Clinical Oncology Society of Australia

Australasian Tele-Trial Model

ACCESS TO CLINICAL TRIALS CLOSER TO HOME USING TELE-HEALTH

A NATIONAL GUIDE FOR IMPLEMENTATION

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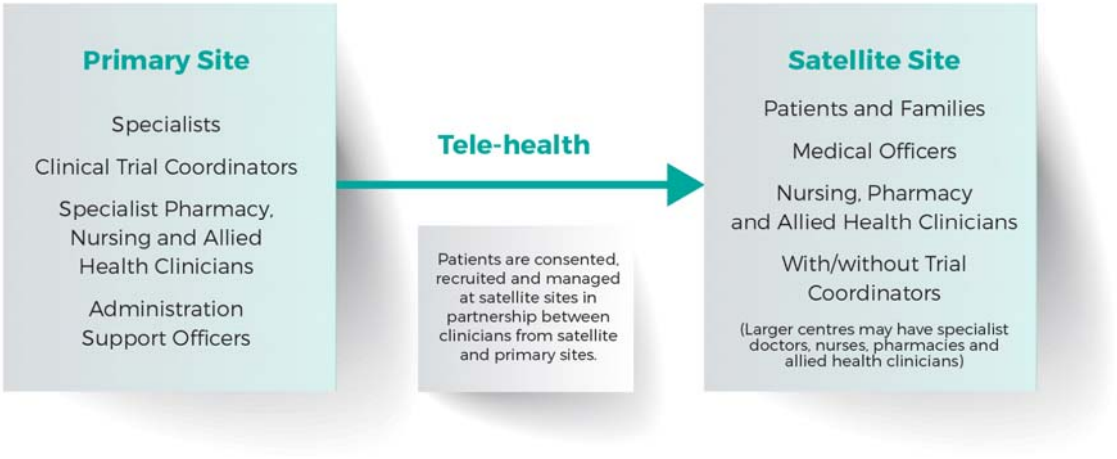
Contents

Executive Summary

The **Australasian Tele-trial Model** has been developed by the Clinical Oncology Society of Australia (COSA) Regional and Rural Group in consultation with clinical trial sponsors, clinicians, health administrators and regulatory bodies.



The purpose of this guidance document is to outline key considerations for increasing access to clinical trials for people with cancer living in rural and remote locations, and outline the contribution of tele-health models to facilitate study activity across rural and remote locations. The benefits of this model are not limited to regional, rural and remote systems. This model has the potential to connect larger centres even within the same city and improve the rate of recruitment to highly specialised clinical trials, including rare cancer trials. This model has been developed in consideration of the requirements for the proper conduct of clinical trials ensuring the protection of the rights and safety of trial participants and quality data for the demonstration of safe and efficacious cancer treatments.

Ethical and safe conduct of clinical trials using this model requires that the following aspects are considered and addressed by implementation plans:

1. Selection of satellite sites and suitable trials including accreditation of sites, supervision plans and site visits
2. Workforce
3. Good clinical practice
4. Roles and responsibilities
5. Training for individual staff, site initiation meetings and trial updates
6. Technology and support
7. Participant screening and recruitment
8. Obtaining participant consent

9. Medication handling
10. Managing and reporting serious adverse events
11. Patient reported outcomes
12. Documentation and reporting
13. Financial considerations
14. Regulatory considerations, Indemnity, Insurance and clinical trial agreements

System improvement using this model is unlikely to be achieved without added cost and additional resources for the Sponsors, hospitals and governments. Simplification and streamlining of site accreditation and selection processes, monitoring requirements, ethics, governance and contractual matters are needed to reduce cost and workload, and to expedite approval processes.

Recommendations

1. Adoption of tele-trial models such as the Australasian Tele-trial Model as part of standard practice by cooperative trials groups, industry, researchers, governments, regulatory bodies, hospitals and insurers.

2. Inclusion of central review processes for site specific authorisations within clusters.

3. Development of overarching contracts for the tele-trial model between sites within clusters in order to simplify the contract processes at local, state and national levels.

4. Development of a pre-accreditation process where the focus is on the capability of the site and the investigator at the satellite, well ahead of any trial. Once pre-accredited, a satellite should be able to recruit to any trial immediately or at short notice, if they have a candidate case. A pre-accredited satellite could then recruit to more than one primary site, provided that the trial of interest has been approved by the primary site governance and ethical approval processes. Any primary site could pre-accredit a number of satellite sites even though different sites may be part of a cluster at different times.

5. Provision of incentives by funding bodies and government and non-government organisations for hospitals, industry or trials groups to accommodate innovative models such as the Australasian Tele-trial Model in their trial protocols to improve access to clinical trials for rural and regional cancer patients.

6. Exploration of the feasibility of adopting remote monitoring systems by Sponsors and auditing authorities.

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Medical Oncology Group of Australia (MOGA)

Medicines Australia and their member pharmaceutical organisations

NHMRC Clinical Trials Centre

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1. Background

Access to specialist cancer care services is a significant issue faced by residents of rural, remote, Indigenous and some regional communities in countries with large rural and outer metropolitan populations.[1] For these communities, the lack of access to specialist services may be due to a lack of specialist oncologists locally, limited scope of practice of other rural health professionals and/or overall rural workforce shortages. Poor access to such specialised health care services could be one of the contributors to the disparity in survival and disease related outcomes that exist between metropolitan and non-metropolitan patients,[2-5] although the authors acknowledge this issue is complex and may also relate to other factors such as behavioural or cultural factors.

It is recommended by leading authorities, such as the National Comprehensive Cancer Network (www.nccn.org) and Cancer Research UK,[6] that support for the provision of clinical trials to people diagnosed with cancer is a core component of providing optimal cancer care through specialist cancer centres, hospitals and other treatment facilities. Indeed, in many cases such guidelines recommend participation in clinical trials as the best option for many cancer patients.

Clinical trials offered to people diagnosed with cancer may include new and experimental drug therapies or imaging technologies, minimally invasive diagnostic or surgical techniques, or supportive care interventions. However, as with access to specialist care, patients living outside of major metropolitan centres face many barriers in accessing clinical trials. Barriers to participation include the limited availability of trial sites closer to home and the increased cost and inconvenience of travel to major centres where the trials are taking place.[7, 8]

While it may be reasonable to establish clinical trials units in large regional cancer treatment centres, the logistics of maintaining a suitably trained workforce and undertaking the ethical and regulatory responsibilities of clinical trials may be difficult in smaller rural and regional sites with limited resources and low patient numbers.

