UTS IMPACCT
Trials Coordination
Centre

Coordinating Principal Investigator (CPI) Manual

(From idea or question to recruitment and beyond)

Contents

Overview

Purpose

This manual has been created for clinicians and researchers who have an idea for a new palliative care or cancer symptom clinical study and who wish to progress this idea into a clinical trial.

The purpose of this manual is to give an overview of the process of developing a new clinical trial, from the first idea to a written study protocol and finally to the implementation of the study at one or more recruiting sites. Also included are resources to support the development and administration of conducting clinical trials.

If you have any questions that are not answered by the resources included in this manual, please contact the email addresses below, or refer to the Contacts section for details about who to contact for specific queries.

Contact us

IMPACCT Trials Coordination Centre (ITCC)

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E: itcc@uts.edu.au

W: uts.edu.au/impacct/itcc

Palliative Care Clinical Studies Collaborative (PaCCSC)

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Cancer Symptom Trials (CST)

E: CST@uts.edu.au

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Version control

DATE	VERSION	COMMENTS	WHO
15/02/2019	1.0	Final approved	L James, L Brown, B Fazekas
11/03/2020	2.0	Two-year review	L Brown
07/05/2020	3.0	Edited	L James
01/04/2022	3.1	Periodic review	L James

Improving Palliative Aged and Chronic Care Through Research and Translation (IMPACCT)

W: uts.edu.au/impacct

The IMPACCT Trials Coordination Centre (ITCC) together with PaCCSC and CST are located within IMPACCT at the University of Technology Sydney (UTS). IMPACCT's transdisciplinary research program is dedicated to improving the care, outcomes and quality of life of people affected by a range of chronic conditions or who have palliative care needs.

Location

W: https://maps.uts.edu.au/map.cfm

W: https://maps.uts.edu.au/directions.cfm

IMPACCT and the ITCC are located in Building 10 on the UTS campus in Ultimo NSW. A UTS campus map is available at the above UTS maps web page. Type 'CB10' into the 'Search maps' field on the maps web page, and press 'enter' to see more details about building access points and amenities, including mobility access ramps.

If you are visiting the campus, please read the *Directions to UTS* web page at the directions link above. It includes information about public transport options and parking.

Please note that parking is limited to metered street parking and user pay parking stations, other than for people with disabilities and those with special permits. Visitors with mobility impairments can access parking on campus by calling UTS Security on 1800 249 559.

Palliative Care Clinical Studies Collaborative (PaCCSC)

PaCCSC is an Australia-wide research network that aims to improve the wellbeing of people with life-limiting illness through:

- the generation of high-quality research evidence to support effective palliative care clinical interventions including medications
- building capacity within the health workforce in the conduct and understanding of high-quality palliative care clinical research
- the translation of palliative care research results into clinical practice and policy.

Public health and clinical advances have led to people living longer and consequently having a higher likelihood of warning of death. Our role is to engage in high-quality research that provides the evidence base to underpin and optimise quality healthcare practice for people with a life-limiting illness.

PaCCSC is a national, member-based research network comprised of a participating network of hospitals and health services, where the benefits of our research can be applied directly to patients and, more broadly, to health policy.

Cancer Symptom Trials (CST)

Cancer Symptom Trials (CST) is one of fourteen Cancer Cooperative Trials Groups (CCTGs) funded by Cancer Australia. CST is a research collaborative within (IMPACCT).

Our work is important for the significant number of Australians who are diagnosed with cancer every year. Through our clinical trials, we research options for improved management of symptoms that can occur due to a cancer diagnosis and related treatments.

Our goal is to ensure the best quality of life possible for people with cancer. We do this by identifying accessible, affordable, and appropriate medicines and therapies for people with cancer, including those living at home.

We acknowledge the significant role that carers play in the lives of people with cancer. They are critical contributors in decisions about the management of symptoms. We welcome their inclusion and participation in our research.

Membership

As a Coordinating Principal Investigator (CPI), you are a member of PaCCSC and/or CST, depending on the clinical trial that you are running. If you are yet to become a member, please submit your details to our membership database via the online membership forms available at the websites below.

PaCCSC membership

W: uts.edu.au/paccsc/membership

CST membership

W: uts.edu.au/cst/membership

Resources

W: uts.edu.au/itcc/researcher-resources

You can find a range of resources for clinical trials' sites on the ITCC Researcher resources web page above. Available resources include Standard Operating Procedures (SOPs), guidelines, templates, information about new study proposals, referral resources and research data management.

Other resources you may need for your trial include pharmacy manuals, site initiation documents, pharmacy initiation, and the REDCap data management system.

Standard Operating Procedures (SOPs)

Standard Operating Procedures (SOPs) enable the operationalisation of the principles required by the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP). They are designed to be applied across PaCCSC and CST trials and support individual study protocols.

Our SOPs are available as a single combined document, or you can download individual SOPs that are relevant to you. We recommend that you become familiar with the available SOPs and that the above link be the first port of call for any operational queries.

Each SOP is supported by a range of guidelines to further explain the detail of the SOP, and templates to enable the SOP to be applied in specific situations.

If you can't find the information you need, please contact us for advice.

