Standard Operating Procedure

Title: Clinical Trial Registration of Investigator Initiated Trials (IITs)

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Reviewed and Approval

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This document is effective from the date of the last approval signature and will be reviewed in three years.

Document History

Version	Modified by	Change No.	Description of Change
1.0	N/A	N/A	New document
2.0	Fiona Williams	001	From April 2020, MCRI will be listed as the Responsible Party for new registrations.
2.1	Kate Scarff	002	Recommendation to investigators to commence applications for trial registration prior to HREC and RGO approvals (to ensure registration in place prior to first participant consented).
2.2	Fiona Williams	003	Updated information on use of the new PRS system (Beta) and other general updates

Contents

1. PURPOSE

To provide guidance to Sponsor-Investigators on the requirements and procedures for registering clinical studies.

2. RESPONSIBILITY AND SCOPE

This standard applies to the following staff:

1) Melbourne Children's Investigators conducting investigator-initiated trials (IITs), either single-site or multi-site, referred to herein as the Sponsor-Investigator.
2) Representatives of the Sponsor-Investigator who have been delegated the task of registering and maintaining registration
3) MCRI's designated clinicaltrials.gov PRS Administrator (currently undertaken by MCTC staff)

The procedures detailed below cover the following aspects of clinical trial registration:

- Selecting a clinical trial registry
- Requesting a PRS user account
- Creating a new record
- Updating and maintaining records
- Approving and releasing records
- Notifying stakeholders of registration
- Submitting summary results, protocol and statistical analysis plan

Note: The process outlined in this SOP for registering a clinical trial may also be used to register observational studies. i.e. the process is the same.

3. APPLICABILITY

Publication

The International Committee of Medical Journals Editors (ICMJE, including editors of the Medical Journal of Australia, Lancet, New England Journal of Medicine and others) requires evidence that a trial was registered in a publicly accessible trials registry prior to enrolment (i.e. consent) of the first participant, before consideration of a trial for publication.

ICMJE has adopted the WHO's definition of clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioural treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events.

For purely observational studies (those in which the assignment of the intervention is not at the discretion of the investigator), registration is not mandatory but some journals, including the Lancet and BMJ, encourage prospective registration of observational studies. BMJ also supports the posting of results in publically accessible registries. For this reason, MCTC recommends prospective registration of observational studies in a primary register of the WHO International Clinical Trials Registry Platform (ICTRP) or ClinicalTrials.gov (see section 4.3 for further details). However, MCTC notes that the format of ClinicalTrials.gov is oriented to the entry of information on clinical trials and

entry of observational studies can prove more difficult.

Clinical registries can consider inclusion in the Australian Register of Clinical Registries maintained by the Australian Commission on Safety and Quality in Health Care (see https://www.safetyandquality.gov.au/publications-and-resources/australian-register-clinical-registries).

Ethical

1. The Declaration of Helsinki explicitly states that "every clinical trial must be registered in a publicly accessible database before recruitment of the first subject". The Declaration is the cornerstone document guiding the ethical conduct of research in humans by physicians.
2. The World Health Organization (WHO) considers the registration of all interventional trials to be "a scientific, ethical and moral responsibility"
3. Australia has also endorsed trial registration in two key documents which guide the conduct of Human Research Ethics Committees and the conduct of Australians undertaking research in humans.
    a. The “National Statement on Ethical Conduct in Human Research” (2023) Section 3.1.7 states: “For any research project that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes, researchers must register the project as a clinical trial on a publicly accessible register complying with international standards (see information on the International Clinical Trials Registry Platform (ICTRP) on the World Health Organisation website) before the recruitment of the first participant.”
    b. “Publication and dissemination of research: A guide supporting the Australian Code for the Responsible Conduct of Research” (2020) was jointly issued by the NHMRC, the Australian Research Council and Universities Australia. Clause 4.6 of this document states that “For any research project that prospectively assigns participants to one or more health-related interventions to evaluate the effects on health outcomes, researchers must register the project as a clinical trial on a publicly accessible register complying with international standards before the recruitment of the first participant.”
4. Ethics committees are increasingly requiring prospective registration as a requirement of ethical approval. The Royal Children’s Hospital (RCH) HREC requires prospective registration for clinical trials.

