Bringing Clinical Trials to the Bush – improving access to innovative healthcare in rural, regional and remote NSW and ACT

Background/Context:

Clinical trials provide the most robust evidence to change clinical practice. Participation in trials, by patients, clinicians and centres, offers early access to new treatments and skills, and brings economic (employment, industry) and scientific benefits. Health care environments active in research and trials have better outcomes[1], due to many factors including better training and retention of staff. Australia has a long track record in leadership in clinical trials which continues to grow, and in which NSW is a key player.

For our potential trial partners, the medical technology and pharmaceutical industry[2], Australia has advantages over other countries: a strong research reputation, excellence of its clinical and scientific communities, its clinical trials regulation (CTX/CTN) and tax incentives; and the willingness of Australians to engage in trials[3]. But the industry also sees disadvantages: the relatively small and scattered population increasing costs, governance and approval delays, and limited consistent, reliable, or sustainable CT infrastructure across the country. Where it does exist, it tends to be in urban areas, or confined to specific clinical areas or types of trials.

In regional, rural and remote (R^3) settings, populations suffer worse health outcomes than in metropolitan areas[4] with shorter life expectancies. People in R^3 areas also lack access to clinical trials, and hence to many innovative therapies. Trials addressing the particular health needs of R^3 populations are rare, resulting in a lack of evidence on how to improve practice in these settings (e.g. addressing delays in presentation, or testing new approaches to delivery of health care). Barriers to research in R^3 settings[5] include geographical isolation, and lack of workforce experience, skills and capacity. These can make trials in R^3 areas unattractive to sponsors. The result is inequality of access to trials and innovation in R^3 areas.

NSW is the most important region in Australia in which to promote R^3 trials, with both the largest population and largest % of population living in R^3 areas (i.e. MMM3-7) of any state in Australia (1.8M people, or 25% of NSW population[6] v 20% of national population[7]). NSW Government Strategy[8] identifies research and a research culture as key within NSW healthcare, and particularly in rural health[6]. NSW is the only state with trial targets in performance agreements of local health districts (LHDs) since 2016, and an established government clinical trial support function (*clinicaltrialsNSW*), reflecting its aim to be a global leader in clinical trials.

Vision and Aims

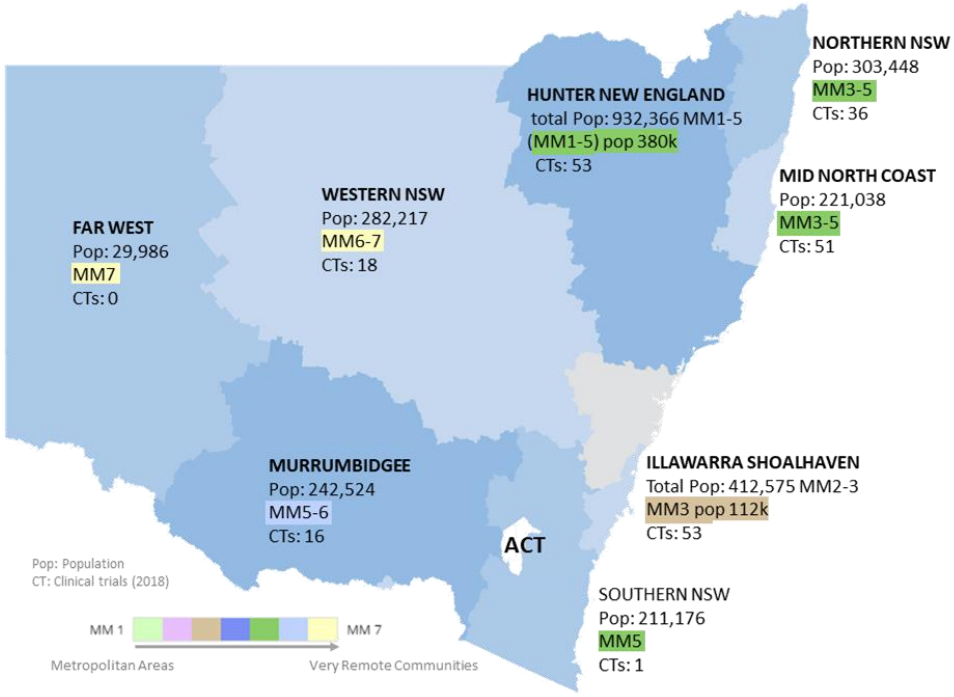
This proposal by NSW Ministry of Health, Office for Health and Medical Research (OHMR) and its partners, including ACT Health, will **deliver increased and more equitable access to clinical trials for patients in rural, regional and remote NSW and ACT**. We will achieve this by refining and implementing a novel model of clinical trial delivery, the virtual clinical trial, as well as by supporting standard face to face trial delivery. We will do this by providing dedicated professional staff, working within a devolved infrastructure network in a hub-and-spoke model, and community awareness building.