Guidelines and Templates

Our guidelines and templates have been developed to ensure consistency in the way information is disseminated, collected, and documented. They will help you to ensure that your site is compliant with clinical trial protocols. The ITCC has a clinical trial protocol template. This document is not available in the public domain but can be shared with CPIs following acceptance/endorsement of their new study idea using the SOP templated by the relevant Scientific Advisory Committee.

Referral resources

We have two plain-English FAQs brochures available at the above web page with information for potential trial participants. You are welcome to download and print these for use at your site.

Research data management systems

We use purpose-built clinical trials data management systems. Access is granted to our members to support their research conducted with the ITCC. Please direct enquiries about these systems to our National Project Officer, Ms Belinda Fazekas.

Name/role	Queries	E-mail	Telephone
Linda Brown National Manager, PaCCSC/CST	Clinical Trials Agreements, membership	Linda.Brown@uts.edu.au	0437 816 884
Belinda Fazekas National Project Officer	Clinical studies Protocols	Belinda.Fazekas@uts.edu.au	0414 190 084

ITCC (PaCCSC/CST) New studies

W: uts.edu.au/itcc/sops

The ITCC (incorporating PaCCSC and CST) actively seek ideas for new clinical medication or intervention studies from the palliative care and cancer symptom management research community and commercial interests that are in line with the existing program of work. There are two Standard Operating Procedures (SOPs), *SOP 6.0.1a New Study Ideas and Proposals (PaCCSC) and SOP 6.0.1b New Study Ideas and Proposals (CST).*

PaCCSC and CST studies have a focus on, but are not limited to, cognitive and neurological disorders, appetite and cachexia, chronic breathlessness, nausea, gut dysfunction, pain, fatigue, sleep and cardiovascular and stroke.

Please note the process for new studies at each of the two collaboratives (PaCCSC/CST) is slightly different so please ensure you are following the correct SOP. If your study is in a cancer only population then you should follow the CST SOP. All other studies in a broad palliative care population will come under the PaCCSC SOP.

The SOPs describe the process that all new study concepts/ideas go through to proceed towards pilot or full study recruitment. The SOP is available at the above link.

Be prepared

W: https://moga.org.au/page/about-acord

Clinical trials require a significant time commitment. Consider the time you will need to dedicate to the trial and balancing that with your other commitments, including employment, study, and family. Identify your key support people and networks and include your supervisors or mentors in your planning.

Getting the right people on your team is important. Your team may include expert clinicians (local/international), consumer advocates, researchers, biostatisticians, project managers or project officers. Maintaining good relationships with your team and other stakeholders, such as funding bodies, is essential.
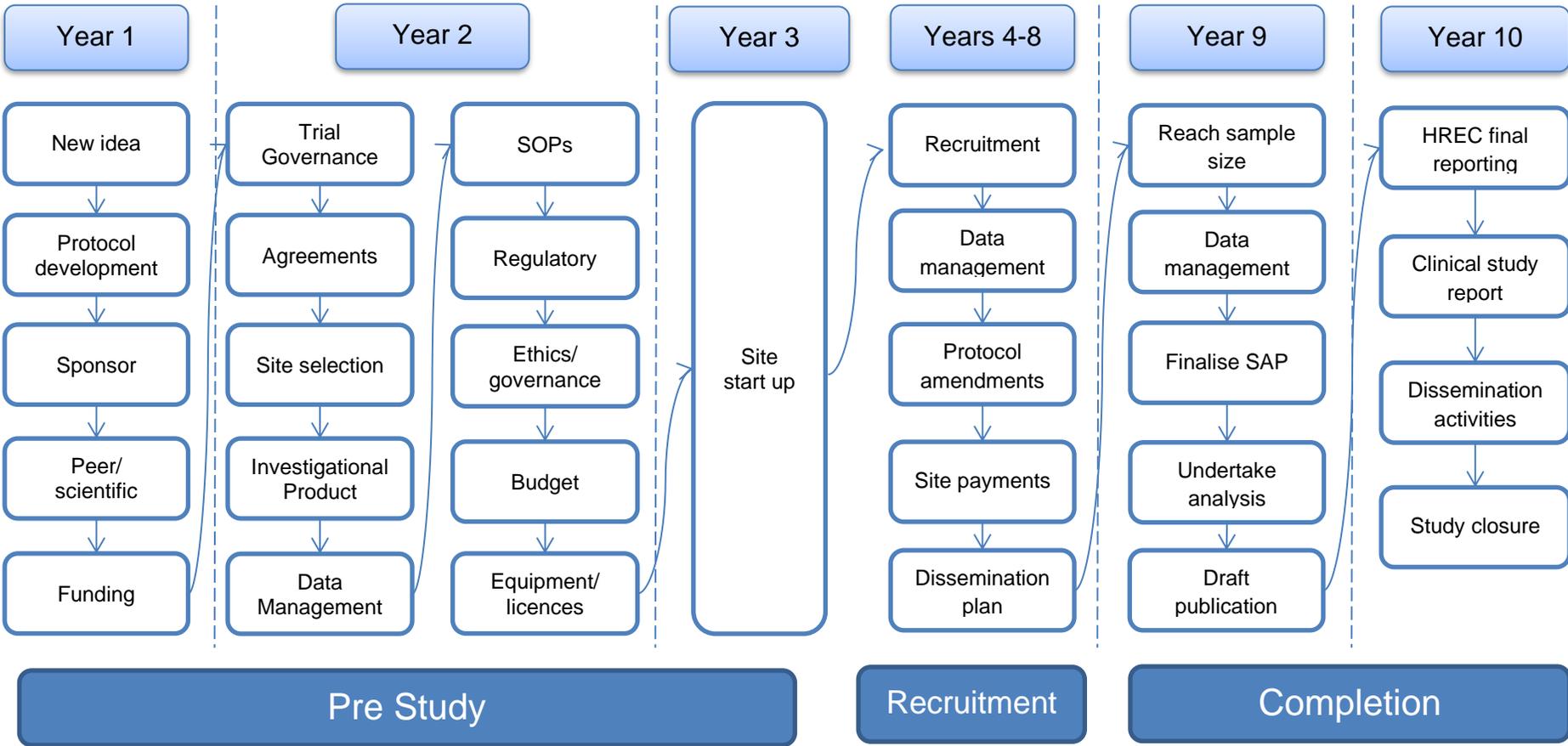
Consider any training needs that you or your team may need and look at workshops related to your trial. The PaCCSC and CST Annual Research Forums and regular Concept Development Workshops as well as becoming a member of one of the symptom node subcommittees in the area of interest, provide an opportunity to present an early idea, gain feedback from experts, and workshop design issues. ITCC/PaCCSC/CST events are promoted on our website and in the member newsletter.

