

# Process of development of decentralised clinical trial methodology for cancer clinical trials in Aotearoa New Zealand

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## ABSTRACT

**AIM:** To develop processes for the development of decentralised clinical trial methodology for Aotearoa New Zealand, focussing on equity of access to cancer clinical trials for Māori, Pacific people, vulnerable communities and those in rural settings.

**METHODS:** A national steering committee supported by Te Aho o Te Kahu – Cancer Control Agency was formed to: guide the adaptation and implementation of overseas decentralised clinical trial models to suit the needs of Aotearoa New Zealand with an equity focus; provide high-level oversight and expertise for direction and development of policies, procedures and infrastructure compliant with ICH GCP R2; and implement a national strategy.

**RESULTS:** Twelve standard operating procedures were developed, as well as a supervision plan and a glossary. These were made freely available on the New Zealand Association of Clinical Research website.

**CONCLUSION:** Decentralised clinical trials offer a novel method of trial conduct that is patient- and whānau-centred. The model allows patients to remain in their local area with whānau and support networks, and their local treating team, increasing clinical trial accessibility and quality of care. This methodology has the potential to support improvement in research capabilities nationally and be utilised beyond oncology. It would benefit from significant investment in national clinical trial infrastructure.

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Māori and Pacific people suffer untenable inequities in health outcomes, especially in cancer.<sup>1–5</sup> Those who live in socio-economically deprived areas also have worse outcomes.<sup>6</sup> *Te Mahere mō te Mate Pukupuku o Aotearoa 2019–2029 (The New Zealand Cancer Action Plan)* has four main goals: i) New Zealanders have a system that delivers consistent and modern cancer care, ii) New Zealanders experience equitable cancer outcomes, iii) New Zealanders have fewer cancers, and iv) New Zealanders have better cancer survival.<sup>2</sup>

Embedding clinical trials within our health system is a priority initiative to improve quality of care and patient outcomes.<sup>7–11</sup> International guidelines recommend clinical trial participation as it significantly benefits many cancer patients.<sup>12</sup> Historically, clinical trial participants have not been diverse, nor have they represented the general population, with under-representation from Indigenous populations, women and marginalised groups.<sup>13</sup> These exclusions have

significant consequences and continue to reduce confidence in institutions and people who are conducting research, as well as limiting the generalisability of results.<sup>14</sup> Recent publications have articulated the goals of increasing diversity in clinical trial participation, which include earning and building trust, promoting fairness and generating biomedical knowledge.<sup>15</sup> Opportunities for participation in clinical trials across Aotearoa New Zealand are inequitable, particularly for whānau (extended family) living outside of major centers and for Māori and Pacific people.<sup>9,10,16,17</sup> However, the majority of New Zealanders (86%) want the choice to take part in a clinical trial.<sup>18</sup>

Traditionally, clinical trials involve whānau attending hospitals for face-to-face interaction with trial staff. Barriers to participation include: the lack of clinical trial availability and resources; infrastructure; staffing expertise close to home; lack of awareness and transparency related to information sharing of available clinical trials; financial and time costs of participation; stringent

trial-related screening criteria; and, in some cases, the impossibility of travel to major centres where the trials are being conducted.<sup>19,20</sup> Decentralised clinical trials (DCTs), also known as teletrials, are a novel model to enable access to a trial independent of where you live.<sup>21</sup> This makes clinical trials more inclusive, accessible and whānau-centred, as DCT infrastructure allows a clinical trial to become available in smaller centres and patients can continue care with their local oncology treatment team.<sup>22</sup> The Clinical Oncology Society of Australia (COSA) has been instrumental in the development and implementation of this model across Australia.<sup>19</sup> This model has also been successfully implemented across Canada and the United Kingdom, and has facilitated increased access to clinical trials at rural and remote sites.<sup>23,24</sup> Internationally, the implementation of DCTs has increased the recruitment of rural patients.<sup>25–27</sup> Currently, there are no reports of the impact of DCTs on the recruitment of Indigenous populations.

