Estimating the Return on Investment of a Randomised Controlled Trial on Telehealth-based Medical Nutrition Intervention in Rural and Regional Australia

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Commissioned by the Spinifex Network

Foreword

Compelling economics of rural health and medical research

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Introduction

As a result of commissioning this economic analysis, Spinifex Network has demonstrated that rural research can provide a staggering return on investment and 'pay its way.' High quality rurally-based research invests in communities and offers the opportunity for rural Australians to be both researchers and embedded participants. The focus on cardiovascular disease is especially important as the health effects of heart attack, stroke and dementia on rural families and communities are profound and potentially preventable. Ongoing investment in rural health services research will pay economic and social dividends and is a down payment on our future.

What is Value of Information analysis?

The Value of Information (VOI) framework is a quantitative approach to prospectively estimate the expected return on investment of research studies.*

Research is valuable in two ways:

1. Collecting more information can reduce the chance of making misguided decisions when the existing evidence is uncertain. Misguided decisions may lead to healthcare costs such as wasting resources on ineffective or unsafe interventions. Collecting additional evidence can reduce uncertainty.

2. Research may influence the implementation of interventions. Collecting further evidence has the potential to improve health outcomes by encouraging the implementation of the most effective and/or cost-effective intervention.

Thus, the expected value of a research study is the sum of its expected value in reducing decision uncertainty and its expected value in improving implementation. These expected research benefits are scaled up by considering the population expected to benefit from research findings and compared to the expected research costs to estimate the return on investment of a research study.

This sophisticated technique can be used for:

- Research prioritisation decisions – the value of the additional information generated by each proposed study can be quantified.

- Research design – studies of different types and scopes will reduce uncertainty to different degrees – the most efficient design maximises the return on the research investment.

* Full references on VOI are available in the main report

- Decisions about reimbursement and coverage of new technologies – e.g. about the costs and benefits of delaying adoption versus obtaining more evidence.

- Efficient decision making over the technology life cycle – e.g. if a technology is not effective/cost effective and the value of information analysis suggests research is not worthwhile, use of the technology should simply stop (rather than more research being commissioned to 'prove' the ineffectiveness).

What is the Spinifex Network?

The Rural Health and Medical Research Network – the Spinifex Network – is a coalition of more than 60 rural and regional health and research organisations trying to build a permanent national rural health and medical research network to deliver on the vision that rural, regional and remote Australia celebrates sustainable, resilient, health communities and economies.

Spinifex exists to:

- Improve access to healthcare that meets the needs of rural communities, through technology, workforce and innovative care delivery; and
- Increase support for sustainable rural communities by responding to the unique health challenges of place.

A funded Spinifex Network will achieve this by work that strengthens Indigenous health, builds rural research capacity and increases rural prosperity.

Why did the Spinifex Network commission a Value of Information Analysis?

Although 30% of the population lives rurally, in 2018 only 2.4% of NHMRC funding went toward research that specifically aimed to deliver health benefits to people who live in rural or remote Australia.[1] There are a number of likely reasons for this situation, but providing a picture of the value of rural research may be useful to allow the architects of current research funding systems to reconsider their approach. This report quantifies potential value for money of an exemplar trial that addresses the healthcare needs of remote and regional populations in Australia.

Why was a trial embedding a telehealth intervention within primary healthcare for reducing diet-related cardiovascular disease risk chosen for analysis?

1. **Cardiovascular disease (CVD) is a big rural problem.** Rural populations have a 20-30% higher CVD prevalence. In 2019 AIHW estimated that 14% of the national burden of disease was due to heart disease (8.9%), costing $10.4 billion annually. Five risk factors account for 38% of this disease burden; smoking (9.3%), obesity (8.4%), diet (7.3%), high blood pressure (5.8%) and high blood sugar (4.7%). Dietary risks rank third, but contribute to all top risk factors, except smoking. Improving dietary patterns is a huge area of need. The Australian Institute of Health and Welfare (AIHW) has estimated that if Australians adhered to the dietary guidelines, national burden attributed to CVD would drop by 62%.[2] Recently it was estimated that achieving all public health recommendations across Australia would

result in large declines in CVD mortality (nearly 15,000 deaths avoided annually).[3] While increasing fruit and vegetable intakes was beneficial across the nation, for rural populations addressing fat and salt intake had higher benefit than for urban patients.[3]

2. Adopting and maintaining healthy eating habits is hard to do alone. Individuals are more likely to improve their dietary patterns if they receive personalised nutrition assessment and feedback, and regular, ongoing support.[4] Accessing medical nutrition therapy interventions (MNT), where therapeutic diets are tailored to medical conditions and monitored by Accredited Practising Dietitians, is a challenge to people living in rural and remote areas due to travel time, cost of consultations, waiting lists, inadequate referral pathways, or lack of service providers.[5] Thus, **there is a need to experiment with different models of care to target improvements in diet-related CVD risk factors for rural populations.**

   This trial tests the feasibility, acceptability and preliminary efficacy of an online MNT platform with electronically generated personalised nutrition reports, personalised goal setting and automated results sent to GPs, both with (intervention) and without (control) tele-health dietitian support.