Another opportunity is the ACORD research development workshops run by the Medical Oncology Group of Australia – find out more via the link above. There are only a small number of the opportunities available with ACORD however support for applications from PaCCSC/CST members can be provided either through workshopping the study idea or via the provision of a letter of support for members applications. There may be other options within your own organisation where ideas and early research ideas can be presented, discussed, and have developmental input.

Average clinical trial life cycle

The conduct of clinical trials with palliative care and cancer symptoms are challenging and are usually run across multiple sites. This increases the complexity of the trials being conducted and the time needed to complete a trial. The ITCC has conducted and completed many phase II, III, pilots and feasibility clinical trials. The experience to date has brought about a reasonable approach to the expected timeframes and the steps involved in the typical span of a clinical trial. This has been developed into a 'Life Cycle'. The following diagram and descriptions will walk new Coordinating Principal Investigators (CPIs) through this typical life cycle to ensure the required steps and procedures are considered throughout the conduct of the trial and to ensure that all regulatory and contractual obligations are met.

Year 1	Year 2		Year 3	Years 4-8	Year 9	Year 10
New idea	Trial Governance	SOPs	Site start up	Recruitment	Reach sample size	HREC final reporting
Protocol development	Agreements	Regulatory		Data management	Data management	Clinical study report
Sponsor	Site selection	Ethics/ governance		Protocol amendments	Finalise SAP	Dissemination activities
Peer/ scientific	Investigational Product	Budget		Site payments	Undertake analysis	Study closure
Funding	Data Management	Equipment/ licences		Dissemination plan	Draft publication	

Pre Study   **Recruitment**   **Completion**

Clinical trial life cycle – year by year.

Year One

New idea

New ideas often occur because a clinician has observed something in practice or raised a clinical question. For example, sometimes a medication works and sometimes it doesn't, or is one medication better to use than another, or can an intervention make a difference to a symptom. There may be little or no evidence in the population you're treating and there is nothing in the current literature and little consensus amongst your colleagues to respond to your questions - this could lead to an idea for a new study.

If you have an idea, we can help with resources and support. The following sections outline the steps to progress your idea to a proposal.

Proposal

W: uts.edu.au/itcc/sops

W: uts.edu.au/itcc/templates

An idea for a new proposal can be presented to the relevant Scientific Advisory Committee meeting for initial presentation and discussion using the new study idea template. This may inform the development of a concept or formulation of a trial development group to progress a concept for formal presentation. The proposal stages are detailed in *SOP 6.0.1a New Study Ideas/Proposals (PaCCSC)* or *SOP 6.0.1b New Study Ideas/Proposals (CST)*, which you can find at the SOPs link above.

New study proposals must be made to the PaCCSC/CST National Manager using one of the New Study Proposal templates (PaCCSC OR CST), which are available at the templates link above.

New study support will be considered for:

- randomised controlled trials (RCTs)
- small pilot studies for proof of concept (feasibility, safety, efficacy)
- sub-studies embedded within a current study, that adds value to the suite of currently running RCTs.

Protocol development

The protocol is the focal point of the whole study. It needs to describe every detail of the study and how it is to be run. The average length of a protocol is 80-100 pages. ICH GCP E6 has a whole section on what is required in a protocol and the ITCC template is based on this. A copy of the ITCC protocol template is available from our National Office – please contact us to request the template. Use of the protocol template is strongly encouraged. This will guide you through the required elements of the study design and description and ensure that you include sections that are important to the support and implementation of the study.

You may find it helpful to read some examples of approved protocol documents. Contact the ITCC office to request help in locating examples.