Legal

Registration of clinical trials is not legally required in Australia or New Zealand. However there is a legal requirement to register FDA-regulated clinical trials that meet the FDAAA 801 definition of an “applicable clinical trial” and were either initiated after September 27, 2007 or initiated on or before that date and were still ongoing as of December 26, 2007.

Sponsors of Applicable Clinical Trials must register their trial and report summary results to ClinicalTrials.gov, the registry managed by the National Library of Medicine and the National Institutes of Health (NIH), in accordance with 42 CFR Part 11 Clinical Trials Registration and Results Information Submission: Final Rule that was published on September 16, 2016.

APPLICABLE CLINICAL TRIALS

It is important to determine whether the product (device, drug, biologic) to be studied in a clinical investigation (trial) is subject to **section 505 of the U.S. FD&C Act** or **section 351 of the U.S. PHS Act** (and therefore regulated by the U.S. FDA). Products deemed subject to these Acts are categorised as Applicable Clinical Trials and are subject to specific registration and reporting requirements under the **U.S. Food and Drug Administration Amendments Act (FDAAA)** of 2007. The **Code of Federal Regulations / Title 42 / Part 11 (42 CFR 11)** details in full the definitions and requirements.

The product itself is just one aspect that will determine whether a clinical trial meets the criteria for an Applicable Clinical Trial (ACT). An *Applicable Clinical Trial* meets the following conditions:

1. Trial of drug product (including biologic products)

Study type is interventional
Study phase is NOT phase 1
Studies an FDA-regulated drug product (including biologic product)
One or more of the following:
- At least one U.S. facility location
- Product manufactured in and exported from the United States
- Conducted under an FDA Investigational New Drug (IND) application

OR

2. Trial of device product

Study type is interventional
Primary purpose is NOT device feasibility
Studies an FDA-regulated device product
One or more of the following:
- At least one U.S. facility location
- Product manufactured in and exported from the United States
- Conducted under an FDA Investigational Device Exemption (IDE)

Therefore, RCH/MCRI IITs that meet the criteria outlined above must be registered on ClinicalTrials.gov, not only for the purpose of meeting ICMJE requirements for publication, but for meeting the legal mandate for registering and reporting summary results required by the FDA. **Note that the timeframe for registration must be before the first participant is consented in order to meet the ICMJE requirements for publication.**

Funding

The NHMRC provides information about different laws, approval requirements and obligations applicable to NHMRC funded research and includes a section on the requirement for clinical trial registration prior to the recruitment of participants into the trial.

Sponsorship

Trials that have, or intend to apply for, MCRI Sponsorship are required to register their trial with ClinicalTrials.gov (CT.gov). As detailed further in section 4.2.1 ClinicalTrials.gov, registering a trial with CT.gov provides sponsorship oversight capabilities that other registrations do not offer, such as ANZCTR. The decision to mandate CT.gov registration for MCRI sponsored trials is impacted by the increased data quality provided by CT.gov's oversight at the stage of initial registration. CT.gov also allows for ongoing sponsor

monitoring that allows MCTC to support researchers keep their records up to date.

The philosophy behind mandatory registration

Registration is designed to increase the veracity of trial results and reduce bias. One aim is to identify the existence of so called "negative trials" which may never be published because they are negative. This reduces publication bias.

Another aim is to prevent sponsors from suppressing results which they don't want made public for commercial or other nefarious reasons.

Lastly registration prevents outcome switching or selective reporting where investigators consciously or subconsciously place undue emphasis on outcomes where there were differences and ignore or downplay outcomes where no difference was found.

Registration for trials is now universally regarded as good research practice. There is also a push for registering analysis plans and/or protocols for observational clinical research and laboratory research prior to conducting the analyses. This has not been mandated by all journals due to logistical complexities but it is increasingly regarded as good research practice.

Registration is good for your science as it helps prevent you from weakening your results by subconsciously slipping into data driven hypotheses and analyses.