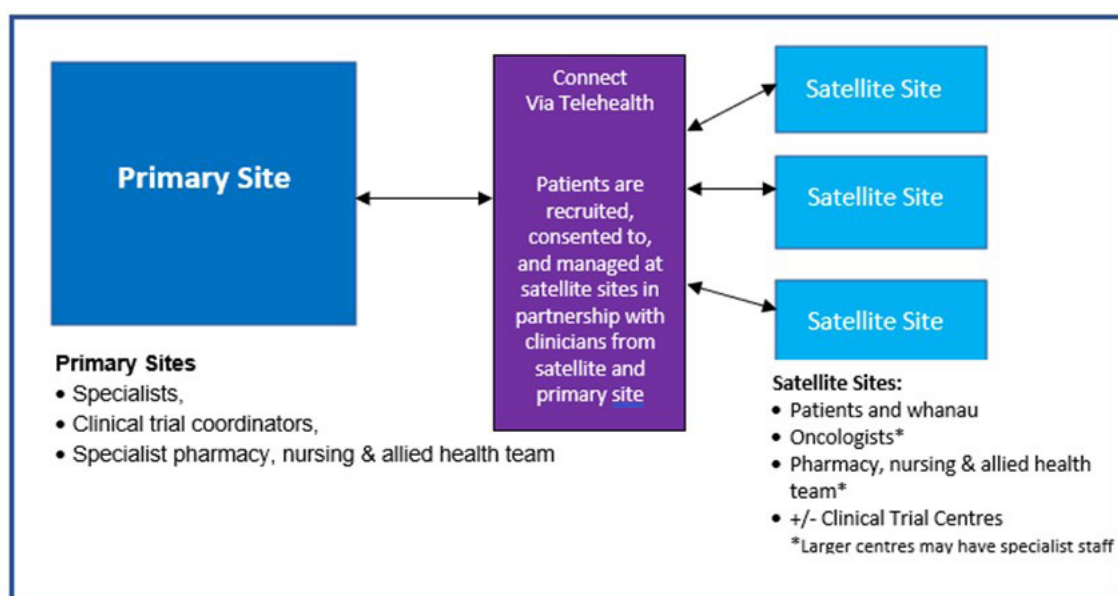
Access to clinical trials through DCTs has been given impetus by the COVID-19 pandemic, which acted as a catalyst for the uptake of new technologies such as telehealth.<sup>28</sup> A cross-sectional survey in 2022 of institutions in the European Union conducting DCTs before the COVID-19 pandemic indicated that DCT methodology was used more often during the pandemic to mitigate its effects.<sup>29</sup> It highlighted concerns including DCT methodology not being accepted by

some regulators, the variety of DCT policies and methodologies both internationally and institutionally and the challenges of keeping up to date with the shifts in the regulatory landscape. Concerns for regulators included participant safety, privacy, source data verification, data integrity and access to internet systems.<sup>29</sup> However, a recent study showed that data integrity can be maintained through this methodology.<sup>30</sup> Other barriers to conducting DCTs include limited engagement with trial sponsors and potential industry partners.<sup>28,29,31,32</sup> Regulatory agencies, including the United States Food and Drug Administration (FDA), have recently published guidelines on the implementation of DCTs to address many of these issues.<sup>24,33</sup>

## What is the DCT model?

In a standard multi-centre clinical trial, the trial lead investigator and trial steering committee take overall responsibility for the conduct of the trial, but delegate responsibility for activities related to the enrolled patients to principal investigators (PIs) at each individual participating trial site (e.g., an individual hospital). In the DCT model, one trial site (called the primary site) works collaboratively with sites in smaller centres and rural areas (called satellite sites) to enrol, consent and treat patients in the trial (Figure 1).<sup>17</sup> Each combination of a primary site with its individual satellite sites is called a cluster.

