to but not precisely at the time points specified in the protocol
    - Only to be reported if they occur to a significant proportion of the participants

Protocol Violations

- Major departures from the approved protocol and/or regulatory guidelines
- Compromise the ethical acceptability of the project and potentially affect the scientific soundness of the research and/or the rights, safety or welfare of research participants.
  - Examples:
    - Failure to obtain participant consent
    - Participant inclusion/exclusion violations
    - Compromises to data integrity
  - Must be reported to HREC where the event occurred

Ensuring the Quality of the Data

- Ongoing process
- Oversee progress of the trial
- Ensure trial is conducted, recorded and reported properly
- To the protocol, Sponsor’s SOPs, GCP and applicable regulatory requirements

Monitoring
Ensuring the Quality of the Data

Audit

- Asses at any given moment
- Systematic and independent
- Ensure trial is conducted, recorded and reported properly
- To the protocol, Sponsor’s SOPs, GCP and applicable regulatory requirements

Inspection

- By Regulatory authority – TGA
- Official review of documents, facilities, records and any other resources related to the trial
- Ensure correct conduct and compliant to appropriate regulatory requirements

What is monitored?

- Training and Education: Everyone involved in the research process
- Recruitment Process: Eligibility Criteria and Consent
- Essential Documents: Site File, Delegation of Duties, CRF/Source, Pharmacovigilance
- Regulatory Approvals: CTX, CTN, HREC, Institute

Monitoring Plan

A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial
What is safety reporting?

• In all types of study, data are gathered in order to monitor the effects of the study and any interventions on the participants to ensure their safety.

• Safety reporting is important in order to protect participant during the study and once a practice or treatment becomes standard care.

How do we assess safety?

• By asking the participant a series of questions at every visit.
• By collecting base line information on the health status of trial participants.
• Being aware of concomitant medications.
• Asking about health and concomitant medications at every visit.
• By recording all untoward medical occurrences as required in the protocol.
• By collecting accurate data as appropriate.
• By reporting within specified timelines.

Safety reports are analysed along with the other study data collected to ensure that the benefits of any potential side effects with every treatment or practice but the likelihood of them occurring and the potential risks associated with them are carefully considered before being approved as standard care.
Adverse Event/Reaction

An Adverse Event (AE) is any untoward medical occurrence – there does not need to be a causal relationship between the occurrence and the study or any treatments administered.

An Adverse Reaction (AR): an untoward or unintended response to a new medicinal product or its new usages.

- Record the details in the source data and check the protocol for reporting requirements.

Serious Adverse Event

Serious Adverse Event (SAE) is any adverse event that:
- Results in death
- Is life threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect

Check the definition of Serious in each Protocol
- Other events are sometimes added by Sponsors as appropriate to each study.

Serious Adverse Reaction

Causality is the difference between an Event and a Related event or Reaction.

Definition of Serious is always the same i.e.:
- Results in death
- Is life threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect

Was the event expected?

- There are potential adverse effects to any procedure or medicine. The Sponsor will provide you with details of known adverse effects associated with any of the research procedures and interventions.
  - Clinical and non-clinical data relating to the investigation product will also be provided in the Investigator Brochure.
- Any event which is not consistent with the known adverse effects is Unexpected.
**SUSARs**

- The most closely monitored events are those where there is a combination of being **Serious**, **Related/Reaction** and **Unexpected**

- In a Clinical Trial of an Investigation Product these are known as SUSARs: **Suspected Unexpected Serious Adverse Reactions**

A Serious Adverse Reaction which is unexpected, the nature or severity of which is **not consistent** with the applicable product information.

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**NHMRC Guidance**

- NHMRC Guidance – Safety Monitoring and reporting in clinical trials involving therapeutic goods

- Addresses the collection, verification and reporting of AEs and ARs of IMPs and IMDs under CTX or CTN schemes

- Includes a number of **new definitions**

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**NHMRC Guidance**

- **Significant Safety Issue (SSI)**
  - A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial

- **Urgent Safety Measure (USM)**
  - A measure required to be taken in order to eliminate hazard to a participant’s health or safety

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**Adverse Event Decision Tree**

- Can we identify an event? (AE)
  - Is it Serious? (SAE)
    - Can the cause be attributed to the study? (Related/SAR)
      - Was it expected? (Unexpected/SUSAR)
**Reporting: Investigator/Researcher**

- **Investigator/researcher**
  - Must capture and report AEs, including SAEs, which occur at their site to the Sponsor in accordance with the study protocol.
  - Must report all SAEs to the Sponsor and HREC immediately (within 24 hours) in accordance with the protocol and GCP guidelines as adopted by the TGA.