We have assembled a NSW Statewide consortium with 8 LHDs with R^3 populations and the ACT which delivers healthcare to much of southern NSW and has strong research experience (see map), other healthcare agencies and academic centres. We will partner with commercial sponsors, national Clinical Trial Collaborative Networks and peak bodies to stimulate placement of clinical trials in R^3 areas. We will demonstrate reliable delivery of trials on time and to recruitment target.

Our proposal will **leverage existing systems, methods and technologies as much as possible** (e.g. Clinical Oncology Society of Australia, COSA, Teletrials), linked to whole-of-jurisdictional systems, to maximise synergies and efficiencies, and to ensure early delivery of trials. It will build on an already solid foundation of existing resources and collaborations, while increasing capacity and capability.

But our approach will be **developmental** also, working with academic partners in how to delivery trials in R^3 areas within the broader Australian trial ecosystem, to keep current with latest methods, and become a national and world leader in R^3T; and hence to ensure sustainability. Although NSW and ACT based at first, our network will actively collaborate with other MRFF R^3 clinical trial infrastructure projects to support a nationally consistent approach to delivery of trials in R^3 Australia.

Figure 1. R^3 areas in this proposal, their MMM3-7 populations (HealthStats) and current clinical trial activity (ANZCTR) (17% of total state trials are undertaken in these LHDs, 62% of these industry sponsored)



The extent of leadership by OHMR is unique in Australia and means that this proposal is deeply embedded in well-integrated and governed systems, and adopts a whole-systems approach of interdependent elements, which UK experience[9] suggests will increase probability of success.

Some key challenges that must be addressed in order to deliver the vision and aims are:

- Implementing a new "virtual trials" delivery model in R^3 areas, running alongside our support for traditional face to face trials, and for extending the reach of metro led studies
- engaging the broader R^3 population – patients, families, researchers, clinicians, primary and allied health professionals, in the opportunities offered by clinical trial participation
- enabling a flexible skilled workforce of sufficient size, in a broad geographic area
- integrating clinical trials into the R^3 health care system

The intended outcomes of this proposal are to:

1. Promote **equality of access** to trials, so that patients and clinicians in R^3 NSW can participate in trials that may improve health outcomes, including multicentre and metro led studies.

2. Provide better **access to novel therapies** available through clinical trials, including those therapies which may only be available in specialised centres.
3. **Increase the number of trials**, commercial and non-commercial, run in R^3 areas, with **increased patient recruitment and increased clinician participation.**
4. Promote and support more **trials specifically relevant to the needs of patients** in R^3 areas.
5. Ensure **quality conduct** of trials, to the highest quality expected by regulatory agencies.
6. **Improve the speed and co-ordination** of clinical trials by removing the barriers to their conduct, speeding governance and delivery, through high quality supportive research services in all R^3 health and care settings.
7. **Develop the workforce** by high quality learning opportunities, and by supporting employment in R^3 settings, and building a community of practice.
8. Ensure the **sustainability** of the network beyond the period of the grant.

The following **principles** will guide our work:

1. **CORE values of NSW Health** - Collaboration, Openness/accountability, Respect and Empowerment
2. **Participant-centred:** We will engage patients, carers and the wider public as partners in all of our activity, to improve research quality and relevance, to ensure patients have an optimal participation experience in clinical trials, and that conditions of greatest importance to patients are well represented in the portfolio.
3. **Inclusive partnership and collaboration:** The project will be a collective endeavour and collaborative working is key to our shared success. We will have strong relationships with our partners, and be responsive to their feedback. Our partners will be:
    a. healthcare providers: to streamline and performance manage CTN support for trials, to ensure that trial conduct is efficient, and to ensure that their support costs are fully covered; to minimise bureaucracy and find pragmatic solutions to problems; to integrate health research and patient care, and promote a strong research culture.
    b. clinical trialists and academics who will drive methods and innovation in delivery
    c. medical technology, pharmaceutical and eHealth industries to meet their trial needs.
    d. counterparts in metropolitan areas, other states and networks.
4. **Effectiveness and efficiency:** We will provide a consistently reliable and excellent service to researchers in all studies, in all parts of NSW, agnostic to discipline/type of trial. We will monitor progress and delivery and adapt as needed.
5. **Development** We will continue to learn and develop the best approaches to delivery of R^3 trials (e.g. refining teletrials model). We will continuously review and improve all our structures and systems to ensure the quality, speed and cost-effectiveness of clinical research. We aim to be a world leader in methodology and delivery of R^3 trials.