Tele-oncology models of care have been shown to satisfy many specialist health care needs of rural and regional patients in countries with large rural populations.[1] Using tele-oncology models many cancer centres have been able to facilitate the administration of complex chemotherapy in rural and regional areas.[9-11] Around the world, such centres have implemented safe and successful tele-oncology models that are acceptable to patients, families and health professionals, save money for health service provision and enhance the capabilities of rural health systems in oncology services to provide cancer care.[10, 12-17] In addition, cancer services can be delivered to rural patients closer to home in a timely manner.[18] Tele-oncology models of care may outline a system-level intervention to address issues of equity and access to clinical trials. For example, adopting this model would enable rural and regional sites with limited resources to provide access to Phase III

comparative effectiveness studies and potentially trials of new and novel therapies for the local population.

This document outlines a feasible and effective tele-health strategy to increase access to clinical trials closer to home, while at the same time ensuring the proper conduct of cancer clinical trials.

1.1 Overview of established clinic and treatment models of tele-oncology in Australia and globally

The Townsville tele-oncology [15] model enables medical oncologists from Townsville, Australia to provide their services to rural sites, using traditional video-conferencing technology or web based systems (Figure 1). At larger rural centres, rurally based doctors, chemotherapy competent nurses and allied health workers accompany patients during tele-consultations. At other rural sites, patients are accompanied by either a doctor or a nurse for post-treatment reviews, toxicity reviews or follow-up visit(s) tele-consultations.[12]

When a patient is assessed as fit for chemotherapy or targeted therapy, medical oncologists write the care plan and send the prescriptions to rural sites where chemotherapy is given by chemotherapy competent nurses. Where electronic systems are available, care plans are made and approved on-line. For oral chemotherapy, authority scripts are sent by medical oncologists to patients, rural hospitals or the local pharmacy after appropriate education by medical oncologists, nurses or pharmacists. Prior to the clinic, informed consent for participation in the tele-oncology clinic is obtained from patients.

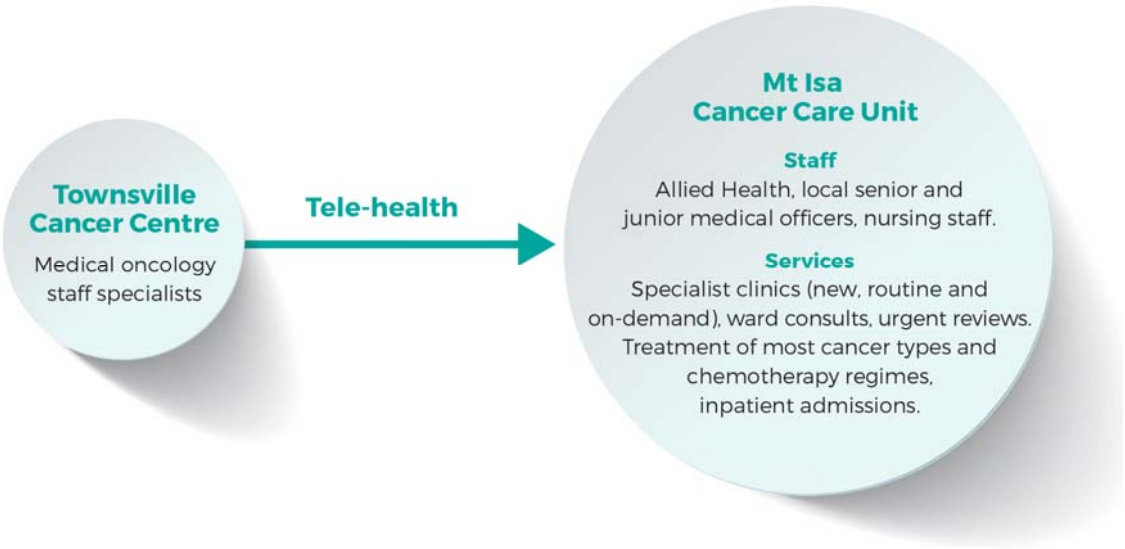

Figure 1: A model of a rural specialist unit with specialist support via telemedicine

Adapted from Sabesan S and Kelly J. Are teleoncology models merely about avoiding long distance travel for patients? Eur J Cancer Care, 2014.

1.2 Remote chemotherapy supervision model

While the models mentioned above are largely medical tele-health models, models such as the Queensland Remote Chemotherapy Supervision (QReCS) model [19] enable rural generalist nurses to administer chemotherapy at rural sites with the support of the rural generalist doctors and pharmacists, under the supervision of medical oncologists and chemotherapy competent nurses from larger centres using telemedicine and tele-nursing respectively (Figure 2).[20]

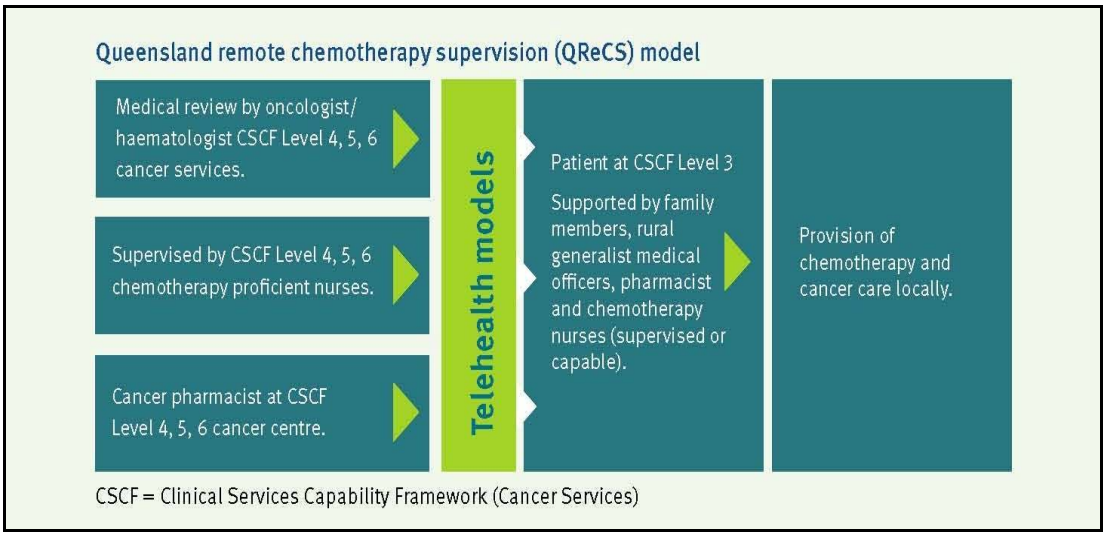

Figure 2: Remote chemotherapy supervision model

2. Core principles of the tele-trial model

The core principles of the tele-trial model are:

1. To increase accessibility to trials thereby reducing the need for people with cancer to travel to larger centres to attend study related visits and undertake study related procedures. Using tele-oncology models, there is an opportunity for patients from rural or regional sites to be recruited, consented, treated and attend follow-up visits – a hub-and-spoke approach between a primary trial site and a satellite site. The roles and responsibilities for each site need to be clearly defined at the outset of each trial and appropriately contracted (Figure 3).

2. To develop collaboration and networking between regional/rural and metropolitan centres, and between tertiary centres even within the same metropolitan setting, with the aim of delivering greater engagement in research activity, improving adherence to evidence based practice, improving the rate of recruitment of patients into clinical trials, reducing the disparity in cancer outcomes for geographically dispersed populations, building clinical trial capacity, and providing trial-related training.

3. To articulate the relationship between the primary site and satellite site as a trial cluster. The trial cluster co-ordinates the trial across multiple sites including a primary site and one or more satellite site(s), ideally through streamlined trial processes (Figure 4). A trial cluster may exist in the following settings: a) larger metropolitan centres as primary sites with other metropolitan centres as satellites even within the same city; b) larger metropolitan centres or large regional centres as primary sites with smaller regional or rural sites as satellites; or c) larger regional centres as primary sites with metropolitan centres as satellites in an attempt to improve the capabilities and community profile of regional centres.

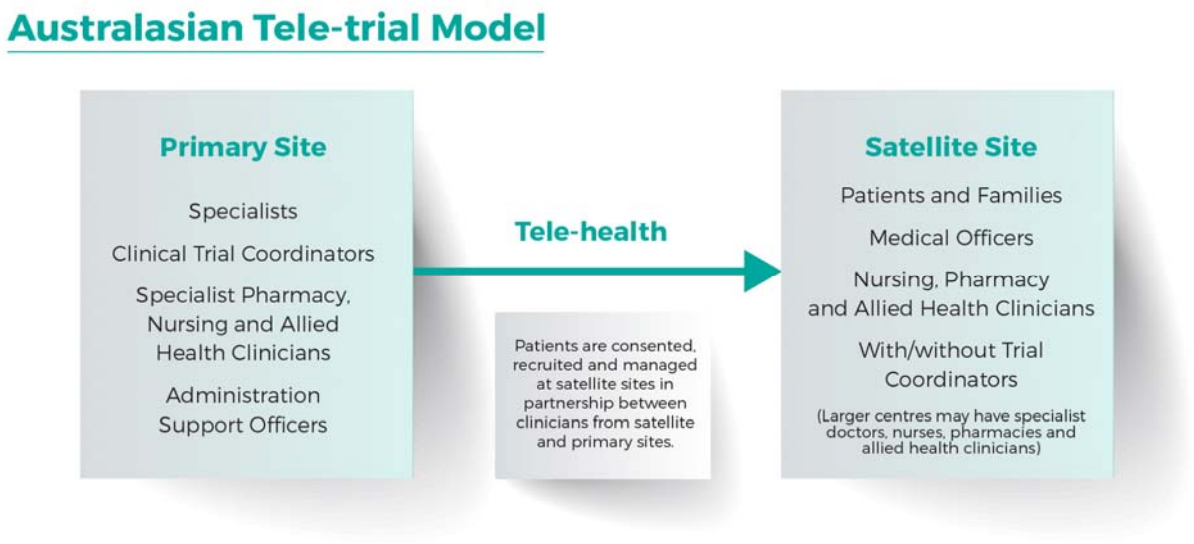

Figure 3: Australasian Tele-trial Model

Adapted from Sabesan S and Zalcberg J. Telehealth models could be extended to conducting clinical trials: A Teletrial approach, European Journal of Cancer Care, in press 2016.

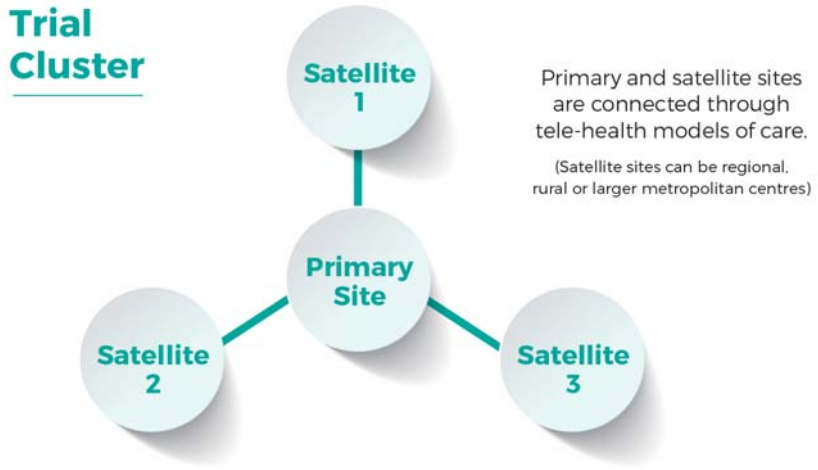

Figure 4: A tele-trial cluster

2.1 Anticipated benefits

Similar to tele-health models for delivering routine cancer care, there are a range of benefits associated with conducting clinical trials using tele-health strategies. Modern informatics supporting technological advancements in communication enable a greater depth of reach to more Australians. Notably the tele-trial model has the potential to make clinical trials accessible to people with cancer from rural and remote centres closer to home. Increasing accessibility for increased participant recruitment may also improve collaboration and networking between rural and metropolitan centres, provide workforce development, facilitate engagement in research activity for improved adherence with guideline recommended care and reduce the disparity in cancer outcomes for geographically dispersed populations.

