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# Access to Clinical Trials Closer to Home Using Telehealth

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Sabe Sabesan and John Zalcberg

Additional information is available at the end of the chapter

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## Abstract

The purpose of this chapter 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. Regional and rural group of the Clinical Oncology Society of Australia (COSA), the peak multidisciplinary cancer clinician body in Australia, has developed the Australasian Teletrial Model in collaboration with its stakeholders to improve rural access to clinical trials. 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 of 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.

**Keywords:** clinical trials, tele-medicine, rural, tele-trials, tele-oncology

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## 1. Introduction

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 as 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](http://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].

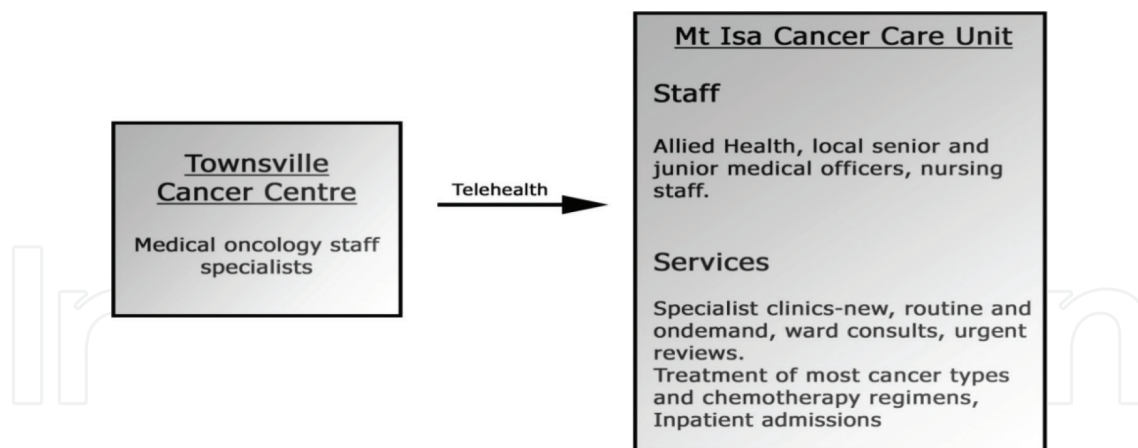
While it may be reasonable to establish clinical trials units in large regional cancer treatment centres, the logistics of maintaining a suitably trained workforce and undertaking the ethical and regulatory responsibilities of clinical trials may be difficult in smaller rural and regional sites with 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, saved money for health service provision and enhanced 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**

Similar to most of the specialist tele-health models around the world, the Townsville tele-oncology [15] model enables medical oncologists from Townsville, Australia to provide their services to rural sites, using traditional videoconferencing 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].