Before you start writing up your protocol, get to know the investigational drug or intervention. Talk to others who have experience with the intervention, read the background literature, identify gaps, and check national and international clinical trial sites to see what other work is already in progress. You may find it useful to write a review paper to bring your research together and focus your hypothesis. Consider presenting your idea at an appropriate forum with colleagues or experts or at a workshop to maximise feedback and gain support.

It is important to recognise that your protocol will go through many versions, so be prepared to be flexible and patient. Be prepared to provide a copy to the ITCC team at least one month prior to submitting the HREC to enable a final review of the entire document.

Sponsor

You need to identify who the study sponsor will be, as the sponsor has a number of legal obligations. Where the study is conducted within a single organisation, that organisation may take on the role as the sponsor. However, organisations are often unable or unwilling to take on this role when the study is conducted across multiple different organisations. The role of being a sponsor for a trial that reaches beyond your own institution or organisation changes vastly when an organisation is asked to sponsor multi-site studies.

Consider who the sponsor will be upfront to reduce any potential delays. Don't just assume that your organisation will take on the sponsor of a multi-site study – find out and get it in writing from someone in authority.

While not all responsibilities of the sponsor can be passed on, the level of sponsorship can change depending on the agreed study conduct between the parties.

- Think about who the most suitable sponsor is - is it your organisation, the grant holder, an academic institution you're aligned with and do they have the appropriate experience in trial sponsorship?

Peer review of the protocol

Having your idea and the subsequent protocol evaluated by experts for scientific, academic and/or professional rigour is essential. If you don't get others to look at it, you won't know whether it's wrong or right, and you won't get the buy-in and support from those around you.

A review can pick up what might happen over time and pick up any logistical issues, for example, pathology, which happens differently at each organisation. Do staff do the collection? Do they have the training? Do they have the facilities to store the collection etc.? It is important to not only get a review of the scientific quality of the protocol, but it is valuable to have the procedures reviewed by trial nurses to give feedback on the feasibility of data collection, timelines and visit schedule.

It is of critical importance that you determine the primary outcome. How will this information be collected? How will it be analysed? Will the information you're collecting answer your question? Remember that your study will rely on the protocol for the duration of research. If it is not documented in the protocol then it won't and shouldn't happen. Being the primary document for any trial the protocol should be as accurate and unambiguous as possible prior to being submitted along with all supporting documentation to a Human Research Ethics Committee (HREC) for approval.

Consider site staff training requirements – a walkthrough of the trial may be helpful so that researchers and staff understand the protocol and timing of measures, they will also have an opportunity to ask questions. This will allow you to review the practicalities and challenges at each site. Allocation of staff to your trial will need to be confirmed with those responsible for staffing/rosters.

Funding

W: https://www.ihpa.gov.au/publications/development-table-standard-costs-conducting-clinical-trials-australia

Consider the bigger picture funding at this point. Estimate your sample size – pick a round figure for the per participant payments (that's how much you will pay each site for recruiting a single participant). This should be an educated guess based on the number of visits or assessments, the amount of nursing or medical time, the estimated cost of study drug manufacture and supply, cost of equipment, pathology costs, pharmacy costs including dispensing, RGO submission and protocol amendment fees etc.

Then double the number, as clinical trials always cost twice as much as initially planned.

Remember that the more sites you have running, the more costs you will incur centrally to set them up, monitor and support. Think about your Investigational Medicinal Product costs – is the drug expensive, will you need blinded packaging, placebos, storage facilities etc.?

Funding can be sought and obtained just using the study concept – you don't need to wait to have a full protocol. Feedback from the funding body can help you with the development and refinement of the protocol. And you shouldn't let the lack of funding or rejections from funding bodies stop the development of the idea.

In June 2015, the Independent Hospital Pricing Authority published the document, *Determination of standard costs associated with conducting clinical trials in Australia.* While this independent review is a little dated, the

document, available at the above website, will assist you in understanding the costs of conducting a clinical trial and what to factor into your budget or funding submission.

Check-in with your mentor at this stage (and regularly) to make sure things are on track with your funding.

Think about dissemination

You will need a plan to disseminate the trial findings. As you develop the protocol, think about how you will disseminate the outcomes and outline what the potential dissemination plan might be. You will extend this in more detail in years four to eight. *SOP 6.15.1 Dissemination and Template 24 Dissemination Plan*

Year Two

Trial governance

You should make plans for who you will need to meet with, how you will meet, and how often regarding the study. You may have already been having regular protocol development meetings that can then move to trials management meetings once the protocol is developed. This meeting structure will need to develop and be maintained throughout the study.

We recommend two levels of regular meetings; Quarterly meetings with the protocol investigators and monthly with the participating sites. Ideally, these meetings should commence during the lead up to trial initiation and opening to recruitment.

From time to time, you may need to hold specialists' meetings for safety reporting, protocol violations or provide upstream or downstream reporting to your sponsor, funding body, lead organisation and participating sites.