There is a second related benefit of the model for Australia's geographic reality, and comparatively small population for which tele-trials may provide a useful solution. This benefit relates to the complexity and innate molecular and phenotypic heterogeneity of cancer. That is, any one tumour type is actually made of multiple discrete sub-groups. Hence, trials requiring the eligible population to have a similar tumour sub-type in order to compare two different interventions are more and more difficult to conduct. Increasingly, these studies involve numerous centres around Australia or indeed internationally. The corollary of such an observation is that individual centres, even large tertiary referral centres will only see a very small number of patients whose tumour fits the eligibility criteria for these studies in any one year. As the cost of establishing and maintaining the infrastructure to open poorly recruiting studies is so high, such centres are becoming increasingly reluctant to open these studies in the first place. Consequently these studies recruit even fewer patients overall than might reasonably be expected because the only trial site(s) recruiting to one of these studies is geographically distant from the potential participant.

Another advantage is workforce development. Exposure to, and involvement in research provides professional development opportunities through collaboration with leading clinical researchers. This may have flow-on benefits for improved access to trials and improved quality of care. There are also advantages for Australia to develop a more flexible approach to the conduct of trials given our relatively small population and geographic barriers to recruitment. Recruiting specific patient cohorts is an ever-present challenge and without multi-site collaboration Australia is less attractive to international trial Sponsors which limits the availability of experimental, life-saving treatments. Developing these clinical trial networks through models like this tele-trial concept, can better promote our capacity to support a wider range of trials.

Tele-trials offer the unique opportunity to impact this inevitable cascade of circumstances that compound the difficulties of defining new treatments for so many cancers in the modern era of molecular characterisation of cancer across regional and rural Australia.

2.2 Anticipated costs and threats

While the benefits discussed above have positive flow on effects on patient care and the Australian Health system as a whole, system improvement using this model is unlikely to be achieved without added cost for Sponsors (including increased site visits, medication transport cost to satellites, etc), hospitals and governments (increased workforce, technological and pharmacy infrastructure). Benefits of improved rural access to clinical trials and enhanced rate of recruitment can offset those extra costs. Reforms on remote monitoring, site accreditation, ethical, governance and contractual processes are required at a system level to reduce financial and human resource cost.

Geographic isolation due to distance may cause several problems including workforce stability, transporting and handling of medications and devices, access to source documents and communication between sites which can be mitigated by implementing the processes outlined in this document.

3. Purpose and definition of a satellite site

The primary purpose of the satellite site is to support trial accessibility across a number of trial sites.

A satellite site is located in a geographically separate health facility and responsibility is delegated by the primary site (clinical trial site) to perform activities associated with the conduct of a clinical trial. Satellite sites can be located in metropolitan, regional or rural settings. Delegated activities to be performed by the satellite site are trial specific and should be agreed and documented at the time of site selection.

For each trial, infrastructure and training requirements for satellites are the same for both the primary and satellite sites.

A satellite site should have the following:

- Appropriately contracted qualified and trained investigator(s) and delegated staff to undertake trial related activities including obtaining informed consent (if required). Study staff are trained in the protocol, study procedures, Adverse Event (AE)/Serious Adverse Event (SAE) reporting.
- Study related documentation including a Master Site File, procedures for managing the security of information and trial data and a process for managing data security or privacy breeches.
- An understanding of the process for storing and ensuring accountability for the Clinical Trials Investigational Medicinal Product (CTIMP).
- A system for safety reporting duties is in place for all study staff.

- Protocol, IB and all study related information is available to staff.
- Sufficient supplies of CTIMP are available, securely and suitably stored.

4. Requirements for implementation of the tele-trial model

Satellite sites (regional, rural or metropolitan) would vary in their capacity to conduct trials based on resources and prior experience. Based on the capabilities of the satellite sites, primary sites may delegate to the satellite sites some or all aspects of trials, in agreement with the Sponsors and satellites.

4.1 Selection of satellite sites and suitable trials

Site feasibility assessments may have to consider the capability of the whole cluster and potential satellite sites are indicated during the site feasibility process. This informs the trial Sponsor of the referral relationship between the primary site and satellite sites within the cluster. The cluster may include hospitals within the same region, network or local health district or hospitals in other regions, networks and local health districts. Once the primary site is chosen, the acceptance of the satellite sites by a trial Sponsor will depend on the prior experience of the satellite site in conducting clinical trials, the complexity of the trial, and the medical, nursing, allied health, pathology and pharmacy research capabilities. Site capacity and trial complexity will determine the ability of the site to conduct trial related activities at the satellite site and will be assessed by the Sponsor at the time of site selection. It is not anticipated the satellite site will undertake ***all*** trial related activities. The provision of all trial related activities would be the role of a '*clinical trial site'* or primary site. Satellite sites that have established trial capabilities are able to take part in complex protocols from the outset. At sites that have no or limited experience in delivering clinical trials, a staged approach may allow for gradual building of clinical trials capacity from simple to more complex trials.

Accreditation of satellites

For sites that have not taken part in clinical trials previously, as required under current practice, it is likely that the Sponsor may wish to perform a site visit. The Sponsor may also wish to delegate this responsibility to the primary site.

Supervision plan

Some registration bodies require that the primary site Principal Investigator (PI) takes responsibility for overall supervision of the trial across a cluster. Tele-health offers a unique opportunity for direct supervision of patient management. A supervision plan agreed between the primary and satellite sites and the Sponsor needs to be developed formalised at the outset of a trial. The supervision plan may include, but not be limited to, details on joint consultations using tele-health, collation and monitoring of documents, frequency of joint trial meetings across a cluster (with minutes of these meetings) and any site visits performed by the PI.

Site visits

While the travel by staff and patients is reduced as the result of this model, Sponsors may wish to undertake site visits for accreditation and monitoring purposes, unless remote monitoring is agreed by the Sponsor and source documents are available at the primary site.