3. The health economic team were able to be given **prospective access to a complete research** design where the research was rurally-based (which was not funded at that point, but this innovative rurally-based trial has now been funded by the Medical Research Future Fund). **The trial was of special interest as its design made it more likely to support ongoing implementation into practice** if the trial result was positive:

   - Full support from the Hunter New England and Central Coast Primary Healthcare Network, including staff as investigators on the research team.
   - Use of systems that are already in routine use: 'PENCAT' to allow ongoing data extraction from GP records and 'Health Pathways' - locally agreed online information tools that help clinicians to make the right decisions about health care together with their patients, at the point of care.
   - Embedded rurally-based researchers based at the University of Newcastle's Department of Rural Health (funded under the Rural Health Multidisciplinary Training program) with expertise in nutrition and dietetics and linked with rural health services.
   - The Australian Government in March 2020 expanded access to Medicare Benefits Schedule items to deliver telehealth services to Australians with an eligible chronic disease management plan, including videoconference and telephone consultations.[6]

Results of the value of information analysis of a telehealth intervention within primary healthcare for reducing diet-related cardiovascular disease risk

The total population of Australia is 26 million, around 30% of the population are older than 45 years, and around 30% live in rural and regional Australia.[7, 8] It is estimated that 19% of Australians older than 45 years

have moderate to high CVD risk.[9] This means that the population expected to benefit from this research is approximately 450,000 people. For the analysis the 'attainable population' was assumed to be 50% of the prevalent population of 450,000 (225,000), given that it is impossible to perfectly implement the intervention in all eligible populations.

The expected value of the proposed trial (with 150 patients in each arm) for the 'attainable population' is estimated to be $20.70 million. If the results of the proposed trial confirm expected benefits of the telehealth nutrition intervention, the implementation of the intervention in practice is expected to improve.

A conservative assumption is made in the modelling that if the randomised controlled trial (RCT) is positive that it will improve the current level of implementation by 10%. With only a 10% improvement in uptake of the intervention as a result of this trial then the expected monetary benefit of improved implementation would be approximately $39.50 million and hence a total expected monetary benefit of approximately $60.20 million. This means that for every 1% improvement in implementation, the expected benefit (in $) is $3.95 million (approximately $ 4 million). This figure can be used to justify investment in implementation strategies. When the measured benefit is compared to the current grant budget of $1.03 million, the expected return on research investment is around 5800%. That is, for each $1 of funding received to support the current trial, the intervention is expected to return $58 in value.

These figures are based on a conservative estimate of the expected improvement in population health as it is assumed that only 50% of the eligible population would be targeted and that the new RCT would result in only a 10% improvement in implementation. (Ten percent is also the figure used by the Australian Clinical Trials Network when estimating the return on investment of clinical trials.) Clinical trials in rural and regional areas may bring additional economic benefits in terms of improving research and workforce capacity, enhancing clinicians and researcher retention and increasing regional prosperity (thus impacting the socioeconomic determinants of disease) – and these have not been estimated.

As a result of this analysis, what should Australian research funders do now?

1. **Consider implementing value of information analysis as one strategy to ensure that new research squarely and efficiently addresses population health needs.** Funders should consider requesting such analyses - estimating the potential impact of proposed research - in order to prioritise investments. This is especially so in the case of the Medical Research Future Fund where the Advisory Board is required to take into account the following:

    - The burden of disease on the Australian community;
    - How to deliver practical benefits from medical research and medical innovation to as many Australians as possible; and
    - How to ensure that financial assistance provided under this Act provides the greatest value for all Australians.

Another needed rebalancing strategy to increase the percentage of research funding provided for work designed to improve rural health is to ensure an adequate rural voice is present on priority setting committees and selection panels.

2. **Identify better methods for ensuring that successful research is translated into practice nationally.**
   These will include:
   - Systematic provision of follow-on funding for replication and scale up research when studies are successful (potentially via Centres for Innovation in Regional Health and Advanced Health Translation Centres).
   - Early involvement of stakeholders responsible for service design and identification of implementation funding.

3. **Recognise the high return on investment from research into models of care in rural settings, in particular those addressing major non-communicable diseases (e.g. cardiovascular diseases, cancer, chronic respiratory diseases and diabetes).** This is even more relevant post-COVID 19. The World Economic Forum Global Future Council on Health and Healthcare recently published expert essays on, 'How to build a better health system.' Commentators noted that: *'The pandemic highlights the need for a flexible and reliable integrated care system to enable healthcare delivery to all people no matter where they live, utilizing approaches such as telemedicine…'*[10]

Now is the time for Australia to make a greater investment in research designed to solve rural health issues and service delivery challenges

List of acronyms

Acronym	Definition
RCT	Randomised Controlled Trial
CVD	Cardio-Vascular Disease
QALY	Quality-adjusted life years
ABS	Australian Bureau of Statistics
AIHW	Australian Institute of Health and Welfare
MNT	Medical Nutrition Therapy
APD	Accredited Practising Dietitians
mHealth	Mobile Health
MBS	Medicare Benefits Schedule
HNECC PHN	Hunter New England Central Coast Primary Health Network
NSW RHP	New South Wales Regional Health Partners
TCL	Total Cholesterol
VOI	Value Of Information
INMB	Incremental Net Monetary Benefit
EVPPI	Expected Value of Perfect Parameter Information
EVSI	Expected Value of sample Information
WTP	Willingness-to pay
ACTA	Australian Clinical Trials Alliance
ASTN	Australasian Stroke Trials Network
IMPACT	Interdisciplinary Maternal Perinatal Australasian Collaborative Trials network
NHMRC	National Health and Medical Research Council

Executive summary

A randomised controlled trial (RCT) has been proposed to embed a telehealth intervention within primary healthcare for reducing diet-related cardio vascular disease (CVD) risk in adults living in rural and remote regions. The RCT is expected to inform policy related to access to cost-effective clinical care for CVD prevention. This report aims to assess the value for money of this RCT as an exemplar of a clinical trial addressing the healthcare needs of remote and regional populations in Australia.