Note that most journal editors will carefully check your registration and will query any discrepancy between your registration and your submitted manuscript. There are also "fraud busters" who scrutinise registrations and published manuscripts and who will write to the journal and post allegations on publicly accessible websites accusing you of fraud and/or research misconduct if they find discrepancies.

4. PROCEDURE

4.1. When should studies be registered?

All RCH/MCRI IITs should be registered before the first participant is consented to be compliant with the International Committee of Medical Journal Editors (ICMJE) and the Declaration of Helsinki.

Note: For Food and Drug Administration (FDA) Applicable Clinical Trials, the timeframe for registration on ClinicalTrials.gov in order to satisfy the Final Rule are below:

1) Registration within 21 calendar days after the first participant has consented.

RCH/MCRI IITs that are conducted under an IND must comply with requirements of IMCJE, Declaration of Helsinki and the Final Rule. In this case, IITs must be registered with ClinicalTrials.gov before the first participant is consented.

The process for registering trials can be lengthy. **As registration must be complete before the first participant is consented, investigators should start the trial registration process prior to receiving HREC approval, RGO authorisation and MCRI Sponsorship – and are strongly encouraged to commence the submission process prior to submission to HREC**.

Note that MCTC will submit the clinicaltrials.gov record to the Protocol Registration and Results System (PRS) only after approval has been granted by the MCRI Sponsorship

Committee. This usually precedes HREC approval and RGO authorisation.

If the trial is registered before receiving HREC approval, the record should indicate that the trial has not yet received ethical approval and that it is not recruiting. Once approval and authorisation have been granted, the record should be amended to:

1) reflect any updates to the protocol that were required prior to HREC approval
2) update the ethical approval status [Human Subject Review Board Status - if using the clinicaltrials.gov registry), Ethics Committee status - if using the ANZCTR registry) and provide relevant details
3) update the trial status to Recruiting (when applicable) and also the site status to Recruiting (for those sites that have commenced) in clinicaltrials.gov. If using ANZCTR, amend to Active or Recruiting.

ANZCTR: grants provisional registration only until such time as the trial has received HREC approval and the relevant details entered into the ANZCTR record. Following this, ANZCTR grants full registration.

4.2. Selecting a clinical trials registry

The primary consideration for choice of registry is that the registry must meet the ICMJE requirement that it is either a primary register of the WHO International Clinical Trials Registry Platform (ICTRP) or ClinicalTrials.gov, which is a data provider to the WHO ICTRP.

Where MCRI is the trial Sponsor, the ClinicalTrials.gov registry MUST be selected* due to the oversight that is provided:

- **The PRS undertakes direct oversight of ClinicalTrials.gov records and also mandates institutional (i.e. MCRI) oversight -** this oversight allows the MCRI Sponsorship Committee to fulfil its sponsor responsibilities.
- ANZCTR does not provide this level of oversight.

*unless there are contractual requirements that require registration through ANZCTR

4.2.2. ClinicalTrials.gov

1) MCTC, delegated as MCRI's PRS Administrator, assists researchers to register their studies and maintain records in accordance with ClinicalTrials.gov requirements.
2) All records undergo QA review by ClinicalTrials.gov, ensuring the data entered conforms to the requirements of the registry and US policies and laws that dictate the regulatory requirements and procedures for submitting registration and summary results information.
3) Summary results can be posted (N.B. this is mandatory for studies conducted under an IND or IDE application).
4) This is the register that must be used for studies of those drugs, devices, biologics regulated by the FDA. [i.e. a study that includes a recruiting site in the U.S. or U.S. territory OR is conducted under an IND or IDE application OR where the product is manufactured in or exported from the U.S for use in this clinical trial – see Section 3 APPLICABILITY for further clarification].
5) It is a high profile registry thereby assisting visibility of research to a wide audience globally.
6) Registration of observational studies is available.

ANZCTR registry automatically copies ClinicalTrials.gov trial registration

records with Australian and/or New Zealand recruitment sites and displays these studies on the ANZCTR. Data from ClinicalTrials.gov are imported and mapped to the corresponding ANZCTR field (where possible).