Partners

Project partners with NSW Health and ACT Health include:

1. Health organisations including NSW Rural Health Research Alliance (including 7 R^3 LHDs), NSW Cancer Institute, NSW Health Pathology, Agency for Clinical Innovation, Centre for Aboriginal Health, NSW Statewide Biobank, and eHealth NSW, Centre for Aboriginal Health, NSW Rural Doctors Network and Canberra Health Services, Illawarra and Shoalhaven LHD
2. Academic organisations, including the Hunter Medical Research Institute, George Institute, NHMRC Clinical Trials Centre; NHMRC accredited Centre for Innovation in Regional Health (NSW Regional Health Partners) and applied health research translation centres (SPHERE and Sydney Health Partners), Australian Clinical Trials Alliance, Melanoma Institute of Australia.
3. Industry: Medicines Australia, Roche, IQVIA, Novartis; Baxter Healthcare Pty Ltd; Praxis Australia Ltd; ARCS Australia Ltd; Tonic Health Media, ClinTrial Refer.
4. Consumer organisations Health Consumers NSW, & Health Care Consumers Assoc. ACT

5. Private healthcare providers, Genesis Care, Macquarie University Hospital.

The Project will leverage the existing capabilities and collaborations of these partners including:

1. established OHMR clinical trial initiatives including clinicaltrialsNSW (a front door for sponsors and tools and services for trial sites, researchers and consumers), and other intersecting initiatives (e.g. Research Ethics and Governance, and International Engagement).
2. national Teletrials pilot experience, and extensive telehealth facilities: NSW was instrumental in the COSA teletrials pilot[10] with several participating sites. NSW Health has invested heavily in telehealth facilities which can also support teletrials
3. support for trials from academic partners: in study design, conduct and analysis, health economics; in evaluation and development of the network and methods for virtual trials, data linkage, electronic trials and more.
4. partnership with Health Consumers NSW and ACT, and the Centre for Aboriginal Health
5. Extensive experience of clinical trials across NSW and ACT: NSW undertakes 40-45% of all new trials initiated across Australia[11]. There is experience of large scale trials such as ASPREE and AUSPICE in R^3 areas, as well as teletrials, and currently 34% of Medical Oncology and 39% of Haematology trial participants reside in regional NSW areas[12].

Project Key Activities

The aim of the project will be achieved through the delivery of 5 interdependent Key Activities (KA):

1. Developing "Virtual Clinical Trials" capacity, and trial delivery
2. Clinical Trial awareness, engagement, recruitment and retention
3. Professionalising rural, regional and remote clinical trial services
4. Local trial delivery by rural, regional and remote clinical trial support units
5. Governance and project coordination

KA1: Virtual Clinical Trials and Trial Delivery

The Virtual Clinical Trial is a new approach to trial participation, rapidly gaining acceptance[13]. Teletrials and "electronic" Trials[14] are examples which bring the trial itself closer to the patient and reduce the need for patients or clinicians to travel for participation. These will increase trial accessibility for patients in R^3, improve recruitment and retention in trials, and lessen the burden on trial sites, allowing them to offer more trials.

We will **embed the virtual trial approach** across the R^3 LHDs. This will be initially based on our experience in the COSA Teletrials pilot[15] [16] which showed feasibility in accelerating oncology trials by providing trials access closer to R^3 patients, using telehealth technologies and by connecting smaller patient volume centres (R^3 areas) with larger centres (e.g. metro). We will fund staff in metro sites running teletrials, linked to R^3 sites (**KA4**) specifically to support R^3 rollout, acknowledging the extra work this will require. We will work with other national networks to support this model, currently active in some centres in our proposed network, until it is superseded by, or develops into, a stronger model with more widespread capability.

This Project will develop and implement the teletrials model across NSW and ACT in 3 stages:

1. Extend commercially sponsored multicentre trials, led from metro primary sites, to existing and new R3 satellite sites.
2. Establish R3 satellite sites will mentor and support smaller hospitals/units within their area to conduct teletrials as satellite sites, increasing trial capacity in R3 areas
3. Conduct commercially sponsored multicentre trials led from R3 primary sites, using R3 satellite sites, where appropriate for the patient population.

Teletrials Development: For the future, we will leverage off the $30M investment in telehealth facilities across NSW, e.g. **myVirtualCare**, a new web-based video conferencing portal, that specifically supports clinical care. We will develop this to a uniform teletrial infrastructure for all therapeutic areas, across R^3 NSW. A NSW Teletrial Framework, to guide use of this infrastructure, is currently being developed by OHMR and Cancer Institute NSW and other stakeholders.

Electronic site feasibility, and patient identification and follow up
Use of routine e-health systems has potential to support both virtual trial and also traditional trial delivery. Feasibility of a trial at a site will depend on the number of suitable patients there – this requires good knowledge of local epidemiology, and access to local health databases is an effective way to do this. Systems and permissions to search electronic health records (EHR) anonymously by our research staff **(KA4)** will be a means of checking feasibility identifying numbers of patients suitable for specific trials. This will also draw on other data collections (e.g. NSW Admitted Patient Data Collection, Emergency Department Data Collection and the PBS) and NSW linkage processes, leveraging the expertise of the Centre for Health Record Linkage (https://www.cherel.org.au/).