Agreements

The required agreements are largely dependent on the study, the sponsor, and the funding body. For example, if you are successful in gaining competitive Category 1 funding through the National Health and Medical Research Council (NHMRC) or the Medical Research Future Fund (MRFF), you are going to need:

- multi-institutional agreements/research collaboration agreements with each associated member on the NHMRC grant regardless of whether they are a participating recruiting site or not
- a research collaboration agreement will be needed between the two entities (if the trial sponsor is not the NHMRC lead agency), and
- Clinical Trial Research Agreements (CTRAs) between the sponsor and the individual, and if your grant holder is different to your sponsor, they will also need to be involved.

Site selection

You need to think about those sites that will enable this study to recruit, on time, in budget and with data you can use. Consider the following questions:

- How many sites will you need to ensure the sample size is attainable?
- Which sites see the patients you want to recruit for this study? What are the likely referral numbers?
- What information would be helpful for decision making about which sites to choose?
- What previous success has the site had with recruitment to clinical trials?
- Are there any known risk/s at the site/s?
- What infrastructure is in place at the site/s? (Office, computer, resources)
- Is the Principal Site Investigator interested in the trial? Do they have a research team to support their involvement?
- How many sites will the study need to reach the required sample size?

Investigational medicinal product (IMP)

Think about the study drug (investigation medical product or IMP). Will it be blinded, and how? Will it be randomised, and who will do the schedules and the allocation following participant consent? What will the study drug look like? If there's a placebo, how easily can it be manufactured to look, feel, taste and smell the same as the study drug? Who will do the manufacturing? What presentation will reduce medication errors and mistakes? How many times will you need to dispense the IMP? Can it be dispensed through a hospital pharmacy or direct to the patient in their home from a suitably licensed community pharmacy? What is the expiry date of the product? Can this be extended if recruitment takes longer than anticipated, and at what cost?

Look at the regulatory environment and ensure they are licensed to manufacture the study drug you require. Remember, in the context of clinical trials, manufacture can mean encapsulation and repackaging. This is not going to be the local pharmacy. Your protocol needs to define all of this, so these processes all go hand in hand.

Make sure you check the regulatory requirements of handling and storage of the IMP. Consider licenses, local and international requirements, scheduling, potential suppliers, and packaging requirements. You need to make sure you can access the product for trial use and that there is adequate funding to use the intervention as planned e.g. cost of repackaging.

Data management

W: uts.edu.au/itcc/sops

Now is the time to also start thinking about data. What do you want, in what format? How will it be collected and who will collect it?

Data Collection Worksheets are developed to capture the data to enable entry into the eCRF via REDCap or similar Research Data Management System (RDMS). A good rule of thumb is to build a worksheet for each interaction/contact with the participant, this way, you'll ensure that you are collecting the data at each timepoint in line with your protocol and the table of study measures. If it's not in the protocol, then the question cannot be asked. The data that is captured on the worksheets will constitute the data at the end of the study. Be careful, be consistent in your use of language, and pilot the forms.

Set up master files. These are detailed in the ICH Good Clinical Practice (GCP) documents, Section 8 (Essential Documents). There are certain documents that you must file and keep at the ITCC, and at each site. The master file will ensure that these are set up and maintained, so everything has its place. Even before you start, think about being able to trust the integrity and rigour of your data.

Think about the data you will get and your plans for monitoring data quality. Think about the role of a Data and Safety Monitoring Committee (DSMC), who can provide some oversight and independence. Each phase III study will require a DSMC with a documented SOP that serves as the Committee's Terms of Reference. An example of this document can be obtained from the ITCC. If your study is a pilot/phase II/feasibility study, a medical monitor might be a more suitable option. Data management SOPs include:

- 4.9.2 Source Data and Documentation
- 5.5.1 Electronic Data Handling
- 5.5.2 Electronic Data Transfer
- 5.5.10 Data Ownership and Utilisation

Good clinical practice

A study may take ten years or more, across numerous sites, with a lot of paperwork. The required archive period is 15 years, so it is possible that there may be some review of the files in 25 years' time. The likelihood is that we may all have moved on in one way or another, the patients may all have died, and some of the hospitals may even have closed.

The reviewers/auditors will only have the quality of the paperwork available to them to assess the quality of the study results. If it isn't documented, it did not happen. The paper trail starts right at the start of the process and continues until the end. In GCP, this continues until the drug is in clinical practice. Trials are only two or three parts of this cycle. Good filing and record-keeping are essential throughout the trial and start at this point. The

shift from paper to electronic files continues, and it's important to understand how your electronic files will be stored, archived and destroyed when the time comes. Electronic infrastructure needs to ensure the safety and security of the data.

Standard operating procedures

W: uts.edu.au/itcc/sops

The use of Standard Operating Procedures (SOPs) is absolutely necessary in multi-site trials. SOPs provide detailed written instructions that enable uniformity across the study. SOPs support the study protocol and allow procedures to be conducted without a detailed description within the protocol. This does not mean they are optional.

The take-home message is to make sure that all participating sites do things the same way, i.e. consent, form completion, patient flow, follow up, and any other procedures that need to be consistent across the entire study. The files need to be comparable across sites. SOPs also ensure that sites are operating in accordance with international regulations and the study protocol.

Regulatory

The World Health Organisation (WHO) regards trial registration as important because the registration of all interventional trials is considered a scientific, ethical and moral responsibility.