**Figure 1:** Schema for decentralised clinical trial cluster (adapted from COSA teletrial design<sup>1</sup>).



There can be more than one cluster per clinical trial, and clinical trials can operate as both multi-centre clinical trials and DCTs.

Health professionals at primary sites and satellite sites work collectively, with their roles and responsibilities formally agreed upon and documented (for example, in supervision plans). The primary trial site(s) takes overall responsibility for the supervision and coordination of trial-related matters for both the primary and satellite sites, in collaboration with the satellite site staff (Figure 1). The PI at the primary site can delegate responsibility to sub-investigators at satellite sites. This methodology enables patients from more remote areas to participate without the need to travel to the primary site.<sup>21</sup> DCTs essentially aim to increase access to clinical trials by decentralising the processes of a clinical trial (consent, randomisation, delivery of investigational products, trial activity and, potentially, trial monitoring).<sup>23</sup> Each supervision plan is unique to the trial being conducted and the sites involved.

### **Development of the Aotearoa New Zealand Oncology Decentralised Clinical Trial Steering Committee**

In February 2019, a National Oncology and Haematology Research Day was attended by delegates across Aotearoa New Zealand and supported by Te Aho o Te Kahu – Cancer Control Agency. Attendees identified the need to provide a DCT infrastructure fit for the Aotearoa New Zealand cancer clinical trial landscape that was relevant for Māori and their whānau. The aim was to improve equity of access to cancer clinical trials for Māori and those in rural settings and to increase the diversity of people participating in trials, and therefore be more reflective of the Aotearoa New Zealand population.<sup>34</sup> Initial discussions and collaboration began with international leaders instrumental in the development and delivery of DCTs, particularly with colleagues in Australia. To ensure that the developed DCT processes were appropriate for Aotearoa New Zealand, there was extensive consultation nationally in the cancer clinical research space. This included consultation with clinicians and research managers based in both urban and rural hospitals with cancer services. Engagement with Te Aho o Te Kahu followed. From this, a national oncology DCT steering committee was formed. This committee's role was to:

- guide the adaptation and implementation of the Australian model to suit the needs of Aotearoa New Zealand;
- provide oversight and expertise to the development of infrastructure, resources and clinical trial research activity for the implementation of DCTs at a national level across radiation oncology, haematology and medical oncology;
- provide high-level oversight and direction with respect to DCT activities including development of policies and procedures, implementation of a national strategy, research compliant with ICH Good Clinical Practice (GCP) R2, and with an equity focus.

Terms of reference were developed based on the following principles:

- commitment to partnership with Māori to ensure DCTs will be relevant and appropriate for whānau Māori;
- commitment to Pacific people and those in rural areas that DCTs will improve health opportunities for patients;
- actively explore opportunities to enable the delivery of DCTs at a national level;
- commitment to the implementation of DCTs to grow research activity;
- create and encourage an environment that addresses barriers to the delivery of clinical trials via the DCT model;
- ensure equity underpins the policies and pathway for DCT implementation in Aotearoa New Zealand.

Members of the committee included three co-leads (including a Māori health researcher), representation from medical oncology, haematology and radiation oncology, research management, rural sites and consumers. In addition, the committee successfully sought funding from Te Aho o Te Kahu (0.6 FTE for 12 months) for a project manager (*ex officio*) to assist with the development of the infrastructure required for Aotearoa New Zealand-specific DCTs.

### **Development of guidelines to enable the conduct of a DCT**

The Aotearoa New Zealand Oncology Decentralised Clinical Trial Steering Committee had oversight of the development of the infrastructure