4.2.3. ANZCTR

Where ANZCTR is selected (noting the proviso listed under Section 4.2), note that ANZCTR does not include the benefits described in items 1) to 3) above or meet the requirement detailed in item 4). Like ClinicalTrials.gov, ANZCTR also accepts observational studies for registration.

Sponsor-Investigators who register their trial with ANZCTR are responsible for the following:

1) Registering the trial
2) The accuracy and completeness of the registered data
3) Ensuring the information on any one trial is submitted only once
4) Communicating with trial collaborators regarding the registration status of the trial and the registration number
5) Ensuring information on the registered trial is kept up-to-date.

You will not be automatically notified by ANZCTR to update your record. Records will be marked "Not up to date" if they have not been updated in the previous 12 months.

To register your trial with ANZCTR, follow the instructions on their website, http://www.anzctr.org.au/Default.aspx

4.3. ClinicalTrials.Gov

4.3.1. Requesting a PRS user account

A PRS User account holder can create and modify their own records but cannot access other users' records unless authorised by the Record Owner or by a PRS Administrator.

To apply for a PRS User account, email mctc@mcri.edu.au (MCRI PRS Administrator) with the following details:

- Name
- Email
- Phone number

MCTC will create a PRS User account, and within two days the applicant will receive an automated email from ClinicalTrials.gov with instructions for logging in to the PRS.

4.3.2. Creating a new record and entering data

To register a trial, you will need to create a record in the PRS and enter information about the trial. For further information about the information required, including optional and mandatory sections, refer to the Protocol Registration Data Element Definitions.

Note: Since April 2020, MCRI has acted as the **Responsible Party** (the Responsible Party is the "Entity or individual responsible for verifying the accuracy of a trial record and releasing it to ClinicalTrials.gov"). The MCRI-designated clinicaltrials.gov PRS Administrator (currently delegated to MCTC

staff) will communicate with the Sponsor-Investigator to ensure that the information entered in the record is complete and accurate.
Note: Other users can be authorised to add information to the trial record either before or after a trial is registered.

1) **PRS home page**
   At the PRS home page, log in:
   - For Organisation enter MurdochCRI
   - Enter the Username and Password you were assigned at the time of requesting a PRS account

   Then click on **Create New Record**.
2) **You will come to the Create New Record screen. Enter the Unique Protocol ID, Brief Title, Acronym, Study Type, Official Title, Secondary ID**
   Enter the Unique Protocol ID, Brief Title, and Study Type (interventional, observational, or expanded access) for your record on the Create New Record page. Note: If the study has not been assigned a Unique Protocol ID, please use any another unique identifier for your record, such as your HREC approval number.
3) **Click Create Record**
   Click Create Record to save.
4) **Continue to enter data for the record**.
   a) Across the top of the screen you will find 4 tabs: Record Summary, Protocol, Study Documents, and Results. Stay on the **Protocol** tab.
   b) On the left you will see a column listing all modules for completion – **select the next module you wish to complete** (e.g. Study Status)
   c) Enter the data – when you have finished click on **Save Edits.**
5) **Select the next module**
   a) Click on Edit to add the data
   b) When finished, click on Save Edits and repeat the process until all modules are complete.
6) **Next steps:**

Review the record (see next section), edit as required and then submit to the MCRI PRS Administrator (see section 4.3.4).

4.3.3. Reviewing the Record

Before submitting the record to the MCRI PRS administrator (currently MCTC), read it carefully checking for accuracy, completeness, errors and system validation messages. Follow the instructions in the next section if you need to edit the record.

To share the draft record with colleagues who do not have a PRS User account, you can download a copy of the record as an Adobe PDF or RTF (go to Actions on the Record Summary Page).

4.3.4. Editing a Record

Follow the process below to modify a record to make edits, update information or enter results:

1) Select **Open** next to the section of the record (Protocol, Results, or Delayed Results) to be modified on the Record Summary page.
2) Locate the data field to be modified and select **Open** or **Edit** for the corresponding module.

3) Make changes on the data entry page.
4) Select **Save** to save changes and return to the section page. Repeat steps 2) and 3) for all modules to be modified.
5) Update the Record Verification Date data to the current date.
6) Select **Entry Complete** (button on top right of screen) to submit your record to the MCRI PRS Administrator - this will generate an automatic email notification to the Responsible Party.