Another critical element is that without registration, your research will no longer be accepted for publication. Once a trial is registered, it is the sponsor's responsibility to actively update the registry if the study changes and at critical time points.

Clinical Trial Research Agreements (CTRAs) set out the terms and conditions between the sponsor and the recruiting sites. Medicines Australia has a template agreement adopted throughout the clinical trial world that we strongly recommend is used unaltered.

Trial registration

W: www.anzctr.org.au

A trial must be registered prior to first recruitment. ANZCTR is an online registry of clinical trials in Australia and New Zealand. There are others; investigate the one best suited to your study.

Clinical Research Trial Agreements

W: https://medicinesaustralia.com.au/policy/clinical-trials/clinical-trials-research-agreements/

Medicines Australia have a standard template agreement for trials and must be used when working with other sites for recruitment.

Clinical Trial Notification with the Therapeutic Goods Administration

W: www.tga.gov.au

Clinical Trial Notification of the study to the Therapeutic Goods Administration (TGA) is required for all trials where the intervention is a medication used outside of the approved population, indication or dose – via online submission

Insurance and indemnity

Both the sponsor and participating sites require clinical trial insurance

Ethics and governance

The process of Human Research Ethics Committee (HREC) submission and approval is arduous. Submission is via online form, the exact format of this changes from time to time, and from state to state, but the appropriate ethics application form needs to be identified and completed in full. This application provides the HREC with specific ethics focus for the review of the study protocol. You will be required to attach supporting documents

such as diaries, questionnaires, and consent forms. Version control is important to make sure the approval that comes back, lists exactly the documents that were submitted.

HREC selection – does it matter who you submit to? Is it convenient or do they have the experience with the type of trial you are developing?

Site-Specific Assessment (SSA) forms are generated after the online application is locked so that each site can submit to their own local research governance office (RGO) for local approval.

In summary, the process is:

1. Identify the likely Lead HREC; this HREC will provide approval for the ethical conduct of the study across multiple sites. Identify the submission process for this HREC.

2. Complete the appropriate submission online, and provide as part of the submission:

    a. the study protocol

    b. patient information sheets and consent forms, using the template required by that HREC

    c. any questionnaires to be completed by participants. Ensure that you have added a date and/or version number for tracking

    d. any diaries or other patient-facing documents

    e. any advertising materials to be used for recruitment, including social media

    f. any instructions, letters, or other documents to be used as part of the study

    g. Case Report Forms do not need to be submitted for approval

3. Obtain an approval document specifically providing approval to conduct the study at the specified sites, with a list of the exact approved documents and version dates/numbers.

4. Once ethical approval has been obtained, each site has a governance office, which assesses the capacity of the site to conduct the study within that organisation. This is the Site-Specific Assessment (SSA) submitted and approved by the Research Governance Office (RGO). The RGO will require:

    a. ethical approval document, and all approved study documents

    b. local versions of the approved study documents

    c. a budget, usually within a CTRA, but may also be required separately

    d. signoff by any impacted department such as pharmacy, pathology, medical records, etc

5. Recruitment can only commence once there is both HREC and RGO approval.

Central records are also important to ensure that the approved versions are being used and there is a record of the approval process and reporting requirements. It can take up to a year to navigate through the regulatory and approval process to the point where you can open to recruitment.

Budget

Once you have funding approved, you will need to develop your budget. Usually, this is based on a *per participant* payment, and other site payments model – probably 50-60% of total funding on average will go towards paying the sites for recruiting participants and entering data into the electronic data capture system being used, i.e. REDCap. Start with working out the staffing and time component you are going to need for one participant to journey through the study. This then forms the basis for your per participant payment.

The overall study budget will depend on the study design, sample size and the number of recruiting sites. . Some items to consider in your budget are:

- Ethics and RGO submission fees (including payments for any future amendments if they are required)

- IMP/placebos, supply, packaging, distributions, pharmacy costs

- Data – RDMS, entry, storage, checking

- Human resourcing/project officer

- Equipment and software

- Site visits/training – initiation, monitoring, closure (more often conducted via zoom)

Questionnaire and Equipment licences

Most questionnaires, tools and scales are the intellectual property (IP) of others, and you may need to seek permission to use them. Look online or check the validation publications to see if this is needed. A fee may be involved but may be waived for investigator- or university-led trials. Keep in mind that questionnaires and assessment tools for use in clinical trials are not the same as for clinical practice, for example, the Mini Mental Status Examination is freely available for use in clinical situations, but a strictly enforced fee is applied for use in clinical trials. Where any uncertainty exists, we strongly recommend that the owners are approached, usually via email, to seek permission to use the tool in your study.

All equipment provided to, or used within, health facilities will need to be approved, checked and tagged, and will need to be maintained. Any programs or software will need to be installed by the IT administrators.

Considerations include:

- What equipment is needed for the study?
- Where can I source the equipment? What is the cost? Does it need testing, calibrating, and maintenance?
- Will staff need to be trained in the use of the equipment?
- Does the equipment need to be insured?
- What assessment tools and licences are written into the protocol?
- Where do I go to seek permission or buy licences to use the tools? How much will it cost? Is the cost per site? Do the licences expire? Do original only versions need to be used?
- Installation issues and firewalls

Year three

Site start-up

You need to have everything ready for the sites so that they can recruit. Ensure they have the approved versions of patient materials that they need. The IMP must be ready and available for dispensing. Make sure the site staff know how to enter data. Ensure they understand the study and identify any training needs.