4.2 Workforce: Roles and responsibilities

The workforce requirements of current tele-health models could be extended to the tele-trial model. While larger rural and regional centres may have resident or visiting medical oncologists, oncology clinicians and trial nurses, satellite sites may have limited specialised services. Under the current tele-health models, urban specialists at a primary site provide their services using video-conferencing. Service delivery is supported and facilitated by doctors, nurses and allied health professionals at a satellite site. The nature of support to and by the rural health professionals would be determined by the complexity of the trial and the clinical capabilities at the site.[21, 22] The delegated responsibilities would need to be agreed by the Sponsor, clearly documented within the master site file and trial related training records provided before this delegation could occur.

Defining roles and allocating specific responsibilities to staff within a cluster can ensure the safe and efficient conduct of clinical trials. The satellite team would need to take part in the Investigator Meeting & Study Initiation Visit so that they are fully aware of the requirements for compliance with the Investigational Brochure (IB), study protocol and the importance of these required processes. Tele-health technologies offer the opportunity to conduct investigator meetings and study initiation visits across geographically dispersed clusters. This is particularly important for reporting and managing adverse events and serious adverse events, and ensuring that patient reported outcomes are completed in a timely manner without excessive missing data.

4.3 Good Clinical Practice

All clinical trials involving CTIMPs must be conducted according to the principles of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and local laws for Good Clinical Practice (GCP). ICH and GCP requirements, local laws and regulations and the Sponsors' protocol and company requirements as outlined in the Australian legislative requirements applying to prescription medicines are contained in the Therapeutic Goods Act 1989 and the Therapeutic Goods Regulations 1990. Accreditation is a legal requirement for all clinical trials involving CTIMPs conducted under the CTN/CTX scheme in addition to the regulatory requirements in Australia. Guidance on GCP for CTIMPs is available from the National Health and Medical Research Council (NHMRC).

4.4 Roles and responsibilities of trial site staff

Prior experience of staff and capabilities of the satellite sites would determine the roles of the satellite trial staff. The Principal Investigator may delegate some or all of the trial related processes to the satellite site staff, in agreement with the Sponsor and satellite staff. It is important that roles and responsibilities are agreed and formalised at the outset.

Primary investigator at primary sites

Some registration bodies require that the PI is responsible for overall supervision of the trial, including satellite sites. Therefore, it is important to develop a supervision plan including cover for holidays and unexpected leave at the outset of a trial and incorporate this into the contract.

1. Participate in trial consultations with satellite site medical officers via tele-health if required.
2. Take part in the consenting and recruitment process remotely or on site as required via tele-health.
3. Communication with satellite investigators regarding protocol revisions.
4. Provide oversight of SAE reporting, ensuring satellite sites provide source documents and reports as required.
5. Be available to consult on the management of Serious Adverse Events and adverse events (SAE/AEs) as required.
6. Maintain a delegation log for all research staff at both primary site and satellite sites.
7. Ensure all staff at both the Primary and Satellite Site are trained in the trial specific activities delegated to each.
8. Develop arrangements for radiology and pathology reviews and for engagement with other clinicians including genetic counsellors, other specialists and allied health professionals, as dictated by trial protocols, across a cluster.

Satellite site investigators

Satellite site medical officers will be the local contact for trial related matters within a satellite unless the PI and the primary site agree to take this responsibility. Depending on the prior experience of satellite site investigators and satellite capabilities, the Principal Investigator may delegate some or all of the trial related responsibilities to the satellite site investigators.

1. Conduct joint trial visits with primary sites when required by the trial Sponsor.
2. Satellite sites would require monitoring visits to review source documents that are not entered into an EMR system or shared between the satellite site and primary site.

3. Undertake ICH-GCP accreditation and training on the study protocol.
4. Take part in the consenting process, perform and document physical assessments.
5. Manage, store and dispense CTIMP if required and accredited to do so.
6. Undertake activities related to study follow-up.
7. Timely communication and management of AEs and SAEs and study reporting in collaboration with primary sites.
8. Develop arrangements in collaboration with the PI for radiology and pathology reviews and for engagement with other clinicians including genetic counsellors, other specialists and allied health professionals, as dictated by trial protocols, within their site.
9. Develop plans for local contacts during periods of cover for holidays and unexpected leave.

Trial co-ordinators

Trial co-ordinators at primary sites act as a contact for coordinators at both the primary and satellite sites.

1. Coordinate the study and monitor progress across the cluster.
2. Collate and coordinate documentation from satellite sites including the preparation of CRFs.
3. Identify staff changes and initiate appropriate training.
4. Conduct trial meetings by including satellite sites.
5. Manage the regulatory processes and reporting requirements to the trial Sponsor, and human research ethics committees as required.

Pharmacy and Pharmacy Facilities

Trial Sponsors may elect to deliver CTIMP directly to the site, dispensing the CTIMP and maintain drug accountability documentation at the site. Sponsors may delegate this responsibility to the primary sites. This requires the primary and satellites sites to work together collaboratively. Both the primary and the satellite site(s) would need to ensure that adequate documentation is in place to allow full drug accountability and be suitably qualified to undertake the following:

1. The primary site pharmacist is responsible for overall service provision in collaboration with satellites, ie: receipt of the IP, storage and handling, dispatch to satellite or trial participant, reconciliation and communicating the management of IP with the satellite site. The primary site pharmacist will be the first point of contact when trials involving CTIMPs are under consideration by the primary site.