Following the value of information framework to prospectively estimate the return on investment of the proposed RCT, the report evaluates the cost-effectiveness of the intervention based on existing evidence and estimates the expected value of the new research. The expected value of research is the sum of the expected value of the RCT in reducing decision uncertainty (i.e., informing decision making) and the expected value of the RCT in improving the implementation of the intervention in practice.

A decision analytic model is built to link the expected change in the primary endpoint in the trial (i.e., total blood cholesterol) to CVD outcomes (e.g., heart attack and stroke). Comparing the long-term costs and effects of the simulated cohorts in the RCT (i.e., intervention and control) shows that the intervention is less costly (i.e., cost saving) and more effective compared with the control. With a mean 0.03 quality-adjusted life-years (QALYs) gained and $250 saved, and at a willingness-to-pay threshold of $50,000 per QALY gained, the incremental net monetary benefit of the intervention is $1,750 per patient, indicating that the intervention is potentially cost-effective. However, the probability of the intervention being cost-effective is only 56%, suggesting that a decision based on the results of this economic evaluation might be uncertain. The expected value of the proposed RCT in reducing decision uncertainty, for a population of 450,000 eligible patients, is estimated to be $20.70 million. If the results of the proposed RCT confirm the expected benefits of the intervention, the implementation of the intervention in practice is expected to improve. If there is only a 10% improvement in the uptake of the intervention as a result of this RCT, the expected monetary benefit of improved implementation is around $39.50 million. Thus, the total expected monetary benefit of the RCT is around $60.20 million. Comparing this figure with the proposed RCT budget of $1.03 million the expected return on research investment is around 5800%.

The proposed RCT is potentially value for money. For each $1 of funding received, the proposed RCT is expected to return $58 in value.

Contents

Tables & Figures

Background and objectives

Cardiovascular disease

The term cardiovascular disease (CVD) is used to describe a group of conditions affecting the heart and blood vessels. These conditions include coronary heart disease (e.g., angina and heart attack), stroke and cerebrovascular diseases, heart failure, and diseases of the arteries. Coronary heart disease and stroke represent the majority (75%) of CVD cases reported in Australia.[11] CVD is the leading cause of morbidity and mortality in Australia and the world. Based on the Australian Bureau of Statistics (ABS) 2017-2018 National Health Survey, an estimated 1.2 million (5.6%) Australian adults self-reported one or more conditions related to heart or vascular disease. CVD is higher among men (6.5%) than women (4.8%), and it increases with age as more than one in four (26%) of those aged 75 have CVD.[11]

CVD is responsible for approximately 1.2 million hospitalisations annually, which is 11% of all hospitalisation.[11, 12] It is the underlying cause of death in 25% of all deaths in Australia. According to the Australian Burden of Disease Study 2015, CVD accounted for almost 14% of the total burden of disease, a decrease from 15% in 2011 and 18% in 2003.[11, 12] Coronary heart disease was the leading individual disease, contributing to 6.9% of the total burden. Stroke was ranked ninth in the leading diseases causing burden, accounting for 2.7% of total burden in 2015.[11, 12] CVD is responsible for almost 9% of total disease expenditure in the Australian health system costing $10.4 billion each year.[11, 12]

The decline in the burden of CVD in recent years has not been equally distributed across the population.[13] The burden of CVD is felt more by lower socioeconomic groups, Aboriginal and Torres Strait Islander people, people from diverse cultural backgrounds and those living in rural and remote communities.[11, 13] The prevalence of CVD is significantly higher among people living in the most socioeconomically disadvantaged areas compared with those in the least disadvantaged areas (6.4% and 4.8%, respectively).[11, 13] Australians living in rural and remote Australia experience higher rates of CVD-related hospitalisation and are more likely to die of CVD than those in metropolitan areas.[11, 13] After adjusting for age, the CVD death rate is 1.4 times as high in remote and rural areas compared with major cities.[11]

A combination of risk factors contribute to the overall likelihood of having CVD in the next five years, this is known as the absolute CVD risk. The more risk factors a person has, the higher their chance of having a heart attack or stroke. Over 90 per cent of adult Australians have at least one risk factor for CVD and 25 per cent have three or more risk factors.[11-13] Heart disease is largely preventable by appropriate population-level interventions targeting the risk factors that increase the chance of developing CVD. The top five modifiable risk factors accounting for CVD disease burden were smoking, obesity, diet, elevated blood pressure and plasma glucose (4.7%).[12] Although dietary risk ranks third, it contributes to all other risk factors, except smoking.

Diet and cardiovascular disease

Adopting and maintaining healthy eating habits is beneficial for CVD risk reduction.[5, 14] The National Vascular Disease Prevention Alliance absolute risk guidelines recommend diet interventions for CVD prevention and

treatment.[14] Recommendations include increasing consumption of fruit, vegetables, polyunsaturated fatty acids, fish, fibre and potassium and/or decreasing consumption of total fat, saturated fatty acids, cholesterol and salt.[14] The Australian Institute of Health and Welfare (AIHW) estimated that if Australians adhered to the dietary guidelines, national burden attributed to CVD would drop by 62%.[12]