EHRs and health record linkage could (with permissions and proper governance including cybersecurity) also be used to identify individual patients to be approached for participation in trials, based on their medical history and protocol eligibility criteria. There are opportunities in this for commercial involvement to optimise artificial intelligence techniques (e.g. ElilE[17], Criteria2Query[18]). EHRs with linkage could also be used for cost-effective long-term follow up in many pragmatic clinical trials with patients' permission.

These approaches are possible with the Cerner 'PowerTrials' module. We will implement this module into the EHR platform already used in 7 of our LHDs. It will also improve trial safety by identifying trial participants and by integrating their care within existing healthcare systems.

Face to Face Delivery: Many of the multicentre or metro led trials offered to and through our network will be traditional in design, and require, e.g. face to face hospital visits. To increase access to trials and innovative therapies in R^3 areas and our capability and capacity, and to be responsive to our stakeholders, our local staff (**KA4**) and facilities will support these as the protocol requires. Where possible and acceptable to sponsors and investigators, we will use elements of the virtual trials model in our delivery, reducing patient and centre burden. Examples of our initiatives here are:

- *'Out of hospital' clinical trial visits*, a model delivered by ACT Health across southern NSW. Leveraging their experience and processes, we will expand this approach to other R^3 areas.
- *collaboration with NSW Health Pathology*: we will pilot the use of NSWHP sites for recruitment and follow up as well as pathology collection (**see KA3**)
- *financial support for in-hospital trial visits*: this initiative will offer financial support for participation if travel to a larger R^3 or a metro centre is required and where no other subsidy is provided (currently available for medical visits, but not research, which is a barrier[19]).

Recruitment in primary care: each year, over 80% of Australians visit their GP or other primary care provider. Recruiting to trials in primary care particularly in R^3 areas is difficult, but can be successful if well supported[20]. Our R^3 clinical trial support units (CTSUs, **KA4**) will help GPs and their patients participate in suitable trials, referring for recruitment or being a recruitment site in their own right by, e.g. providing busy clinicians with trial delivery staff at sites, and support training and governance. Developments may include accessing GP computer systems with permission (e.g. extension of Lumos and Medical Director software). We will partner with the NSW Rural Doctors Network (RDN), a non-government charitable organisation and the designated Rural Workforce Agency (RWA) for health.

KA2: Clinical Trial awareness, engagement, recruitment and retention

Key to our success is securing partnership with the community, thereby recruiting and retaining both patients and clinicians. Many trials fail to recruit to target, or recruit slowly, increasing cost and delaying important clinical results and slowing innovation. Industry sponsors are frustrated by both failure to accurately assess feasibility at sites, and then to deliver promised recruitment. Recruiting to R^3 trials poses particular issues: there may be very few patients meeting entry criteria in a given site, and patients may not be willing to participate because of practicality issues and inconvenience. The former is addressed by feasibility assessment, derived from epidemiology/data linkage and local knowledge (**KA1, KA4**); the latter by our strategies on virtual trials but by our also supporting more standard approaches to trial delivery (**KA1**).

We aim to build partnership with the R^3 population, and provide ways by which potential trial participants can be involved within local settings, thereby translating to increased trial recruitment. Patients and clinicians need to become more aware of trials: in general, of their importance, and of what involvement in a clinical trial means practically, as part of creating a culture where trials are part of routine healthcare; and more specifically, of what trials are available for participation.

Patient Involvement: processes that involve health consumers and community members are needed: their input is required at every level, in co-design of studies, in the governance and activities of the local trial infrastructure, in awareness campaigns, and trial recruitment and retention strategies; and to ensure that the network meets patient priorities for future research. Methods to identify these issues and to prioritise them will be developed within this proposal (e.g. citizen juries). The Consumer Advisory group (**KA5**) is key to embedding a culture where such involvement is seen as routine and expected, not exceptional, particularly important in R^3 trials and research. Other local groups, e.g. LHD consumer groups, will also be involved to ensure that local voices are heard.

Aboriginal communities: it is particularly important to partner with Aboriginal organisations in R^3 areas, as Aboriginal people have a sensitive history with research and trials. The network will build relationships and respectfully understand the needs and desires of the community, their health priorities and how the community might wish to be involved in research: and respond to them. It also needs to offer researchers guidance and feedback on being inclusive in their projects where appropriate. We are engaged with the NSW Health Centre for Aboriginal Health, who will facilitate access to a range of other organisations, and relevant strategies, tools and resources.

ClinTrial Refer – patient referral app: this is an app based clinical trial recruitment platform that connects patients, doctors and trial sites. Developed within NSW Health, it has received numerous awards, and has proven effective in recruiting to melanoma studies[21] in R^3. It allows clinicians to *directly* refer patients to an active clinical trial in their local area. We will integrate ClinTrial Refer services for use by GPs, specialists and consumers across R^3 NSW and ACT for R^3 trials.