4.3.5. Approving a Record

The Responsible Party* must approve the record before releasing it to the PRS for PRS Review. The Responsible Party must review and approve the record using the following process:

1) Select **Open** Record next to the record ready for approval
2) Review the record for accuracy, completeness, errors and system validation messages and modify as required.
3) Update the Record Verification Date to the current month and year.
4) Select **Approve** on the Record Summary page.

* As mentioned previously, the MCRI PRS Administrator (currently MCTC staff) acts as the Responsible Party and communicates with the Sponsor-Investigator to ensure that the information entered in the record is complete and accurate.

4.3.6. Releasing a Record

After the record is approved, the last step is for the Responsible Party to release it for PRS Review. As noted in the previous section, records generated prior to April 2020 may list the Sponsor-Investigator as the Responsible Party – for these records the Sponsor- Investigator will continue to take on the responsibility for releasing a record.

The Responsible Party must follow the process below to release the record:

1) **Open** the record
2) Select **Release** on the Record Summary page
3) Check the box to update Verification Date automatically
4) Select **Release** to submit the record to ClinicalTrials.gov for PRS Review.

4.3.7. PRS Review Process

Review of records with registration information takes approximately 2 to 5 business days. Review of records with results information should take up to 30 days but may take longer.

PRS Staff will add comments to the record if they identify potential problems and an email notification will be sent to the Record Owner, Responsible Party and last PRS User to update the record.

Comments should be addressed as follows:

Major Comments: The Responsible Party must address major comments **within 15 calendar days (registration information)** or **25 calendar days (results information)** of the date on which PRS Staff sent the notification.
* Where an MCRI PRS Administrator acts as the Responsible Party, they will communicate with the Sponsor-Investigator in order to address the comments.

This will ensure that the information entered in the record is complete and accurate.

Advisory Comments: These should be addressed to improve the clarity of the record.

If the PRS team requires further changes, the record is returned so change can be made and the Review process is repeated.

Note: If an MCRI PRS Administrator (i.e. MCTC) makes changes to an Approved record, it does not need to be approved again. However the record must still be released.

Once the record meets PRS Review criteria, it is posted on the ClinicalTrials.gov website and made available to the public.

4.3.8. Maintaining Records

The Terms & Conditions for organisations and individuals submitting data to ClinicalTrials.gov include the following:

1) The submitting organisation, or individual designated as the Responsible Party, is responsible for the completeness and accuracy of the data submitted to the PRS.
2) Notice of changes in recruitment status must be provided as soon as possible, but no later than **30 days** after such changes. This includes changes to individual site status, overall recruitment status and completion date.
3) All other data must be reviewed, verified, and updated as necessary and no less than **every 12 months**. ClinicalTrials.gov recommends that the Record Verification Date be updated at least every 6 months for studies that are not yet completed, even if there were no changes to the record.

See How to Edit Your Study Record for details on updating study information.

IT IS THE INVESTIGATOR'S RESPONSIBILITY TO KEEP THE REGISTRATION UP TO DATE. CHANGES TO THE PROTOCOL MUST BE MIRRORED BY CHANGES IN THE REGISTRATION. FAILING TO KEEP YOUR REGISTRATION UP TO DATE WILL COMPROMISE YOUR CHANCE OF PUBLICATION AND POTENTIALLY LEAD TO ALLEGATIONS OF MISCONDUCT.

4.3.9. Submitting Results for Applicable Clinical Trials

Results need to be submitted to ClinicalTrials.gov if the trial meets the definition of an applicable clinical trial.

What needs to be submitted?

The Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11) clarifies and expands the requirements for submitting clinical trial registration and results to ClinicalTrials.gov in accordance with Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA 801).

The responsible party for an applicable clinical trial must submit summary clinical trial results information to clinicaltrials.gov. The information to be

submitted depends on the following:

1. Whether the investigational product is:
    a. Approved, licensed, or cleared by the FDA
    b. Not approved, licensed or cleared by the FDA
2. If the primary completion date is before or on/after January 18, 2017 (date the Final Rule was implemented).