required for DCTs: standard operating procedures (SOPs), a supervision plan, a glossary and a document explaining the terms commonly used in DCTs. The aim of the SOPs (Appendix Table 1) was to outline the variations to normal clinical trial procedures that need to be followed when undertaking DCTs in Aotearoa New Zealand. These were adapted from guidelines already in place in Australia.<sup>35–37</sup> The infrastructure developed was deliberately planned to be suitable for use for both academic- and pharmaceutical-sponsored clinical trials. The SOPs were designed to support DCT methodology and should be used in conjunction with local institutional SOPs, rather than as a replacement. The SOPs encompass ICH GCP E6 R2 and align with the guidelines from the New Zealand Association of Clinical Research (NZACRes),<sup>38</sup> the Ministry of Health *Guidelines on the Regulation of Therapeutic Products in New Zealand – Part 11*<sup>39</sup> and the New Zealand Medsafe guidelines.<sup>40</sup> Each SOP focusses on a particular purpose (Appendix Table 1). Collectively, they encompass all aspects of clinical trial conduct including documentation, ethics, governance, delegation of duties, investigational products (IP) and consent.

Under the Aotearoa New Zealand DCT model, the co-ordinating investigator (CI) is the health professional who is the investigator at one of the primary sites, who is assigned the responsibility for the overall conduct of the study, and the coordination of investigators at different sites participating in a multi-centre trial under the international committee on ICH GCP guidelines. (MEDSAFE uses the term “principal investigator” for the CI role.) The PI is the investigator responsible for the conduct, management, monitoring and reporting of a trial at their own site and the associated satellite sites. Other personnel include sub-investigators (sub-i) based at satellite sites and the study staff at primary and satellite sites. The roles and responsibilities of these staff are outlined in the SOPs (Appendix Table 1).

The DCT supervision plan is a key document that details the roles and responsibilities of those at the primary and satellite sites for each cluster for a specific clinical trial. It includes how sites communicate with each other, and gives details of who is responsible at each of the sites for staff training, fund management, research governance (which includes initial application and any amendments), start-up procedures, IP used in the trial, consent and randomisation, data and electronic case report form management of

participants, clinical trial decisions, staff cover, safety reporting and safety management and satellite closing-out responsibilities. The financial implications for each site are considered as part of this.

The supervision plan ensures that the primary and satellite sites set out an agreed pathway for reviewing the appropriate support and oversight of the satellite site. This will ensure that any challenges with protocol adherence or quality are identified early, and the supervision plan can be adapted to reflect this.

This supervision plan is complementary to:

- the feasibility assessment
- the site selection process
- site initiation
- the protocol
- the delegation log
- standard processes according to ICH GCP
- the SOPs at the primary site and satellite sites
- clinical trial research agreements

To ensure the SOPs and the supervision plan template were appropriate to the Aotearoa New Zealand clinical environment they were developed and peer reviewed by research managers and clinicians from different clinical trial research units throughout Aotearoa New Zealand, the members of the steering committee and finally by NZACRes. The SOPs are now freely available on the NZACRes website ([https://www.nzacres.org.nz/contract\\_templates/](https://www.nzacres.org.nz/contract_templates/)).

## Current context

Following the development of the infrastructure and processes for DCTs, elements of this methodology have now been utilised for a small number of cancer clinical trials in Aotearoa New Zealand. This choice of whether to use DCT methodology should be considered at the time of assessment of trial feasibility, not later. Early discussion with the trial sponsor is vital, as are discussions with potential satellite sites. While it may not be possible for all aspects of a trial to be decentralised, the DCT model allows components of the trial to be delivered remotely to reduce the burden of travel for patients and their whānau. This DCT methodology is an important part of a larger solution to increase more equitable participation in clinical trials.

## Future considerations

It is important to ensure that equity and the articles of Te Tiriti o Waitangi underpin the DCT infrastructure, and that this enables DCTs to be conducted in a way that is relevant and appropriate for whānau Māori. The Aotearoa New Zealand Oncology Decentralised Clinical Trial Steering Committee has received further funding support from Te Aho o Te Kahu to develop an evaluation framework to assess the implementation of the DCT methodology. This work is currently underway, with key focusses on programme evaluation, Māori and Pacific people accessibility, participation and quality of care. Interviews will be conducted with a wide range of stakeholders including patients, whānau, clinicians and research staff to identify the barriers and enablers to the set-up, establishment and participation in DCTs, particularly for Māori and rural participants, while also considering the processes involved including governance, data quality and patient safety.