A systematic review on knowledge translation of dietary evidence in CVD management found that little knowledge is translated to the end user, which means that most people do not have access to evidence-based information to improve diet-related health.[5] Adopting and maintaining healthy eating habits is hard to do alone. Individuals are more likely to improve their dietary patterns if they receive personalised nutrition assessment and feedback, and regular, ongoing support.[4] However, there is a major lack of programs available through primary care, especially in regional and remote areas, that use Accredited Practising Dietitians (APDs) to target diet-related CVD risk management. Accessing medical nutrition therapy interventions (MNT), whereby therapeutic diets are tailored to medical conditions and monitored by APDs, is a challenge to people living in rural and remote areas due to travel time, cost of consultations, waiting lists, inadequate referral pathways, or lack of service providers in rural areas.[5]

Technology-based dietetic services including telehealth-delivered nutrition consultations and other digital health modalities such as web-based programs, software programs and mobile health (mHealth) options may offer a flexible modality to provide effective and cost-effective MNT.[15, 16] In March 2020, in response to the COVID-19 pandemic, the Australian Government temporarily expanded access to ADP for Medicare Benefits Schedule (MBS) items to deliver telehealth services to Australians with an eligible chronic disease management plan, including videoconference and telephone consultations.[17]

In a recent position statement, Dietitians Australia stated that people can receive high-quality and effective dietetic services such as MNT delivered via telehealth.[15] It affirmed that the implementation of telehealth interventions can address health and service inequalities, improve access to effective nutrition services, and improve the diet-related health and well-being of Australians, regardless of their location, income or literacy level.[15] However, the position statement highlighted the need for larger clinical trials to evaluate the implementation and outcomes of telehealth consultations in populations with chronic diseases and in vulnerable populations, including those in regional and remote areas.

A new randomised controlled trial

A randomised controlled trial (RCT) has been proposed to embed within primary healthcare a MNT program for primary and secondary prevention of diet-related CVD risk in adults living in rural and regional areas. By assessing the effectiveness and cost-effectiveness of an evidence-based, technology-supported intervention that provides system-generated, personalised dietary feedback, the RCT aims to inform health policy related to access to cost-effective clinical care for CVD.

The RCT will include participants with a moderate-to-high CVD risk (≥10%) using the National Vascular Disease Prevention Alliance absolute CVD risk calculator from their most recent heart health check.[18] Participants will be identified from practices within the Hunter New England Central Coast Primary Health

Network (HNECC PHN), a key member of NSW Regional Health Partners (NSWRHP). The RCT will compare a personalised tailored MNT intervention with and without up to five telehealth APD consults over 12 months. Each consult will last between 20 to 30 minutes. Electronically generated personalised nutrition reports, personalised goal setting and automated results sent to GPs, both with (intervention) and without (control) telehealth dietitian support.

The primary outcomes will be total cholesterol (TCL) level analysed at accredited pathology services at baseline, 3, 6 and 12 months. To detect a change in TCL of 0.51 mmol/L, with 80% power and alpha 0.05, the trial is designed to include 150 participants per arm. This was based on a small Australian study on the effectiveness of an ADP-led dietetic intervention for hyperlipidaemia adults using individually-tailored dietary feedback.[19] From a baseline of 6.79 ±1.10, as significant reductions in TCL (-0.51 mmol/L; 95%CI: -0.77,-0.24) was observed in the 39 participants included in that study.[19]

Value for money of the new RCT

Health research is vital to inform policy and medical decision making; however, research funds are limited, and therefore, it is essential to assess the value for money of research projects.[20] The estimated budget for the proposed RCT is $1,028,236 over three years. But with this requested budget, is this RCT value for money?

There are analytical approaches to quantify the value of evaluative research (i.e., clinical trials and cohort studies).[20-28] The underlying principle of these approaches is to estimate the expected benefits of research for improving health outcomes (e.g. quality of life or overall survival), which can be expressed in monetary terms using a willingness-to-pay value for an additional unit of health outcome (e.g., $50,000 per life-year gained).[21, 22] The expected monetary benefit is compared to the expected costs of conducting the proposed research study to inform if this research proposal is cost-effective (i.e., value for money).

Whilst return on research investment can be estimated retrospectively after the completion of a research study using quantitative methods such as the payback of research approach, prospective evaluation of return on research investment is important to inform budget allocation before any funds are committed to a particular research study.[21, 22] Identifying and directing funds to research studies with the highest return on investment will maximise monetary benefits from limited research budgets.[25, 26]

The Value of Information (VOI) framework is a rigorous quantitative approach to prospectively estimate the expected return on investment of research studies.[28-32] This approach considers that research is valuable as it informs decision making in two ways (Figure1). First, collecting more information can reduce the chance of making misguided decisions when the existing evidence is uncertain (e.g. due to sampling error).[33-35] Misguided decisions may lead to healthcare costs such as wasting resources on ineffective or unsafe interventions. Collecting additional evidence (e.g., in a larger RCT) can reduce uncertainty by providing more precise estimates of the parameters of interest, which in turn better informs decision making to avoid the costly consequences of suboptimal decisions.[33-35] Second, research may influence the implementation of interventions (e.g. changing practice) by adding to information and evidence.[23, 34, 36, 37] Collecting further evidence has the potential to improve health outcomes by encouraging the implementation of the most

effective and/or cost-effective intervention. Thus, the expected value of a research study is the sum of its expected value in reducing decision uncertainty and its expected value in improving implementation.[23, 37] These expected research benefits are scaled up by considering the population expected to benefit from research findings and the evidence durability (i.e., the time over which evidence is useful). Then, the expected value of research at the population level is compared to the expected research costs to estimate the return on investment of a research study.[28-32]