ClinicalTrials.gov will tailor the results information required for the record based on the registration information provided.

Results to be submitted include participant flow, demographic and baseline characteristics, primary and secondary outcomes and adverse event information.

What supportive documents must submitted?
For Applicable Clinical Trials with a primary completion date on/after January 2018, the Final Rule requires the submission and posting of the full version of the protocol and the SAP (if a separate document) [as specified in 42 CFR 11.48(a) (5)]. These documents are required to provide a resource for researchers to enhance the understanding of the trial and enable a more complete evaluation of results.

The protocol and SAP (if submitted as separate document), including all amendments approved by the HREC/IRB, must each contain a cover page that lists the Official Title (title
of the clinical trial corresponding to the title of the protocol), NCT number and the date of each document.

When must results be submitted?
As specified in as specified in 42 CFR 11.44, results for primary outcome measures (including the protocol and separate SAP if SAP not included in the protocol) must be submitted no later than one year after the primary completion date.

If clinical trial results information has not been collected for a secondary outcome measure(s) or additional adverse event information by the primary completion date, the results must be submitted no later than one year from the date on which the final subject is examined or receives an intervention for the purposes of final collection of data for that secondary outcome measure.

Delayed submission and waivers for results submission requires certification from ClinicalTrials.gov prior to the date on which clinical trials results information would otherwise be due. Applicants should refer to 42 CFR 11.44 (b) and 42 CFR 11.54, respectively, for further details.

4.4. Voluntary submission of the protocol and SAP

Submission of the protocol and SAP is mandatory for Applicable Clinical Trials, as previously discussed in Section 4.3.9.

Although not mandatory, Sponsor-Investigators of trials that do not meet the definition of an Applicable Clinical Trial are able to submit the protocol and SAP to the primary register

(ClinicalTrials.gov or ANZCTR, as applicable) if they wish.

4.5. Saving Evidence of Study Registration and Notifying Stakeholders

The Sponsor-Investigator must notify the following stakeholders once the study is registered:

1) Approving HREC
2) Local Principal Investigators at Participating Sites (applicable for multi-centre studies)

The Sponsor-Investigator must provide stakeholders with evidence of registration that includes the date of registration and the trial registration ID, e.g. NCT number (ClinicalTrials.gov) or ACTRN (ANZCTR).

Please refer to instructions below for providing evidence of registration when using ClinicalTrials.gov or ANZCTR.

ClinicalTrials.gov

The Sponsor-Investigator/delegate should provide stakeholders with a copy of the PDF Receipt. To download a PDF Receipt:

1) Open your record from your Record List and select **Receipt** in the Record Status box.
2) Save the file with the following information in the file name: [Unique Protocol ID_PDF Receipt_DDMMMYY].
3) Change the file location so that the document is saved to your Trial Master File (Study Binder)

ANZCTR

The Sponsor-Investigator should provide stakeholders with a copy of the View Full Record, saved as a PDF. To download the View Full Record and save as a PDF:

1) Open your record and select **View Full Record**
   Right click with the mouse and select **Print**
2) Click save and change the file name to the following format: [Unique Protocol ID_PDF Receipt_DDMMMYY].
3) Change the file location so that the document is saved to your Trial Master File (Study Binder)

Note: ANZCTR does provide the option to select records for download but the format of downloaded files is not print-friendly. Hence it is recommended you follow the procedure detailed above.

5. GLOSSARY

ANZCTR

The Australian New Zealand Clinical Trials Registry (ANZCTR) is a not-for-profit online register of clinical trials being undertaken in Australia, New Zealand and elsewhere. The ANZCTR includes trials from the full spectrum of therapeutic areas of pharmaceuticals, surgical procedures, preventive measures, lifestyle, devices, treatment and rehabilitation strategies and complementary therapies.

Key points about the ANZCTR as published on their website include:
All details of trials registered on the ANZCTR are made publicly available
Registration is voluntary, but if a registrant chooses to register a trial, certain fields are mandatory

The sponsor (Sponsor-Investigator in the case of investigator-initiated trials) is responsible for registration, including the accuracy of the information submitted and maintaining the record to keep it up-to-date.