Another important consideration for the development of DCT infrastructure within Aotearoa New Zealand is to consider a capability framework to guide and support the growth of clinical trial units and support DCTs' long-term sustainability with appropriate funding. The state of Victoria in Australia has developed a capability framework to assess what is needed to conduct trials safely (i.e., resources, processes and practices) and how to target investment appropriately for these.<sup>41</sup> Similarly in Canada, the Canadian Remote Access Framework for Clinical Trials (CRAFT) has been developed.<sup>26</sup> In Aotearoa New Zealand, there has been recent work undertaken to provide an evidence base to inform the development of an infrastructure roadmap and operating model to support a sustainable and nationally coordinated clinical trial enterprise and contribute to improved and more equitable health outcomes for New Zealanders.<sup>42</sup> This could be built on further by developing a capability framework that details clinical trial workforce capacity and capability in a systematic way and with infrastructure funding to support clinical trials at rural and remote sites that currently do not have research capability.

The DCT model would be further enabled by the streamlining of governance structures. For example, the current system of individual locality approvals for sites participating in a DCT throughout Aotearoa New Zealand would be more efficient if this could be done through one approval process. It is anticipated that the recent

changes in the Aotearoa New Zealand health system with the introduction of Health New Zealand – Te Whatu Ora may enable this. There also needs to be an efficient way for funding to be transferred from a primary site to the satellite sites that are participating in a DCT. Having appropriate frameworks and governance structures in place means that potential satellite sites can be opened within a short timeframe. In Australia, due to the streamlined regulatory and ethical review processes, studies can be commenced within 5–6 weeks of submission to ethics.<sup>43</sup> Governance structures need to be enabled in Aotearoa New Zealand (a much smaller country than Australia) to make this possible here too. This will make us more attractive to industry sponsors and support the DCT aim of people in Aotearoa New Zealand having equitable access to clinical trials.

Digital enablement is important for DCTs to operate safely, especially with respect to patient confidentiality and privacy. With the internet being a prominent communication vehicle between primary and satellite sites in DCTs it is essential that internet systems of health providers and participants are accessible, robust and protected from cyber-attacks, and that patient data are stored and transmitted safely with no breaches of privacy. Source data verification and data integrity are also important to reduce human and instrument errors.<sup>29</sup> International guidelines have been published by the FDA and the European Medicines Agency to guide robust DCT processes.<sup>23,44</sup> The establishment of a national clinical trial management system may help mitigate some of this risk.

Digital enablement also needs to be considered at a patient level. Access to Wi-Fi and technology may still remain a barrier for some. The Ministry of Business, Innovation and Employment predicted that by the end of December 2023, 87% of New Zealanders would have access to fibre at their home and 99.8% would have improved broadband access. However, rural-based New Zealanders have reduced quality connectivity and some remote and rural New Zealanders have little or no connectivity at their principal residence.<sup>45</sup> In order to overcome digital barriers for those of lower socio-economic status, DCT methodology can be used with patients attending local hospitals in person, with support from local staff and infrastructure (including digital infrastructure).

To ensure the long-term success of DCT infrastructure in Aotearoa New Zealand there

needs to be adequate long-term funding within the health system. The current reform of the Aotearoa New Zealand health system provides an ideal opportunity to streamline processes, and investment in clinical trial infrastructure has the potential to significantly improve both patient care and access to clinical trial opportunities. It is important to acknowledge that while there is a cost to implementing and supporting DCTs, clinical trials have significantly wider economic benefits. In 2017, an economic evaluation of investigator-initiated clinical trials in Australia showed the overall consolidated benefit-to-cost ratio for the networks is 5.8:1, or a return of AU\$5.80 for every \$1 invested.<sup>25,46</sup> There are also considerable benefits in terms of access to unfunded interventions (usually expensive pharmaceuticals) and cost saved through clinical trial participation.<sup>47</sup> A single haematology clinical research unit demonstrated AU\$3,971,357 in financial benefit from early access to subsequently approved investigational new drugs from 36 clinical trials involving 245 participants, \$12,209,538 in financial benefit from accessing approved medications not Pharmaceutical Benefits Scheme-listed and \$6,728,576 in government cost avoidance.<sup>47</sup>