Multi-channel community awareness campaign: This Project will deliver a sustained clinical trial awareness campaign to over 1.8m NSW R3 patients by multi-media campaigns across 800+ NSW R^3 point-of-care locations, including 40 Indigenous Aboriginal Medical Services: via social media, via Tonic Health Media (Australia's largest cross-platform health media network with 16 million audience, and a unique vehicle for health messaging via integrated multimedia assets within point-of-care waiting rooms) channels, e.g. myDr.com.au and the Aboriginal Health Television channel; and via a Geo-targeted digital campaign.

Research Register: This patient recruitment approach is based on 'SHARE'[22], a proven Scottish model where individuals agree to their contact details being held within a secure database that researchers can use to make direct contact with potential participants. With parallel consent for linkage to

routinely collected data, research opportunities can be targeted specifically towards those with relevant disease conditions. This Project will build on the proof-of-concept stage of the Research Register supported by George Institute for Global Health, with a pilot over the grant period, and on the raised community awareness initiatives above. If successful, it can be scaled nationally.

NSW Health Pathology (NSWHP): Pathology point-of-testing clinical trial enrolment is a new recruitment approach that leverages the existing infrastructure of NSWHP. NSWHP has over 300 collection centres across NSW and are the main pathology provider with over 2 million patient encounters and 10.5 million tests per year (20% of the state's total) in R^3 areas. This network is linked with an established NATA accredited point of care testing project, and is the world's largest managed service, where encrypted patient data are transferred securely to the EHR.

This Project will pilot the potential of NSWHP to screen and recruit patients to clinical trials through real-time review or patient demographic, diagnostic and observational data against the clinical trials screening criteria, by development of database architecture. Patients could consent to receiving further information about a trial at the time of routine blood collection, and a referral pathway developed. In addition, trial samples can be included (with consent) into the NSWHP-run Statewide biobank, to enable both post marketing and post therapeutic surveillance, enriched by linkage to administrative health data via CHEREL. Again, if successful, this can be scaled nationally. Biobanking can also support epidemiological research such as influenza serotypes or biomarker development.

KA3: Professionalising R^3 clinical trial services

Currently clinical trials in R^3 areas are often managed at the 'site' level within individual departments of hospitals. This creates fragmentation, inefficiencies and duplication. It risks patient safety and data quality, and deters commercial sponsors who must produce the most robust data possible for presentation to regulatory authorities. Professionalising trial support will address this and is also important to meet expectations for hospital accreditation[23] and other governance frameworks. We will improve facilities, equipment, services and systems in R^3 NSW and increase research capacity, by providing the tools, training and the core stable staff (**KA4**) to professionalise the conduct of clinical trials to the highest international standards across the network.

Professional development, education and training for clinical trials staff and consumer advocates
We will engage existing partners (eg Health Consumers NSW and ACTA, Praxis Australia and ARCS) to deliver accredited clinical trials training (ICHGCP, quality management systems, project and business management, and more, at basic and advanced levels as appropriate) and consumer involvement training to research staff, clinicians, and patient advocates, across R^3 areas. This will:

- support the tools already developed by OHMR clinicaltrialsNSW such as the Clinical Trial Toolkit[24] (including site Standard Operating Procedures and budget templates), ACTA Consumer Involvement and Engagement Toolkit[25] and Health Consumers NSW[26]
- meet the internationally recognised competency-based frameworks (e.g. TransCelerate, in ICH-GCP, or ISO14155 for medical devices) that are required by commercial Sponsors
- support the new ACSQHC Clinical Trial Governance Framework and TGA Inspections, and ensure R^3 clinical trial sites meet national and international regulations and best practice.
- extend training to the broader healthcare workforce not currently engaged in clinical trials, to build capability that both supports clinical trial activities routinely conducted on wards and create a pool of trial-trained staff to meet fluctuating workforce demands, building from the Cancer Institute NSW's eviQ online learning project for newly qualified oncology nurses.
- increase the ability of consumers, community members, researchers and clinicians to work together in co-design and governance

Training will led by a devolved training team (**KA4**), after needs assessment, and delivered locally by the R^3 Clinical Trial Support Units, and supervised by a training subcommittee (**KA1**). Training and education will be provided in modalities that support access by the R^3 population including podcast, video conference, on-line and group face to face, using systems already established and available to project partners. Training and education will be delivered early in the Project to consolidate capability and increase capacity. This will be further developed to support future growth through a Train the Trainer model where accredited training capability is embedded directly in the R^3 CTSUs (**KA4**) to provide regular re-certification and training of new staff and consumer representatives.

R^3 Clinical Trials Community of Practice: Training alone is not enough, especially for staff working in isolated settings. Communities of practice (CoP) are groups who engage explicitly in collective learning in a shared domain. They have common interest and passion, and interact regularly to learn to do it better.[27] Based on evidence[28] [29], a supported CoP for NSW R^3 clinical trial co-ordinators and research nurses will be established. This will ensure that experienced NSW (R^3 and metro based) trial staff can provide mentoring and guidance to less experienced, and that a peer-led pragmatic problem-solving resource exists. It will build shared enthusiasm and commitment, and a common identity. A CoP co-ordinator will be integrated into the training team. Cohesion will be further supported by an annual meeting and local sector catch ups with visiting experts.