**Reporting: Sponsor**

- **Sponsor**
  - All adverse reactions that are both serious and unexpected are subject to expedited reporting to the TGA.
  - **Fatal or Life-Threatening Unexpected AR**
    - As soon as possible but no later than 7 calendar days after first knowledge by the sponsor.
    - Follow-up, complete report as possible within 8 additional calendar days.
  - For all other serious and unexpected ARs
    - Full report no later than 15 calendar days of first knowledge by the sponsor.

**Pharmacovigilance**

- The process of evaluating the safety of trial subjects receiving an Investigational Product.

**Investigator Brochure**

- **Brief description** of the drug substance and the formulation including the structural formula.
- **Summary** of pharmacological and toxicological effects of the drug in animals and, if known, in humans.
- Summary of information relating to safety and effectiveness in humans obtained from prior clinical trials.
- A description of possible risks and side effects to be anticipated on the basis of prior experiences with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.
Investigator Brochure (cont.)

• Sponsor will update the Investigator Brochure (IB) every 12 months or sooner if any significant new information becomes available.

• Principal Investigator must provide a record (usually a receipt), signed and dated upon receipt of the IB.

• If a drug is licensed and used within licensing indications, a Product Information Sheet may be provided by a Sponsor as an alternative to the IB.

Session Wrap-up

Covered:

- Standards and why we have them
- Study Set-up – responsibilities, approvals and essential documents
- Informed Consent
- Case Report Form, Source Data and Data Entry
- Safety Reporting
2 GOOD CLINICAL PRACTICE - ADDITIONAL NOTES AND RESOURCES

2.1 GOOD CLINICAL PRACTICE – 13 PRINCIPLES

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.

10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

   This principle applies to all records referenced in this guideline, irrespective of the type of media used.

11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

   Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.
2.2 GENERAL WEBSITE LINKS

- Australian Clinical Trials: https://australianclinicaltrials.com/clinical-trials/
- Australian Clinical Trials Alliance: http://www.clinicaltrialsalliance.org.au/

2.3 GUIDANCE DOCUMENT LINKS

WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (October 2013 version).
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

National Statement on Ethical Conduct in Human Research (Updated 2018)

Australian Code for the Responsible Conduct of Research, 2018 (the 2018 Code)

Integrated Addendum to ICH E6(R1): Guidance for Good Clinical Practice E6(R2)

Clinical investigation of medical devices for human subjects -- Good clinical practice ISO 14155:2011
http://www.iso.org/iso/catalogue_detail?csnumber=45557

The Australian Clinical Trial Handbook (October 2018)

WA Health Research Policies & Procedures

Safety Monitoring and reporting in clinical trials involving therapeutic goods

Guidance on clinical safety data management: definitions and standards for expedient reporting

Values and Ethics - Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research
Human Research Ethics Application (HREA)


Health Research Privacy Framework

Privacy Act

Ethical Considerations in Quality Assurance and Evaluation Activities (NH MRC)

Guide to good manufacturing practice for medicinal products annexes

2.4 FORMS

CTN Form

CTX Form

Ethics Application Forms

Amendments and monitoring forms

2.5 TEMPLATES

Trial Master File
http://tmfrefmodel.com/2015/06/16/version-3-released/

Protocol
http://www.spirit-statement.org/

Participant Information and Consent Forms

Contracts and Agreements
2.6 WA Health Guidance and Principle Origins

- World Medical Association “Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects” 2008;
- National Health and Medical Research Council, Australian Research Council and Australian Vice-Chancellors’ Committee “National Statement on Ethical Conduct in Human Research” 2007 – Updated 2018 (National Statement);
- National Health and Medical Research Council, Australian Research Council and Universities Australia “Australian Code for the Responsible Conduct of Research” 2018 (The Code);
- National Health and Medical Research Council “Values and Ethics: Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research” 2003;
- Relevant Commonwealth or State legislation and guidelines including the Department of Health “Occupational Safety and Health Policy” 2005.