2. Designated pharmacy staff providing a clinical trial service must be adequately qualified, trained and experienced to assume clinical research responsibilities and should be able to provide up-to-date GCP training records.
3. The pharmacy must hold training records and signature logs for those staff involved in a clinical trial in the pharmacy department. These will be held at the site and should include all staff involved at either the primary site or satellite sites. These records may also be held in a central location and should be readily available for inspection if required.
4. Appropriate facilities should be available before agreeing to support a clinical trial particularly one involving radiopharmaceuticals or Advanced Therapy Medicinal Products (ATMPs) such as gene therapy and cell therapy. The pharmacy lead site for clinical trials should liaise with, and seek advice from, satellite sites with experience in handling these types of products.
5. The institution (pharmacy department) is required to hold a GMP licence as per the TGA annotated guidelines annex 13.
6. Manufacturing must be performed to GMP and release performed by a Qualified Person – in certain circumstances labelling may be performed at a site but the facilities have to be certified and reach GMP standards etc.
7. If the satellite site does not have access to a local GMP qualified facility they would not be able to participate in trials with this requirement.
8. Pharmacies should have facilities that allow for CTIMPs to be stored separately from normal pharmacy stock in an area with access restricted to pharmacy staff. Licensed products used as CTIMPs do not have to be stored separately as long as there is a process in place to ensure traceability.
9. CTIMPs that are returned by patients or have expired should be stored separately from unused CTIMPs. Quarantined medication should be clearly identified and segregated from working stock.
10. Regular temperature monitoring of CTIMP storage facilities should be undertaken and records maintained for both primary and satellite sites. All CTIMP storage areas should be fitted with calibrated temperature monitoring devices that record minimum and maximum temperatures, with a robust system to alert staff if the temperature falls outside of the specified range. The temperature monitoring devices should have a valid calibration certificate which is maintained for reference. The pharmacy should have written procedures in place for the actions to be taken when the storage conditions are outside of the specified range.
11. Pharmacies should have an approved destruction policy that outlines the process for destroying; although some Sponsors may require unused, expired or returned CTIMP

study medication to be returned to a Sponsor nominated central licensed facility for destruction.

12. Pharmacy files will be kept by the primary site and where requested, may develop additional accountability logs and files for satellite site usage.
13. Suitable archiving facilities will be required for pharmacy trial files. The system used for archiving must allow for prompt retrieval of any pharmacy study file or of non-study specific documentation (such as pharmacy standard operating procedures, original pharmacy temperature monitoring records and training records of pharmacy staff).
14. Pharmacies should receive funding for providing a clinical trial service. This funding should reflect the workload and cover costs involved and is separate to the prescription charge.
15. Procedures for unblinding must be made available to the satellite site in the case of an emergency.

Patient compliance with taking the medication will be monitored by the dispensing pharmacy, nursing and medical officers. During joint consultations, primary site clinicians can also reiterate to patients.

Pathology and radiology

Pathology and radiology requirements are dealt with at the feasibility questionnaire stage and arrangements agreed by Sponsors. Biopsy and Biomarker and pharmaco dynamic studies may require onsite centrifuge, processing and storage. If the satellite site does not have these capabilities, private pathology could be used and considered subcontractors or agents of the primary site in agreement with the Sponsor. Similar arrangement could be made for radiology requirements. For sites that have never participated in trials, the Sponsor may wish to conduct a site visit to assess these aspects.

4.5 Training

Training requirements are the same for both the primary and satellite site staff involved in clinical trials within a cluster.

Training for individual staff

All investigators and trial staff at each site are required to have undertaken GCP training and certification. Individual staff members should ensure GCP competence is commensurate with their roles and responsibilities in relation to the study protocol and the management of CTIMPs. Whilst it may be the case that some staff carry out trial related tasks that are part of their normal role, they should be certified in the principles of GCP. A mentorship program would be of benefit where staff from the satellite site have the opportunity to observe and

have hands on experience at the primary site is one such example. Primary and satellite staff training is required to ensure staff are competent to participate in the conduct of, or for providing the supporting and delegated activities of, a clinical trial. Both the primary and satellite sites must retain training records and signature logs for those staff involved in the clinical trial. These records should be readily available for inspection if required. GCP training can be accessed through the Australian Clinical Trials website: https://www.australianclinicaltrials.gov.au/researchers/good-clinical-practice-gcp-australia

Site initiation and trial update

Site initiation meetings and site staff training on the trial protocol for primary and satellite sites in a cluster could be undertaken via video-conferencing across a large geographical area. Site initiation meetings could also be used to reiterate the roles and responsibilities of staff across all sites. Joint consultations and regular trial meetings are also useful forums for discussing trial related matters and updates.

> It may be helpful to forward a powerpoint presentation ahead of time to the satellite sites in case technology fails and therefore the satellite site can be talked through the powerpoint presentation over the phone.

4.6 Technology and support

A web-based system or video-conferencing equipment are required for interactive consultations. Availability of the electronic medical record (EMR) would enable seamless sharing of clinical data between sites. However, where the EMR is not available, source documents will need to be provided to the primary sites for data verification and trial monitoring purposes unless the Sponsor wishes to conduct trial monitoring visits themselves. While a tele-health approach may support the visit process both the primary and satellite sites need to understand the critical need for reliable source documents. In cases of technical failure, a secondary source of web based technology should be available to ensure continuity of clinical encounters.

4.7 Participant screening and recruitment

It is expected that all processes and activities related to recruitment are coordinated by the primary site in communication with the satellite site. Satellite sites that have adequate resources could assist with screening and referral of patients for recruitment. Doctors, nurses and trial coordinators are able to identify patients, provide trial related information and notify the primary sites, prior to participant consent being obtained.

NB: It is important to note that the National Statement has special requirements when enrolling special populations, for example Indigenous members of the community, therefore sites need to ensure these requirements are met where appropriate.

4.8 Obtaining participant consent

Patients from satellite sites are screened and recruited and provide consent for trial participation in collaboration with doctors and nurses at primary and satellite sites using video-link or on-site in a process approved by the Sponsor and the HREC.

Options for obtaining consent

The process for obtaining consent remotely via tele-health or on-site would be reviewed by the Sponsor and approved by the HREC. Satellite sites can be delegated responsibility to obtain informed consent.

For sites that do not have prior experience in clinical trials, it is important that the PI is directly involved in the trial consent process. In this option, the participants and the satellite site investigator sign the consent form, observed by an investigator at the primary site. This process is documented concurrently at both the primary site and satellite sites. At sites that have prior experience in trials, the satellite site investigator may be delegated to complete the consent process on-site. A copy of this final consent form can be given to the participant and stored in the medical record and in the primary trial site file. The mode of transfer for these documents (fax, emails and/or posts) needs to be agreed by the Sponsor according to their privacy policies.