Clinical Trial Management System (CTMS): this off the shelf software helps manage planning, performing and reporting functions of clinical trials. We will support its implementation within R^3 LHDs so that it integrates with existing processes and systems. This will provide:

- real time operational oversight of clinical trials (e.g. recruitment, appointment attendances)
- detailed analysis and reporting of performance metrics such as number of trials and patients
- financial management of the trial portfolio including billing compliance and revenue recovery
- staffing/resourcing management to clinical trial projects
- support for compliance with ICH-GCP, ACSQHC Clinical Trial Governance Framework and TGA inspection by reporting on outcomes of clinical trial implementation projects.

Pharmacy services – ensuring provision of quality clinical trial product (drugs) to participants
Integrity of clinical trial drug supply is essential. Challenges in R^3 areas include timeliness, distance, product shelf-life, sponsor requirements, product tracking and scalability. We will partner with Baxter Healthcare (currently involved in over 110 clinical trials in ANZ, and partners with metro and R^3 sites in the Teletrial model) and other pharmacy providers, to address these. We will support further development of a R^3 supply model through engagement with key stakeholders to identify roadblocks and risks, including ensuring tamper proof and cold-chain shipping containers and transport to R^3 areas. This will develop a framework for compliant and validated clinical trial drug supply in R^3 areas that can be scaled nationally.

Facilities and equipment: We will undertake a facilities and equipment needs and gaps analysis to determine what is available (e.g. in LHD or NSWHP facilities), and what can be used more effectively; and then providing where needed. This would mostly be room/space rental, fridges, freezers (both with external alarm and monitoring capabilities), centrifuges, dedicated secure pharmacy storage. More specialist equipment for trials is generally provided by the Sponsor.

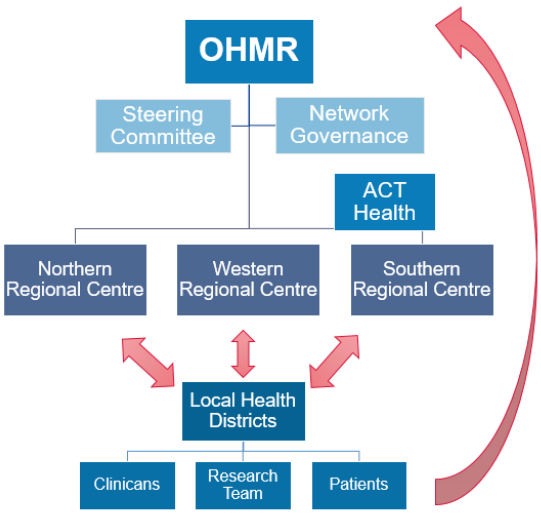
KA4: Local trial delivery by R^3 Clinical Trial Support Units

We will establish a network of three clinical trial support units (CTSUs), located in MM3-7, across the 8 NSW R^3 LHDs and the ACT, coordinated by OHMR (see diagram). The R^{3}CTSUs will facilitate and deliver clinical trials across a geographical area or cluster of LHDs - northern, western and a southern NSW/ACT cluster. The CTSUs will undertake tasks relevant to supporting local trial delivery, but will

also lead specific tasks on the part of the network as a whole, reducing duplication: eg training is a core task and based in all CTSUs, but training support will be led from one R^{3}CTSU on behalf of all.

Tasks for R^{3}CTSUs are to:

- operationalise the project key activities across the 8 NSW R^3 LHDs and the ACT
- support and facilitate all clinical trials (commercial, collaborative network and investigator initiated) in all therapeutic areas across all trial sites (primary and teletrials sites); aiding e.g. metro led studies, by facilitating patient screening for such trials regionally, travel to have initial treatment in major centres, and where feasible follow-up in R^3 areas. This will support standard trial delivery as well as local aspects of virtual or teletrials
- undertake local feasibility assessment of sites, considering capacity and skills, and numbers of patients to potential studies, drawing on local knowledge and data.
- help manage local trial start-up and close-down, allowing clinical trial sites to focus on consenting participants, completing study visits, prioritising patients' health and safety
- support/coordinate recruitment activities (**KA2**) for trials within their cluster or across clusters to meet trial enrolment targets
- build a critical network of skilled staff based directly in R^3 areas (**KA3**)
- liaise with local LHD and consumer groups
- develop and support local research/clinical leaders and champions
- business development services
- acting as lead CTSU for a given study, being a single point of contact for Sponsors during study initiation phase, negotiating contract, completing HREC and RGO submissions, and ensuring that the contractual obligations of the trial are delivered.
- finance services: develop trial budgets, managing trial finances
- monitor trial and data quality,
- offer to broker academic trial expertise when needed, particularly to support the development of investigator-initiated capability in R^3 areas.