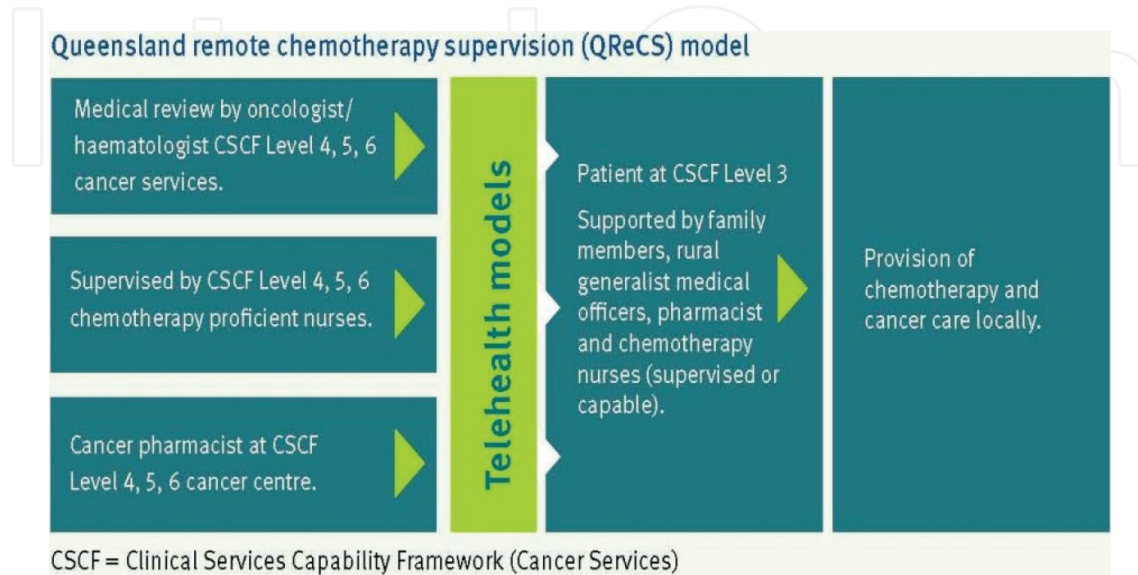


**Figure 1.** A model of a rural specialist unit with specialist support via tele-medicine model of care. Sabesan et al. EJCC, 2015.

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 online. 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 the patients.

**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] enables 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 tele-medicine and tele-nursing respectively (**Figure 2**) [20].



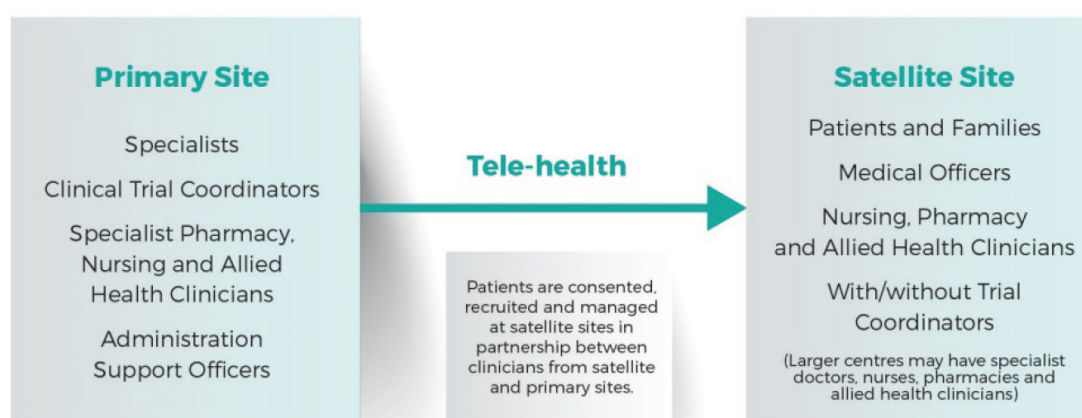
**Figure 2.** Remote chemotherapy supervision model.

## 2. Core principles of the tele-trial model

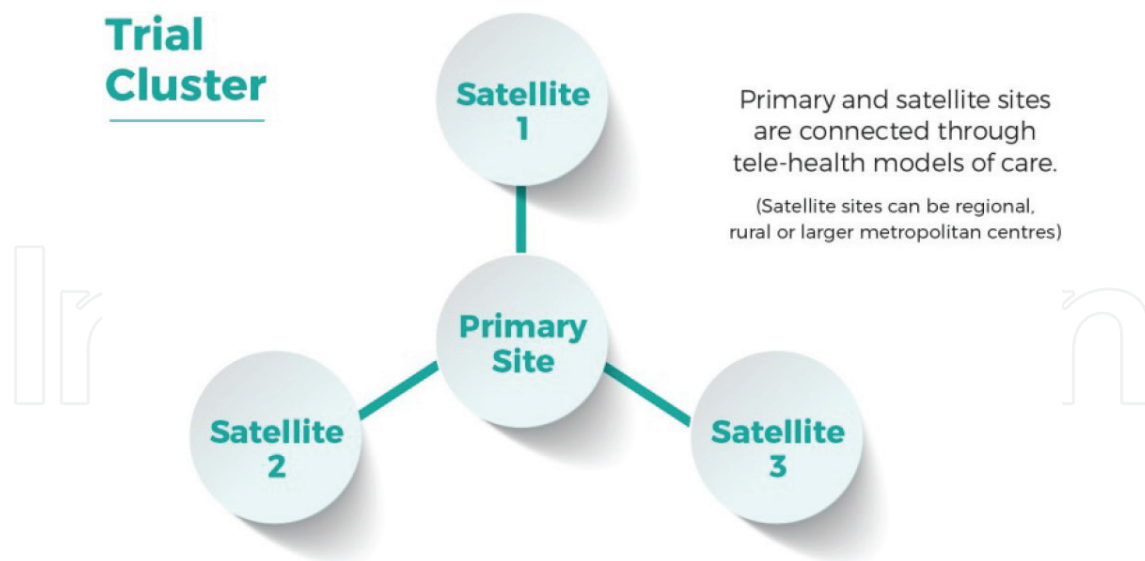
The core principles of the tele-trial model are as follows:

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, and treated, and to 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, improve 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.

### Australasian Tele-trial Model



**Figure 3.** Australasian teletrial model. Adapted from Sabesan and Zalberg [21].



**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 subgroups. Hence, trials requiring the eligible population to have a similar tumour subtype 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. Without multisite 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, we 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 the 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. Requirements for implementation of the tele-trial model**

Satellite sites (regional, rural or metropolitan) would vary in their capability 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 aspect of trials, in agreement with the sponsors and satellites.

### **3.1. 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. 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.

#### *3.1.1. 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.

#### *3.1.2. Supervision plan*

Some registration bodies require that the primary site Principal Investigator (PI) take 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 and 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.

#### *3.1.3. 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.

### **3.2. 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 videoconferencing. 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 [22, 23]. 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.

### 3.3. Good clinical practice

All clinical trials involving Clinical Trial of Investigational Medicinal Products (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.

### 3.4. 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. PI 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.

#### 3.4.1. 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.

#### *3.4.2. 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 PI 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 electronic medical record (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.

#### *3.4.3. 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.

### 3.4.4. 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, i.e. 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 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. Pharmacy 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.

The 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.

#### *3.4.5. Pathology and radiology*

Pathology and radiology requirements are dealt with at the feasibility questionnaire stage and arrangements agreed by Sponsors. Biopsy and biomarker and pharmacodynamic 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.

### **3.5. Training**

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

### *3.5.1. 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 sites 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 that 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>

### *3.5.2. 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 videoconferencing 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.

## **3.6. Technology and support**

A web-based system or videoconferencing 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.

## **3.7. 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.

### 3.8. 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.

#### 3.8.1. Options for obtaining consent

The process for obtaining consent remotely via tele-health or onsite 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 onsite. 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. Mode of transfer for these documents (fax, emails and/or post) needs to be agreed by the Sponsor according to their privacy policies.

### 3.9. 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.

### **3.10. Managing and reporting adverse events (AEs) and serious adverse events (SAEs)**

#### *3.10.1. Management at routine clinics*

During planned trial consultations, the history of AEs and SAEs is obtained. Clinical trial staff needs 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 primary or satellite site will report SAEs to the Sponsor and follow the local procedure for documenting and reporting adverse events to the approving Human Research Ethics Committee (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 onsite 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.

#### *3.10.2. Additional consideration 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 is 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 to the primary and/or satellite site staff of their concerns. 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.

### **3.11. 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.

### **3.12. 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 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.

### **3.13. 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. 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 remunerated for coordination of trial activities and preparation of regulatory documentations across clusters.

### **3.14. 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.

### **3.15. Indemnity, insurance and clinical trial agreements**

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 are indemnified as per each state and territory health department provision. For industry-sponsored studies the indemnity is provided by the trial Sponsor (<https://medicine-saustralia.com.au/policy/clinical-trials/indemnity-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.

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.

## **4. Conclusion and recommendations**

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.

#### **4.1. Recommendations**

1. Adoption of tele-trial models such as the Australasian Teletrial model as part of standard practice by cooperative trial 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 sites 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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#### **Author details**

Sabe Sabesan\* and John Zalcborg

\*Address all correspondence to: [sabe.sabesan@health.qld.gov.au](mailto:sabe.sabesan@health.qld.gov.au)

COSA Teletrial Consortium Steering Committee, Clinical Oncology Society of Australia (COSA), Sydney, Australia

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