4.9 Medication handling

Sponsors may prefer to deliver CTIMP or devices directly to primary and satellite sites to reduce the cost of medication transport. At the request of the Sponsor, the primary site pharmacy may transfer clinical trial medication for administration or collection to satellite sites. Medications may include the investigational product and/or non-investigational medications related to the clinical trial. The following Sponsor approved medication could be managed in the following way:

a. Medication is dispensed and/or prepared according to protocol and accountability logs are completed.

b. Medication is sealed in a non-transparent bag clearly labelled with the patient details.

c. An acknowledgement of receipt form and a copy of the prescription are attached to the outside of the bag of medication.

d. The bag of medication is placed into a suitable container (e.g. box or padded envelope) and labelled and packaged for transport.

e. Cold pack and temperature monitor should be included for medication requiring refrigerated storage being transported from the primary site.

f. As per IB / Sponsor or manufacturers instruction.

g. Completed CTIMP containers being returned to the primary site are not required to be temperature monitored. However, if a temperature monitoring device is supplied by the Sponsor, the primary pharmacy will include it with the parcel with instructions to be followed by satellite site.

h. The pharmacy at the receiving satellite site is contacted by telephone to notify them of the delivery.

i. The courier service is contacted to arrange suitable pick-up/delivery.

j. The faxed signed copy of the Acknowledgement of Receipt from the satellite site is filed with the original prescription in the primary site Pharmacy folder.

k. In the event that the Acknowledgement of Receipt is not received by the primary site Pharmacy within 48 hours, the satellite site is contacted to check that the parcel has been received.

Tele-pharmacy may also be an option for improving the collaboration between primary site and satellite site pharmacists.

4.10 Managing and reporting adverse events (AEs) and serious adverse events (SAEs)

Note: The NHMRC is currently updating their recommendations for the reporting of SAEs etc. *https://www.nhmrc.gov.au/research/clinical-trials/nhmrc-clinical-trials-initiatives/promoting-consistency-in-safety-monitoring*

Management at routine clinics

During planned trial consultations the history of AEs and SAEs is obtained. Clinical trial staff need to be aware that drug intervention studies will require minimum reporting times and the occurrence of AEs/SAEs are to be reported to the primary site in the usual within 24 hour plan by any satellite staff, medical practitioner, nurse or data manager. SAEs are managed according to the protocol and documented in the EMR or medical charts by medical specialists/medical officers at satellite sites. If EMR is not available, certified copies of the source documents may be required and sent to the primary sites for monitoring purposes. Mode of transfer for these documents (fax, emails and/or post) needs to be agreed by the Sponsor according to their privacy policies. Upon notification of an AE or SAE, the trial coordinator at the primary or satellite site will report SAEs to the Sponsor and follow the local procedure for documenting and reporting adverse events to the approving HREC and local site governance office.

Roles of trial staff regarding this aspect of care need to be outlined in the site responsibility form, agreed upon by both primary and satellite sites and the Sponsor and incorporated into the contracts. Engagement with other specialists either via tele-health or on-site needs to be finalised according to the trial protocol. This is important for managing immune related and unusual side effects of medications including trial medications.

Additional considerations for unplanned presentation during and after hours

In cases of presentation to hospital between medical consultations, the on-site investigator needs to be contacted by emergency staff who in turn will notify the primary site staff within 24 hours. Trial coordinators at the primary site and medical specialists are informed by any satellite staff who are the first to become aware and a joint review may be initiated using videoconferencing.

A '*trial patient alert'* process would be useful for alerting the emergency staff or general practitioners that a patient is on a trial so that on-call specialists can be contacted. The name of the trial and contact details for the PI at both the primary and satellite sites needs to be included.

Patients and their families need to be educated of the need for seeking urgent medical attention and reporting any concerns to the primary and/or satellite site staff. Patients could also be given letters or brochures for communication with clinicians in an emergency situation. Not all situations may be able to be managed at the satellite site. Inter-hospital transfers may be required in consultation between primary and satellite medical officers in some cases.

> In most cases, satellite and rural sites are staffed by generalist doctors. If the on-call medical specialist at the primary site needs to review patients urgently, it could be done via tele-health.
>
> Unlike face-to-face models where a clinical trial participant is experiencing an SAE and is managed by another site without direct supervision, the tele-trial model allows for the supervised management of SAEs at satellite centres by the primary sites through video-link; thus further improving the safety of patient care.

4.11 Patient reported outcomes (PROs)

Some trials will include PROs, including quality of life endpoints, usually as secondary endpoints but sometimes as primary. It is a matter of equity that rural and remote patients have the opportunity to self-report aspects of their health and quality of life as specified in the trial protocol.

PROs are typically assessed with questionnaires, either handed out to trial participants by the research nurse or completed online. The specific questionnaires, mode(s) of administration, and timing relative to recruitment and treatment need to be followed as per trial protocols. It is also important to develop mechanisms to minimise missing data as far as possible and record reasons for missing data, so patient engagement is essential.

Many trials groups have reported success of centralised monitoring systems for maintaining high PRO completion rates. Staff should have access to ongoing training and written guidance and understand the importance of PROs.

Two relevant resources are provided at the PoCoG QOL Office website:

QOL-PRO Protocol Checklist http://www.pocog.org.au/docview.aspx?id=212

QOL-PRO Administration Checklist http://www.pocog.org.au/docview.aspx?id=355

4.12 Documentation and reporting

During trial consultations a detailed patient history including the documentation of AEs and SAEs is obtained by doctors at primary or satellite sites or at both sites simultaneously. Results of investigations are available online at most centres. If results are not available online, the primary site will ensure certified copies are provided by the satellite site.

Physical examination may be performed by the doctor at the satellite site with or without observation by the primary site doctor and as per ICG-GCP the PI can only delegate to those with the necessary experience, training and qualifications. When joint medical consultations are conducted via tele-health, clinical encounters are documented at the site with the delegation to perform the specific study related activity. If EMR is not available, certified copies of source documents may be required and sent to the primary sites for monitoring purposes. The mode of transfer for these documents (fax, emails and/or post) needs to be agreed by the Sponsor according to their privacy policies.

When medical officers change at the end of term, or trainees are in charge at satellite sites, direct observation of physical examination or referral to a senior medical officer for examination may be necessary. This person should also be listed on the trial site responsibility form.