Staffing at CTSUs: Staffing will be determined by needs assessment of skills, and potential for growth in trials; but will on average be five full time equivalents (FTE)/CTSU: a clinical trial manager, clinical trial assistants, accounts/finance manager, quality assurance and training manager (**KA3**); and linked staff (0.5, based in metro sites) to support teletrials (**KA1**). In addition, there will be staff based outside the CTSUs in other recruitment sites, averaging initially per LHD 0.6FTE clinical nurse consultant and 0.6 trials assistant, and a part time clinical trial pharmacist: exact numbers and location will depend on activity, and population size.

KA 5: Governance and Project Coordination

The OHMR clinicaltrialsNSW unit will coordinate the project (see diagram above), answerable to the NSW Health Executive. Staff in OHMR will be 0.25FTE clinical director, experienced in R^3 trials, two FTE grade 9/10 and one FTE admin assistant. OHMR will be responsible for:

i. overall governance and oversight of the project
ii. coordinating operational activities and developing shared processes in R^3, e.g. moving regulatory and ethics and governance systems to mutual acceptance

iii. financial management and contracting, complying with government procurement processes
iv. project management including development of detailed implementation plans in consultation with key stakeholders, implementation, risk management, monitoring and reporting to MRFF, project evaluation.
v. secretariat support to steering committee and advisory groups.
vi. alignment with other clinicaltrialsNSW enabling initiatives, e.g. clinical trial Standard Operating Procedures and tools, Frameworks for Early Phase Clinical Trials and Teletrials.
vii. coordinating the activities of the regional centres (see KA3 below)
viii. alignment/interaction with other R^3 trial infrastructure initiatives nationally

There will be an overarching **Steering Committee**, chaired by the clinical director, with stakeholders including OHMR, ACT Health, R^3 LHD Research Directors, and project advisory group chairs.
Three advisory groups will provide input to the steering committee on specific areas:
Clinical & Scientific Advisory Group – responsible for portfolio management, method development and evaluation: members will be clinician investigators and trials scientists, academic experts, senior clinical trial staff from the 3 R^3 CTSUs and representative from LHDs' trial teams; ensuring representation from a range of therapeutic areas/disease groups.
Consumer Advisory Group – health consumer partners, and Aboriginal community representatives
Industry Advisory Group – commercial Sponsors including pharmaceutical, biotech and medtech companies and contract research organisations, with representatives from peak bodies such as Medicines Australia, Medical Technology Association of Australia, AusBiotech and MTPConnect.
Some specific cross-disciplinary subcommittees, e.g. for training or IT, will be set up.

Outcomes and Impact

The major impact of the project should be on rural health and healthcare processes, but this will be difficult to measure within the timescale of the grant: nevertheless, establishing a framework (by specific case studies using the established HMRI FAIT model[30]) and early baseline data for this is an important role of the Clinical/Scientific committee. Performance indicators are in the appended application form: but will be year-on-year increase in numbers of trials open for recruitment in R^3 areas, commercial and non-commercial (funded by public sources); numbers offering access to novel and otherwise unavailable therapies; numbers led from R^3 areas; numbers of sites and clinicians active in recruitment; numbers of patients screened, and recruited annually; numbers of trials delivering on time and to target (benchmarks for these exist elsewhere, e.g. the UK); and the income and costs of the networks. Other measures will be of capacity development (e.g. numbers of staff trained and active in trials); patient and clinician experience (e.g. reduced burden of trial participation); client (sponsor) satisfaction; and engagement with other R^3 consortia. An independent evaluation of impact is planned in year 5.

Sustainability: the measure of success of the network will be its sustainability beyond the life of this grant. For this, the network must attract both commercial and non-commercial sponsors, based on its systems, processes and its growing track record of successful delivery of trials on time, on budget and on target; achieved using the established CTSUs and enduring core systems (CTMS, MyVirtualCare among others) catalysed by this grant. We believe that these will make the network increasingly cost effective at scale, reducing the costs per patient, and that the use of these approaches in trials, e.g. for drug licensing, is becoming more accepted as sponsors and regulators realise that traditional models of clinical trials are unsustainably costly.

Discussion with Medicines Australia and key pharmaceutical companies and CROs suggests a strong demand for this type of network and a commitment to placing trials in the network, and the project partnership is designed to drive commercial investment in the network. We estimate that 20-40% of the commercial trial income can be reinvested to sustain the long term R^3 clinical trial strategy. This

approach will be tested through this grant, with the CTMS and the CTSU finance manager roles providing transparency to return on investment.