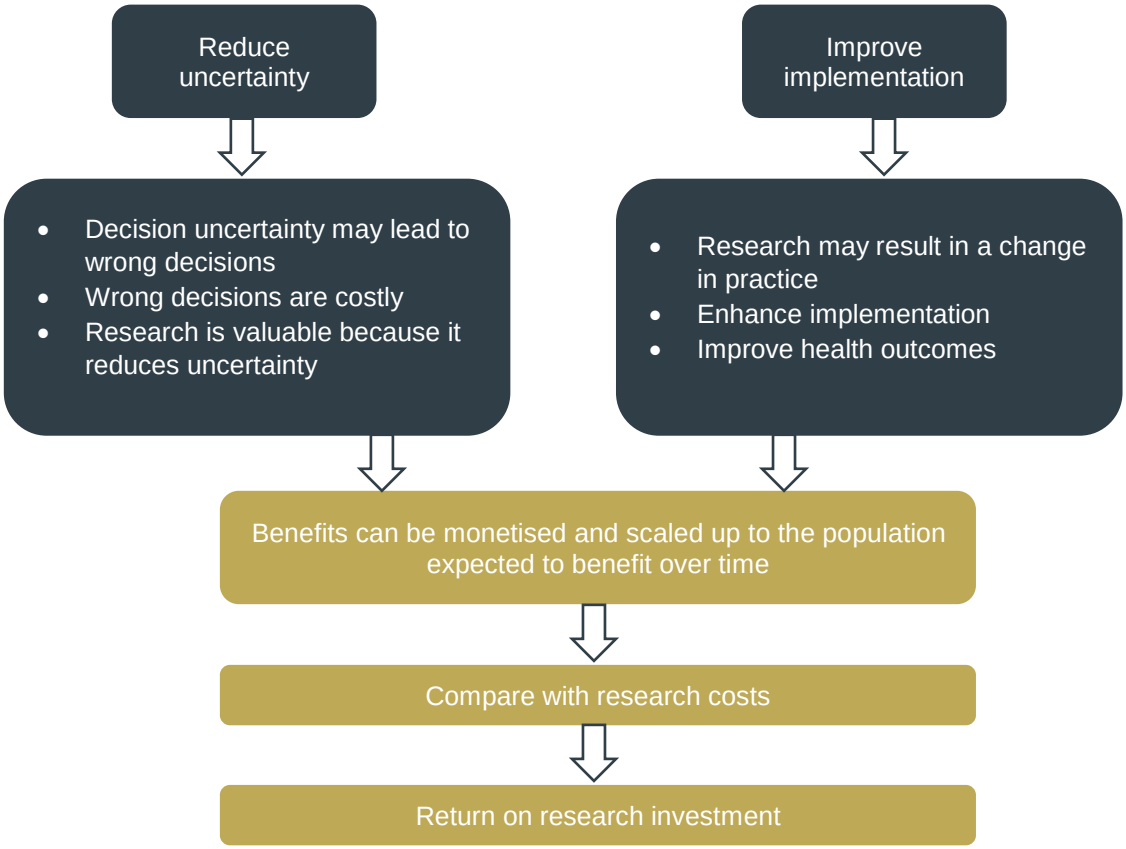

Figure 1: Value of information framework

Aim and objectives

The aim of this report is to assess the return on investment of the intended telehealth-based MNT in adults with moderate to high CVD risk in rural and regional Australia. This will be achieved through the following objectives:

1. assess the cost-effectiveness of the intervention and characterise decision uncertainty;
2. estimate the value of the RCT in reducing decision uncertainty;
3. estimate the value of the RCT in improving implementation; and
4. compare the expected monetary benefit with the RCT costs.

Methods

Cost-effectiveness analysis

A cost-effectiveness analysis is conducted from the perspective of the Australian Department of Health using a decision analytic model. The minimal modelling approach suggested by Meltzer *et al* is followed whereby the decision model accounts for the population studied, the primary clinical outcome of the trial, and, if that outcome is intermediate (i.e., surrogate), an epidemiological link between that outcome and a comprehensive outcome (e.g., life years gained).[27, 38-40]

The model simulates a hypothetical cohort of patients who have moderate-to-high CVD risk (≥10%) using the National Vascular Disease Prevention Alliance absolute CVD risk calculator.[18] Patients in both the control and intervention groups will receive electronically generated personalised nutrition reports, personalised goal setting and automated reports sent to GPs. In addition, the intervention group will receive up to five telehealth APD consults, with each consult lasting between 20 to 30 minutes.

Patients in the intervention group are expected to achieve a lower TCL level, which is expected to be (-0.51 mmol/L; 95%CI: -0.77,-0.24), based on the study by Schumacher *et al.*[19] This reduction in TCL is linked to a reduction in the baseline CVD risk over five years. Based on the National Vascular Disease Prevention Alliance absolute CVD risk calculator, a reduction in 0.5 mmol/L will translate into a 1% reduction in the absolute CVD over 5 years.[18] To evaluate the long-term outcome of the reduction of CVD risk, a three-health state Markov model was developed using TreeAge Pro 2019 (TreeAge Software Inc, Williamstown, MA). The three health states in the model are: 'No CVD', 'CVD' and 'Death'. Patients move between the health states based on their risks of developing CVD disease and mortality due to CVD disease or age-related mortality.

Model costs are set by identifying key resources that are expected to be used by patients, and valuing these according to costings from national reports (e.g., Medicare Benefits Schedule) and the literature. The utility scores for health states in the model are obtained from the literature. These scores range from zero to one, with zero being equivalent to death and one equal to the best possible health state. Utility scores are applied to survival in each health state, to obtain quality-adjusted life years (QALYs). Key modelled input parameters including transition probabilities, costs and utilities are summarised in Table 1.