4.13 Financial considerations

Consideration also needs to be given to how satellite sites will be reimbursed for undertaking trial specific procedures (e.g. blood tests; radiology procedures etc).

There are administrative efficiencies if the co-ordination of invoicing or journal transfers for trial related expenses at satellites sites are coordinated by the primary site. All institutions

involved in the trial would need to sign the CTRA and be indemnified by the Sponsor. Generally most of the expenses related to staff will be covered by existing work contracts and funding mechanisms that exist for routine operations. Remuneration of sites for trial related activities should equate to the proportion of work the site undertakes and should be negotiated between Sponsor, primary and satellite sites at the outset. Primary sites need to be renumerated for coordination of trial activities and preparation of regulatory documentations across clusters.

4.14 Regulatory considerations

Many of the regulatory aspects of clinical trials are governed by local and state jurisdictions and are therefore beyond the scope of this document. It is important to engage with health service executives, ethics committees and research governance officers to expedite approval processes within clusters. However, a simplified and streamlined approach at state and national level may reduce the cost and expedite the approval processes.

It is recommended that the primary site takes the responsibility for preparation and submission of documents related to ethics, contracts and site specific assessment forms (SSAs) in order to streamline and expedite the trial approval processes. Contractual, ethical and governance processes can be expedited when common standards and strong collaboration are established between primary and satellite sites within clusters.

> It is prudent for clinicians or cancer centre managers who wish to participate in this model to get the support of their managers and chief executive officers especially in developing trial clusters between centres located within other health service districts and states so that governance and contract processes can be streamlined.

Human Research Ethics Committee (HREC) Approval

Processes related to ethics are streamlined through the national mutual acceptance model and therefore a separate full application is not required by most ethics committees located in the same jurisdiction. Additionally, single ethics review is not just limited to a jurisdiction. https://www.health.qld.gov.au/ohmr/documents/regu/nma_organisations.pdf

Local Site Research Governance Office (RGO) Approval

Processes related to SSAs are governed by jurisdictional and individual site policies. Individual RGOs within a cluster may wish to separately review and approve the SSA forms under the current policies and frameworks. In this case, separate applications for each site may be required. Whilst it is beneficial to create clusters so that Sponsors are minimising the opening of new sites, if each satellite site requires an SSA this could be costly for

commercial Sponsors (i.e. each SSA/RGO approval typically costs $3,750). When clusters are formed, a simplified and streamlined approach may reduce the cost and expedite the approval process. This needs to be negotiated at local levels with CEOs or at state level through the research and governance offices.

4.15 Indemnity, insurance and clinical trial agreements

Indemnity

Primary sites and the Sponsor assume responsibility for ensuring that criteria for safe care are met by all sites within a cluster. When undertaking investigator lead trials, both the primary and satellite sites are indemnified as per each state and territory health department provision. For industry sponsored studies the indemnity is provided by the trial Sponsor. (https://medicinesaustralia.com.au/policy/clinical-trials/indemity-and-compensation-guidelines/)

The Sponsor of a clinical trial takes overall responsibility for the conduct of the trial, including protocol design and the investigational product. The Medicines Australia indemnity covers product liability (faulty drug manufacture) and professional indemnity (negligently written protocol) and as such should not exclude satellite sites.

Sites subcontracting with sub-sites from different legal entities (different LHDs within a state and sub-sites from other states) may require an internal contractual solution as per the advice of the Sponsor.

Insurance

Commercial Sponsors are required to provide evidence of insurance that provides current professional indemnity, product liability inclusive of clinical trials cover and its indemnity. For example, in NSW sites are indemnified by the Treasury Managed Fund (TMF). The TMF insures each of the state-based entities, Local Health Districts (LHDs), whether a primary or satellite site. A blanket approval from the TMF is not provided for clinical trials for non-commercial Sponsors. Through the TMF, NSW Health provides cover for the Sponsor-related liabilities of clinical trials initiated by NSW Health Staff and conducted at Public Health Organisations within NSW. Each site may have different coverage under TMF. Not-for-profit Sponsors external to NSW Health are required to have sufficient insurance and indemnity to cover their Sponsor-related liabilities (refer to the NSW Health Policy Directive PD2011_006 Clinical Trials – Insurance and Indemnity, NSW Ministry of Health). Given the scenario described in the comment above, to relay concerns of the satellite site, the Sponsor is able to separately list each of the satellite sites in addition to the lead site on the Certificate of Currency. This would then allow the satellite site to have legal channels directly with the Sponsor rather than via the Institution party to the clinical trial research agreement.

Clinical Trial Research Agreement (CTRA)

Agreements between sites within a cluster could be in the form of formal contracts, or overarching agreements such as Service Level Agreements (SLA). This matter needs to be solved at the local level between health services or at the state level through research and governance offices in collaboration with the Sponsors.

The current versions of the Clinical Trials Research Agreement are available below:

- Clinical Trial Research Agreement – Medicines Australia Standard Form
- Clinical Trial Research Agreement – CTRA: Contract Research Organisation acting as the Local Sponsor
- Clinical Trial Research Agreement – Collaborative or Cooperative Research Group (CRG) Studies
- Clinical Trial Research Agreement – Phase 4 Clinical Trial (Medicines) https://medicinesaustralia.com.au/policy/clinical-trials/clinical-trials-research-agreements/

5. Examples of trial complexity

	Low complexity trials	Medium complexity trials	High complexity trials
Examples	Observational studies, comparing standard practices	Phase II-III clinical trials comparing medications already available for other indications	Phase II-III clinical trials (excluding phase 1 studies) of new oral or intravenous therapies or behavioural interventions
Workforce Requirements			
Primary site	Medical specialists	Medical specialists	Medical specialists
	Trial coordinators	Trial coordinators	Trial coordinators
	Oncology pharmacy	Oncology pharmacy	Oncology pharmacy
Satellite sites	Medical officer	Medical officer	Medical officer
	Chemo-competent nurses or QReCS type model	Chemo-competent nurse or QReCS type model	Chemo-competent nurses
	Pharmacy with oncology support from primary sites	Pharmacy with oncology support from primary sites	Pharmacy with or without oncology support from primary sites
	Engagement with other clinicians including genetic counsellors, other medical specialists and allied health professionals as per protocol		

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