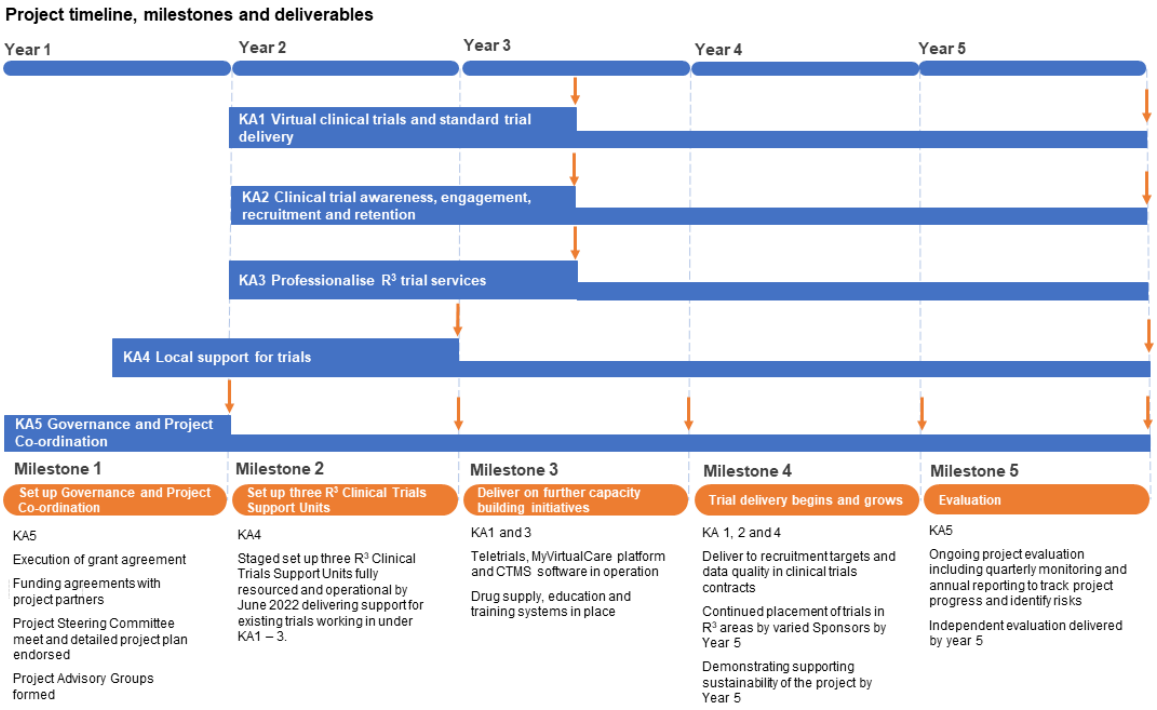
We expect the network to generate growing income from the conduct of trials from the end of year 2. This will be used to pay for recruitment sites' participation and expanded study delivery activities, in proportion to the workload required, but should increasingly generate a surplus. The project Steering Committee will track the revenue and surplus over the years 3-5. It will model the financial risk/challenges in future years, revising the budget annually, in the light of growing efficiencies that will reduce costs and of revenue increase. We recognise that not all of the initiatives in this proposal will be equally useful, and the proposal is a test of which can achieve the long term aim of a sustainable infrastructure for trials in R^3 areas: hence a rigorous evaluation of this proposal and its elements is essential to inform decisions regarding sustainability within the broader context of the clinicaltrialsNSW enabling program. The Steering Committee will advise on approaches to the network's transition to long term sustainability, e.g. creating a surplus target of one year's operating cost by end year 5, with a trend suggesting for future years continuing viability of a revised network, and the potential to continue expanding the research capacity of the partners.

The network may also support other funded research, e.g. epidemiology, biomarker development or validation, if there is spare capacity. While not the network's prime purpose, this would develop the research culture and is often valuable to commercial and non-commercial partners.

Lastly, this project will be active in efforts to develop a truly national approach. It will ensure compatibility, develop common systems, and share best practice with other MRFF project consortia. We believe our approach is scalable across Australia, and that the vision of a national system can be achieved in time with experience and testing, and with support from the public and patients, professions, federal and state governments, and industry partners.

Milestones

The Gantt chart outlines the major tasks and the timelines for their delivery.



Budget

The budget ($30M) is detailed in the application form. It is mostly spent on staff (over 80% employed in R^3 areas) and training, initially to establish the network, and later on pump priming the support of delivery. There is no direct funding for trial conduct, which must be provided in the usual manner by sponsors or by public sources. Funding is provided for methods development and for evaluation.

It will be important to bring in revenue from delivery of trials as soon as possible and to demonstrate growth in that income: to encourage clinicians and healthcare facilities to participate, as a means of developing their skills and the services that they can offer; and to increase employment in R^3 areas; The Steering Committee will be advised by the Clinical & Scientific Advisory Group on the use of any surplus, for network development (e.g. new IT systems) or testing methods, e.g. novel approaches to conducting trials effectively in R^3 settings; or on investment to secure a national infrastructure.

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