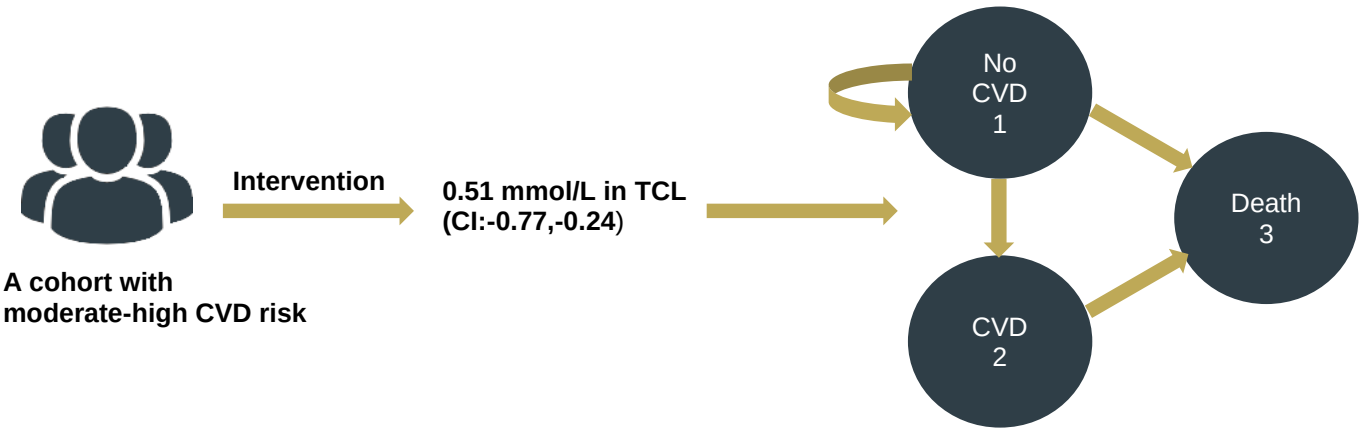

Figure 2: The decision analytic model structure

The Markov model has a cycle length of one year. Patients will be followed until the age of 85, based on the life expectancy of Australian population.[41] Costs are presented in Australian dollars (2020 values), and both costs and effects are discounted at 5% annual rate. The incremental net monetary benefit (INMB) is calculated, which is the difference in effects multiplied by the willingness-to-pay threshold for an additional unit of effect, minus the difference in costs. The willingness-to-pay threshold is set at $50,000/QALY, a commonly used threshold in Australia. A positive INMB indicates that the new intervention is cost-effective compared with the control.

Uncertainty in modelling results is characterised using probabilistic sensitivity analyses, whereby parameter values are randomly sampled using Monte Carlo simulation from a priori defined probability distributions.

Table 1: Key model input parameters

Parameter	Mean estimate (SE)	Distribution	Source
Start age; follow up	50 (5.0)	Normal	Assumption
Baseline TCL	6.50 mmol/L (0.5)	Normal	Schumacher 2016 [19]
Baseline 5-Y CVD risk	15 % (2.5)		National Vascular Disease Prevention Alliance absolute CVD risk calculator [18]
Reduction in TCL	0.51 mmol/L (0.13)	Normal	Schumacher 2016 [19]
CVD mortality ratio	2.00 (0.4)	Normal	AIHW CVD in Australia [11]
Cost of CVD maintenance	$2,750.00 (1,350)	Gamma	Ademi 2010 [42]
Cost of CVD hospitalisation	$14,150.00 (7,000)	Gamma	Ademi 2010 [42]
Cost of the intervention	$200.00 (25)	Gamma	4-5 sessions (30 min each at $90/hr wage)
Utility baseline	0.85 (0.02)	Beta	Clemens 2014 [43]
Disutility with CVD	Year 1: -0.09 (0.005) After Year 1: -0.05 (0.005)	Gamma	Hayes *et al* 2016 [44]

The expected value of reducing decision uncertainty

The results from the probabilistic analysis (Monte Carlo simulation) are used to estimate VOI measures. The detailed algorithms for VOI calculations are presented in the Appendix. The two VOI measures calculated to inform the value of the RCT in reducing decision uncertainty are the Expected Value of Perfect Parameter Information (EVPPI), and the Expected Value of Sample Information (EVSI).

The first VOI measure to calculate is the EVPPI for the parameter of interest, which is the reduction in TCL as the primary outcome of the trial. The EVPPI represents the monetary value of the additional information that would resolve uncertainty surrounding the parameter of interest.[33-35] In theory, resolving parameter uncertainty (i.e., achieving perfect precision) requires an infinite sample size. However, this is impossible in practice, and hence, what the EVPPI represents is the maximum value (i.e., the upper-bound) of research monetary benefit. The EVPPI is estimated by calculating the difference between the expected net monetary benefit of a decision with perfect information (i.e., no parameter uncertainty) and the decision made based on current information (i.e., with uncertainty).[33-35]

The EVSI, on the other hand, estimates the value of a clinical trial of a given sample size in reducing, but not resolving, decision uncertainty in the parameter of interest.[33-35] The EVSI is estimated by calculating the difference between the expected monetary benefit after collecting data on the parameter of interest and the expected monetary benefit with current information. Conceivably, the data collected from additional research is not known at this stage but could be predicted by simulation.[33, 35, 45, 46] As we increase the sample size of the clinical trial the EVSI will increase, reflecting and increasing reduction in uncertainty with larger sample sizes. However, increases in sample size may come with incremental cost.[47-49]

The above VOI measures calculated using the algorithms in the Appendix are per-person estimates; however, it is necessary to estimate the value of information for the population expected to benefit from the research outcomes. This is calculated by multiplying the per-person estimates by the number of individuals expected to benefit from the research outcomes. The total population of Australia is 26 million, around 30% of the population are older than 45 years, and around 30% live in rural and regional Australia.[7, 41] For the epidemiology of the disease, it is estimated that 19% of Australians older than 45 years have moderate to high CVD risk.[9] This means that the population expected to benefit from this research (i.e., affected by a decision informed by this RCT) is approximately 450,000 people (i.e., 26 million x 0.3 x 0.3 x 0.19).