Applicable Clinical Trial
An applicable device clinical trial or an applicable drug clinical trial.

Applicable device clinical trial
A prospective clinical study of health outcomes comparing an intervention with a device product subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360(k), 21 U.S.C. 360e, 21 U.S.C. 360j(m) against a control in human subjects (other than a small clinical trial to determine the feasibility of a device product, or a clinical trial to test prototype device products where the primary outcome measure relates to feasibility and not to health outcomes);
A paediatric post-market surveillance of a device product as required under section 522 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 3601); or
A clinical trial of a combination product with a device primary mode of action under 21 CFR part 3, provided that it meets all other criteria of the definition under this part.

Applicable drug clinical trial
A controlled clinical investigation, other than a phase 1 clinical investigation, of a drug product subject to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or a biological product subject to section 351 of the Public Health Service Act (42 U.S.C. 262), where “clinical investigation” has the meaning given in 21 CFR 312.3 and “phase 1” has the meaning given in 21 CFR
312.21. A clinical trial of a combination product with a drug primary mode of action under 21 CFR part 3 is also an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part.

ClinicalTrials.gov
ClinicalTrials.gov is an online register that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. The website is maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH).

Most of the records on ClinicalTrials.gov describe clinical trials. ClinicalTrials.gov also contains records describing observational studies and programs providing access to investigational drugs outside of clinical trials (expanded access).

ClinicalTrials.gov does not contain information about all the clinical studies conducted in the United States because not all studies are required by law to be registered (for example, observational studies and trials that do not study a drug, biologic, or device). See FDAAA 801 Requirements for more information.

ClinicalTrials.gov was created as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA). FDAMA required the U.S. Department of Health and Human Services (HHS), through NIH, to establish a registry of clinical trials information for both federally and privately funded trials conducted under investigational new drug applications to test the effectiveness of experimental drugs for serious or life-threatening diseases or conditions. NIH and the Food and Drug Administration (FDA) worked together to develop the site, which was made available to the public in February 2000.

The ClinicalTrials.gov registration requirements were expanded after Congress passed the FDA Amendments Act of 2007 (FDAAA). Section 801 of FDAAA (FDAAA 801) requires more types of trials to be registered and additional trial registration information to be submitted. The law also requires the submission of results for certain trials. This led to the development of the ClinicalTrials.gov results database, which contains summary information on study participants and study outcomes, including adverse events. The results database was made available to the public in September 2008. FDAAA 801 also established penalties for failing to register or submit the results of trials. In September 2016, HHS issued the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11) clarifying and expanding the registration and results information submission requirements of FDAAA 801. This regulation took effect in January 2017.

Investigator
An individual responsible for the conduct of a clinical trial at a trial site and ensures 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.

Investigational Device Exemption (IDE)
An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. Investigational use includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. All clinical evaluations of investigational devices, unless exempt, must have an approved IDE **before** the study is initiated.

Investigational New Drug application (IND)
An Investigational New Drug Application (IND) is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans.

Observational study
Observational studies consist of medical research in which the investigator does not assign human subjects to interventions. Observational studies include prospective cohort studies in which individuals receive interventions as part of their medical care, after which the investigator studies pre-specified outcomes to examine the impact of those interventions. Observational studies also include retrospective reviews of patient medical records or relevant literature.

Sponsor
The sponsor is defined by the NHMRC and Therapeutic Goods Administration (TGA) as "an individual, company or institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial"

Sponsor-Investigator
Sponsor-Investigator is a term used for investigator-initiated studies. It is an individual who is responsible for both the initiation and conduct of a study. The term does not include any person other than an individual. For multi-centre investigator-initiated studies, the Coordinating Principal Investigator will be the Sponsor-Investigator.

Standard Operating Procedure (SOP)
Detailed, written instructions to achieve uniformity of the performance of a specific function.

Trial Master File (TMF) / Study Binder

The TMF contains all the essential trial specific documentation prepared/collected before the trial commences, during the conduct of the trial and at trial completion in accordance with Good Clinical Practice.

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