Start-up will take time as it is unusual for all the sites to have approval at the same time in order to be ready for recruitment.

Site start-up requires the development of several site files to prepare the site to conduct the study correctly. These will include:

1. Site investigator File
    a. This should be in electronic form and should include a method for keeping track of and filing everything to do with the study at that site. The contents of this file must be consistent with the requirements of the Essential Documents as part of ICH GCP

2. Pharmacy file (if a medication trial)
    a. This file should contain all the relevant information and logs to enable the pharmacy to handle the Investigational Product during the study

3. Study files
    a. These folders should contain all the documentation required for each participant on the study, the data collection worksheets, information sheets and consent forms, instructions, questionnaires etc.
    b. A single example folder is usually sufficient.

Time spent now on processes will save time when things get busy during patient recruitment and data entry and fielding questions. Implement a robust filing system at the beginning to make sure all documents remain in a

logical order. Ensure that sites have a way of dealing with the paperwork and can easily file and retrieve documents either in paper or electronically, the latter being increasingly preferred

Site recruitment is closely related to the time of first participant recruitment. The time period between site initiation and recruitment of the first participant needs to be monitored as an early indicator of success.

Years four to eight

These are the recruitment years of the trial, where you will see if the protocol is working and what the data looks like. This period can vary - it might be short, or it might be years which could result in problems with sites becoming disengaged and potentially demoralised. As staff move on or recruitment is slow, details may be overlooked.

Recruitment

During this time, while you need to keep track of recruitment, there are many procedural issues that arise.

There may be new sites that require training. Consider how feedback on recruitment will be handled and how the study stays on track. The patients being referred may change from site to site, and over time. The way the study is explained might change very slightly over time, impacting the consent rate. This is a time to monitor progress continually and the monthly site meetings become essential communication tools.

Recruitment strategies will need to be reviewed (or developed if not already) to ensure all possible potential participants are referred to the study. Consideration should be given to advertising posters and materials, email and local reminders, meeting attendance, journal clubs, etc. Recruitment will only happen with constant reminders, others will not remember your study, and face-to-face, on the ground reminders are vital. While much of this is undertaken at each recruiting site, your study depends on this, so oversight and planning of recruitment strategies is important.

Data management

Continue to monitor and report safety. You need to be aware of any safety concerns with the study - there will always be some – and how concerns are reported.

Regular reporting is required. Trial Governance will inform what is being communicated to the ethics committee and to the DSMC. Reporting of adverse events is required; there needs to be a way to collect and arrange the events to enable this reporting.

Data management also means keeping track of recruitment through tracking progress and key performance indicators (KPIs). You will need to keep track of all data for CONSORT reporting and to determine the information that needs to be reported.

Do you know what your recruitment needs to be? Do you know if you're not reaching your expectations? Will you reach your sample size in the timeframe? Can you improve recruitment by introducing strategies, and do those strategies make a difference?

Trials are all about data. You need to ensure the data collected is accurate. Monitoring is about verifying the existence and accuracy of the data. It can take a variety of forms. The format of your monitoring is related to risk, funding, capacity, and other factors.

Data monitoring should ensure that the data collected matches what is required, and you need to be able to trust it. The monitoring process should be explained in the protocol and you will need to ensure that it is working. Monitoring can be focused on certain critical data such as consent, eligibility, safety, and study drug accountability. It does not need to wade through every blood pressure and QOL score.

If there are issues with capturing or monitoring data, consider whether you can change the way it is captured and change the Data Collection Worksheets to remove ambiguity and interpretation. For example, do not allow for answers to be left blank; specify measures, times, and conversions.

The ITCC has a team that oversees data collection and entry. The data is checked and amended if there are errors. We track data quality issues that surface over time and implement changes to minimise work at the end of the study.

The ITCC log the data to track if data has been collected, entered and checked, and if the source data has been monitored, and all errors have been corrected. This ensures that the data is reliable at the end of the study. An audit trail is required, and we must be able to show if data was changed for any reason.

Protocol amendments

There are some circumstances where you will need to change a protocol. Reasons may be related to recruitment (or lack of recruitment), safety, inconsistency in implementation, internal inconsistencies, misunderstanding or unclear external factors, such as medication safety warnings.

If a protocol amendment changes your data, you will need check if the Data Collection Worksheets can accommodate the changes. We work with online data entry, which means making changes to a live database, which presents some risks.

If you are changing a protocol, you will need to review your budget to see if there are any financial implications if these haven't already been considered prior to commencement. Along with RGO fees there may be other financial implications associated with a protocol change such as an additional dispensing etc. A change may also delay recruitment.

Site payments

Your budget should include per participant payments and other non-patient related payments (admin fees, RGO fees, pharmacy fees etc.) that have been agreed in the CTRA. Sites will invoice for payment per participant, per completion. The timing of invoices depends on the model and time period of the study intervention, as you may have staggered payments related to critical timepoints.