The expected value of improved implementation

The health and economic benefits of the new trial would only be realised if its findings influenced clinical practice. This is the second component of the VOI framework which links the generation of new evidence through research studies and the realisation of population health impacts.[36, 37, 50] Of course, there may be other factors driving the actual implementation of an intervention in clinical practice (e.g., capacity building, incentives). However, we can estimate the expected monetary benefit from the change in the level of implementation that may be attributed to the new RCT as clinicians and decision makers are more convinced by the effectiveness and/or cost-effectiveness of the new intervention. Thus, the value of research in changing

the level of implementation is the difference between the expected monetary benefits of the intervention from an improved level of implementation and the monetary benefits based on current uptake levels.

Typically, current implementation and projected levels of implementation are informed by expert opinion or using historical data from the same or similar interventions. However, these estimates are often static in nature as they provide a snapshot of the dynamic development of implementation over time.[37] Implementation changes over time, following a diffusion process.[23, 37] The Bass model is used to forecast the implementation of the MNT telehealth intervention as it can represent distinctly different patterns of adoption (e.g., slow versus rapid adoption).[37, 51] The assumptions in the Bass model are based on the results of diffusion research, and it requires three parameters: 1) the number of attainable adoptions (*m*) reflecting the size of the target population, 2) the coefficient of innovation (*p*) which reflect the probability of taking up the intervention without external influence (i.e., early adoption), and 3) the coefficient of imitation (*q)* which is the probability of taking up the intervention due to interaction with other users (i.e., following others).[37, 51] Even when no data exist for a new intervention or technology, the parameters from interventions with similar characteristics can be used to in the model.

For this analysis the attainable population is assumed to be 50% of the prevalent population of 450,000 (225,000), given that it is impossible to perfectly implement the intervention in all eligible populations. The coefficient of innovation and the coefficient of imitation are set at 0.11 and 0.47, respectively as reported by Kim *et al* for telemedicine adoption in rural areas in the US.[51] The model predicts the expected implementation over 10 years with and without the proposed RCT. A conservative assumption is made that the proposed RCT will improve the current level of implementation by 10%.[52] The difference between the average cumulative adoptions with and without the influence of new trial is calculated and multiplied by the mean incremental net monetary benefit.

Comparison of the RCT's total monetary benefits and costs

The expected value of research (i.e., the proposed RCT) is the sum of the expected monetary benefit from the reduction in decision uncertainty and the expected monetary benefit from improved implementation. The monetary benefits are compared with the total cost of the RCT. The total cost of the clinical trial includes fixed costs (e.g., set up costs and salaries) and variable costs (per patient).[25, 53] From the budget of the RCT proposal, the fixed cost is $852,012 and the variable cost is $176,224 ($587/participant) with a total budget of $1,028,236 over three years. The return on research investment (ROI) is the total monetary benefit minus the total cost, divided by the total cost.

Results

Cost-effectiveness analysis

Compared with the control group, telehealth based MNT is cost saving with a mean cost saving per patient of $253. In addition, the incremental mean QALYs is 0.03 (12.75 versus 12.72) per patient. The telehealth intervention is dominating the control as it is cost saving and more effective. When comparing other health

outcomes including life years gained and CVD cases avoided, the telehealth intervention results in 0.14 years gained and 0.02 CVD cases avoided per patient. Table 2 summarises the base case results of the cost-effectiveness analysis.

Table 2: Cost-effectiveness analysis results

Outcome	Control	Intervention	Difference
Life Years	24.01	23.87	0.14
CVD cases	0.61	0.59	0.02
QALY (discounted)	12.72	12.75	0.03
Cost (discounted)	$15,194	$15,447	-$253

At a willingness-to-pay threshold of $50,000 per QALY gained, the INMB is approximately $1,750 (i.e., 0.03 x $50,000- (-$253)). A positive INMB indicates the intervention is cost-effective. This means that the telehealth-based MNT intervention will generate, on average, $1,750 additional value per patient compared with the control group. Figure 3 depicts the INMB across a range of willingness-to-pay thresholds.