There are also considerable and important indirect benefits in terms of improved patient care and outcomes in hospitals that participate in clinical trials, attributed to them more broadly implementing the higher standard of care demanded in clinical trials.<sup>7</sup>

It is important to recognise that the DCT methodology is one part of a larger solution to increase access to clinical trials across Aotearoa New Zealand. There will still be some studies

better suited to the multi-site model and some studies that lend themselves to a combination. It is important that, as we look to increase trial opportunities, we continue to explore multiple models for our patients and their whānau.

## Conclusion

DCTs offer a novel method of trial conduct that is patient- and whānau-centred. The model allows patients to remain in their local area with their whānau and support network, as well as their local treating team. It reduces the burden on patients to travel and have time off work while participating in clinical research. Internationally, the DCT model has increased recruitment of patients from rural areas to clinical trials, but the impact on Indigenous populations is unknown.

The model developed in Aotearoa New Zealand will be evaluated to ensure that it is relevant and appropriate to whānau Māori and Pacific people and is fit for the purpose to improve equity of access to clinical trials. The DCT model will not be appropriate for every trial but is a key component of a larger solution to increase more equitable participation in clinical trials, particularly for those in smaller regional centres. DCTs have the potential to support improvement in research capabilities nationally but require significant investment in national clinical trial infrastructure to be successful. Long term, this will grow and support research staff and clinicians across centres leading to a more resilient system that enables more trials to be conducted.

**COMPETING INTERESTS**

Nicola J Lawrence received support from Te Aho o Te Kahu for a project manager for this work and is co-lead of the New Zealand DCT committee.

Marina Dzhelali is a New Zealand Association of Clinical Research board member.

Ngapei Ngatai received support from CTNZ for this manuscript.

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## Appendix

**Appendix Table 1:** Standard operating procedures (SOP) and purposes.

<b>SOP number and name</b>	<b>Purpose of SOP</b>
SOP-01 <b>Decentralised cancer trial processes</b>	To describe the variations to normal clinical trial procedures when undertaking a decentralised clinical trial in New Zealand.
SOP-02 <b>Informed consent</b>	To describe the procedure for obtaining informed consent of participants for enrolment in a clinical trial.
SOP-03 <b>Clinical trial training</b>	To describe the procedure for documenting training that has been undertaken by members of the study teams.
SOP-04 <b>Delegation of duties</b>	To describe the procedure for delegating clinical trial-related duties undertaken by members of the study teams.
SOP-05 <b>Handling investigational products</b>	To describe the procedure for the management of all aspects of the investigational product (IP), either medicinal product or device.
SOP-06 <b>Management of safety information</b>	To describe the procedure related to the management of safety information.
SOP-07 <b>Handling and shipping of biological samples</b>	To describe the procedure for handling and shipping biological samples.
SOP-08 <b>Hosting a regulatory inspection sponsor or other audit</b>	To describe the procedure and activities for facilitating a regulatory inspection, either by the sponsor or an initiated audit by the Health and Disability Ethics Committee (HDEC).
SOP-09 <b>Archiving</b>	To describe the procedure for archiving essential documents for clinical trials for primary site (PS) and satellite site (SS).
SOP-10 <b>Document management version</b>	To describe the procedure for the creation and implementation of standard operating procedures (SOP) documents used for Decentralised Clinical Trials NZ, including version control and tracking amendments.
SOP-11 <b>Essential document management</b>	To describe the procedures relevant to the collection and maintenance of essential documents for clinical trials at the primary site (PS) and satellite site (SS).
SOP-12 <b>Ethics and governance</b>	To describe the procedure for obtaining ethical and governance approval for new and existing decentralised clinical trials.