There are various other payments such as lead site and other annual based payments. Payments and data are absolutely interlinked. If there is no data, there is no payment.

A study log to track each participant's journey through the study and link to payment time points may assist -The ITCC can help with this. Good record-keeping is essential.

Dissemination plan

Think about and determine who needs to know about your study or who you want to know about your research and the results when they become available. Make a list of key stakeholders who you should liaise with. Determine your dissemination techniques – presentations, publications, letters, academic detailing, social media.

Check if you need to withhold your results until they are peer-reviewed. Peer review is important because it confirms the rigour of the study process and conduct so that the results/data are reliable and can stand up to scrutiny.

Year nine

Reach sample size

When you think you've got the numbers for your sample size, make sure you perform a number of checks to confirm. Closing your study too early can interrupt the momentum of the study – it is better to keep going and have a few more patients than to stop early and fall short. Think about these questions:

- Have you got all the data to support the numbers?

- Do you need to wait for any specific element of data from the sites?

- Have you checked the total numbers in the arms to see that they're even?

- Have you met with your statistician and the Investigator team to review the protocol violations to see if any will result in data being removed from the study?

Data management

W: uts.edu.au/itcc/sops

At this point, you should check all the data for completeness and accuracy. Check the SOPs to ensure all data management procedural steps have been followed. You should have an audit trail that shows compliance with the SOPs.

Finalise Statistical Analysis Plan

Check the Statistical Analysis Plan (SAP) developed by the statistician against the protocol to ensure consistency. Ensure any planned tables outlined in the SAP display the information correctly.

The complexity of the SAP can vary, but it ensures that the analysis is decided before you unblind. It means that you're not mining for the result you think you should get, or for anything that shows what you were looking for – you let the data tell the story.

Analysis

W: http://www.consort-statement.org/

Unblinding is the process where you reveal the allocations for each participant. You need to be confident in the randomisation schedules you developed in Year 2 to ensure you know who got what and that you can trust it.

Start building up demographic tables to describe the population.

CONSORT is a set of guidelines, accessible at the above website, that determines the information that needs to be reported in a clinical trial for publication and in fact, in the trial registration (ANZCTR or similar) way back in year two.

The CONSORT diagram structure is determined by an international committee of journal publishers to ensure that study results are transparent. The diagram ensures that every single patient can be accounted for from the time they are screened for the study (pre-randomisation), to the time they exit the study, and for what reason - it tracks the patient's journey.

Look at secondary outcomes as described in the protocol and consider what the results mean in the context of the population and the use of the medication. Decide how you will present the results related to any secondary outcomes and if the analysis should be included in the primary results paper or are significant for additional papers.

This is a time when the protocol and authorship teams look critically at the data, knowing they can trust what they have, and start to interpret what they see in the status output. The previously developed SAP now becomes the statistical analysis report.

Draft publication

W: uts.edu.au/itcc/sops

Don't put off starting to draft your article of publication. Think about this at each stage of the trial so that you capture the information you want to communicate. Both positive and negative outcomes are important to capture and publish as all outcomes contribute to better outcomes.

Determine authorship, including lead author, who else should be involved, and what criteria will you use to determine this.

The ITCC SOP uses the International Committee of Medical Journal Editors (ICMJE), which requires each individual author to meet certain criteria and make a signed statement indicating that they meet the criteria.

You need to consider what happens if there's a dispute. Know which journal/s you are going to target. The lead author takes responsibility for the timeliness, drafting, version control and submission.

Please note that although you may have been involved in patient recruitment, you may not necessarily have authorship rights, as this alone does not meet the ICMJE criteria for authorship.

Year ten

Human Research Ethics Committee (HREC) final reporting

Final reporting requires a report back to the approving committee. It needs to be a comprehensive report of the study. You may need to use the templates, and if the analysis is not yet complete, you may need an extension of approval. It is possible that you may need to provide the results at a later time.

Clinical study report

Populate the Clinical Study Report (CSR), including the statistical analysis report. It is a 32-page template. This report collects all information from the past ten years of your work. The CSR is a significant body of work, and you should allow yourself several weeks to complete it.

You will depend on your record-keeping and filing for this report, as you need to retrieve the records, minutes, reports, data monitoring and tracking that you recorded during the course of the study.

Dissemination activities

Review your dissemination plan developed during years four to eight and update as required.

Your dissemination of information will generally commence with presentations. Post-peer review publication takes on a circulation program to get the results into practice and get policyholders thinking.

Dissemination is a whole mini project on its own as you try to influence changes in practice and policy. You might like to consider a 12-month post-publication follow up to see if there's been any implication on clinical practice from your research findings.

Study closure

The study must be formally closed. This will involve final reports and records archiving.

Most Australian states have a record archiving process that you must comply with. Before you can archive the final closure, each site needs to be checked off to ensure the central materials can be closed up in the knowledge that all the site materials are complete.

We use a checklist that each site completes and signs, then sends to us for logging. Once all sites have returned this to us, we can log complete closure. This ensures that each site has completed the activities required to close a study locally, and the ITCC can also then close their own central files for central archiving further down the track.