2.7 Sponsor Responsibilities

- Ensuring QA and QC systems are in place to ensure trials are conducted, data is gathered, and subsequently reported, in compliance with GCP, the trial protocol, and any TGA requirements.
- Ensuring medical expertise is on hand for trial-related medical queries or patient care
- Trial design and appropriate analysis
- Data Handling, record keeping, and overall trial management
- Selection of appropriate investigator(s) and institution(s)
- Definitive, unambiguous allocation of trial related duties and responsibilities
- Securing agreement in writing from all involved parties
- Provision of appropriate insurance and indemnity for the trial and trial-related staff, as well as measures for subject compensation for trial-related injury
- Ensuring the confirmation of endorsement from the relevant HREC(s) and notifications of the approval etc. to the TGA
- Ensuring appropriate manufacture, packaging, labelling/coding and distribution to trial sites of all investigational medicinal products
- Ongoing safety evaluation and Suspected Unexpected Serious Adverse Reaction (SUSAR)/Unanticipated Serious Adverse Device Effect (USADE) reporting
- Compliance with Monitoring/Audit/Inspection requirements
- Notification of any premature termination of the trial in question
- Completion of Clinical Study Report

2.8 Principal Investigator Responsibilities

- Ensuring that informed consent is properly obtained from research participants
- Overall conduct, management, monitoring and reporting of research at a site, including annual progress reports, final report to RGO
- Submits the project for site authorisation (RGO approval)
- Delegation and supervision of duties to study team
- Sign-off to say staff are competent to work on the research
- Oversight and management of Investigational Medicinal Product
- Safety reporting signature on notifications from Sponsor if required

2.9 Protocol Deviations/Serious Breaches


2.9.1 Protocol Deviations

Must be reported to the trial sponsor

- **Minor** or **Administrative** departures from protocol
- **Do not affect** the scientific soundness of the research or the rights, safety, or welfare of research participants
- Examples:
  - Follow-up visits outside of protocolled time frame due to participants schedule
  - Blood samples obtained close to but not precisely at the time points specified in the protocol

2.9.2 Serious Breaches

Must be reported to the reviewing HREC. Must notify the site’s principal investigator where the serious breach occurred.

- **Major** departures from the approved protocol and/or regulatory guidelines
- **Breach** that is likely to affect to a **significant degree**
  a) The safety or rights of a research participant, or
  b) The reliability and robustness of the data generated in the research project
- Examples:
  - A participant was dosed with IMP from the incorrect treatment arm. In addition, some months later, the participants in an entire cohort were incorrectly dosed with IMP three times daily when they should have been dosed once daily.
  - Participant safety was compromised because repeat ECGs were not performed, as required by the protocol.
2.10 Protocol Deviations/Violations


2.10.1 Protocol Deviations

- **Minor** or **Administrative** departures from protocol
- **Do not affect** the scientific soundness of the research or the rights, safety, or welfare of research participants
- Examples:
  - Follow-up visits outside of protocolled time frame due to participants schedule
  - Blood samples obtained close to but not precisely at the time points specified in the protocol
  - Only to be reported if they occur to a significant proportion of the participants

2.10.2 Protocol Violations

- **Major** departures from the approved protocol and/or regulatory guidelines
- **Compromise** the ethical acceptability of the project and potentially affect the scientific soundness of the research and/or the rights, safety or welfare of research participants.
- Examples:
  - Failure to obtain participant consent
  - Participant inclusion/exclusion violations
  - Compromises to data integrity
  - Must be reported to HREC where the event occurred

2.11 Ensuring the Quality of the Data

2.11.1 Monitoring

- Ongoing process
- Oversee progress of the trial
- Ensure trial is conducted, recorded and reported properly
- To the protocol, Sponsor’s SOPs, GCP and applicable regulatory requirements

2.11.2 Auditing

- Asses at any given moment
- Systematic and independent
- Ensure trial is conducted, recorded and reported properly
- To the protocol, Sponsor’s SOPs, GCP and applicable regulatory requirements

2.11.3 Inspection

- By Regulatory authority – TGA
- Official review of documents, facilities, records and any other resources related to the trial
- Ensure correct conduct and compliant to appropriate regulatory requirements
2.12 Investigator Brochure

- **Brief description** of the drug substance and the formulation including the structural formula
- **Summary** of pharmacological and toxicological effects of the drug in animals and, if known, in humans
- Summary of information relating to **safety and effectiveness** in humans obtained from prior clinical trials
- A description of **possible risks and side effects** to be anticipated on the basis of prior experiences with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.
- Sponsor will update the Investigator Brochure (IB) every 12 months or sooner if any significant new information becomes available
- Principal Investigator must provide a record (usually a receipt), signed and dated upon receipt of the IB.
- If a drug is licensed and used within licensing indications, a Product Information Sheet may be provided by a Sponsor as an alternative to the IB.

**Recommended GCP Courses**

- Research Education & Trainnig Program (RETP) - WA Health Translation Network (WAHTN)
  [https://www.retp.org/portfolio-item/good-clinical-practice-v-3/](https://www.retp.org/portfolio-item/good-clinical-practice-v-3/)
  *(Transcelerate accreditated training)*

- Global Health Trials
  [https://globalhealthtrials.tghn.org/elearning/](https://globalhealthtrials.tghn.org/elearning/)

- ARCS Australia