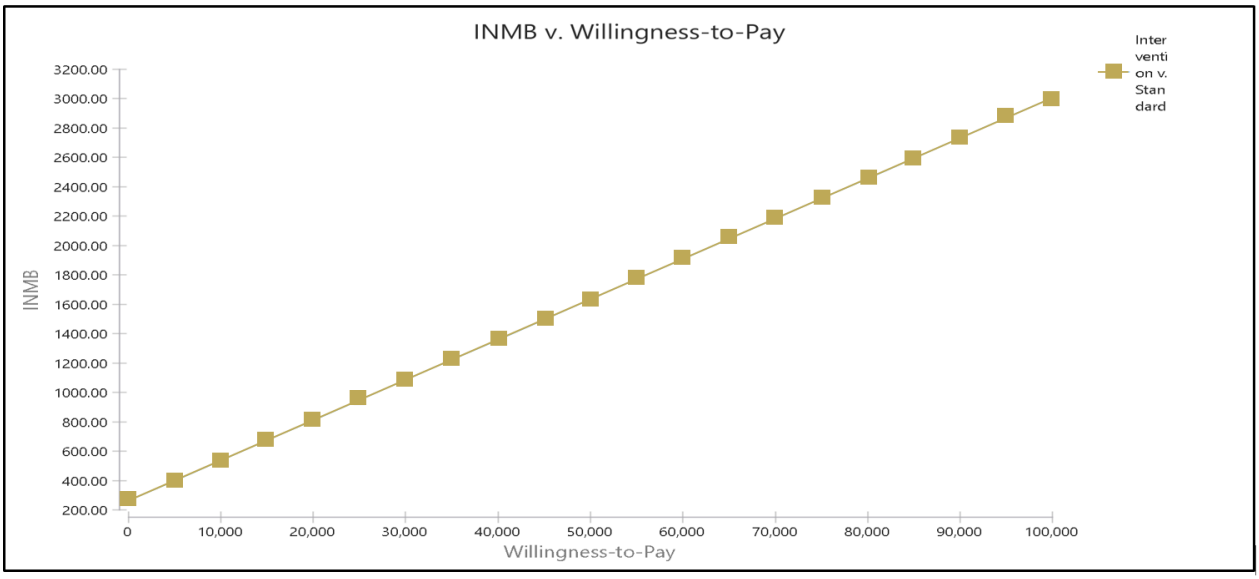

Figure 3: Mean incremental net monetary benefit over willingness-to-pay thresholds

Varying the model input estimates in a one-way sensitivity analysis (Figure 4) shows the INMB is sensitive, in addition to the change in TCL, to the mean age of the study population, the cost of the intervention, the annual cost of CVD, and the change in utility scores.

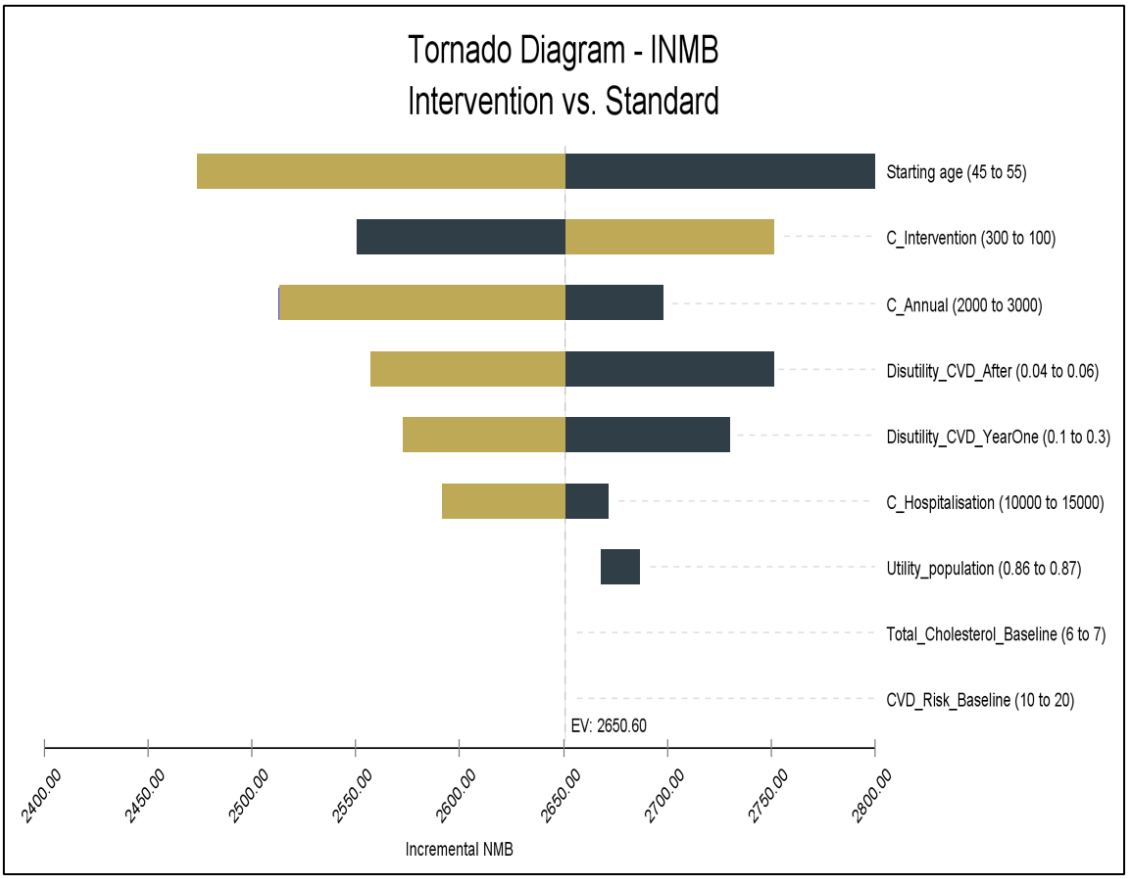

Figure 4: One-way sensitivity analyses

The uncertainty in the results of the cost-effectiveness analysis is characterised using 10,000 Monte Carlo simulations to sample from the probability distributions of the model parameters. The probability of the telehealth intervention being cost effective, at the $50,000 willingness-to-pay threshold is 55% (Figure 5). This means that the probability of the control being cost-effective is 45%, which represents the probability of making a wrong decision when adopting the telehealth intervention.

The cost-effectiveness acceptability curve in Figure 6 presents the probability of the telehealth intervention being cost-effective over a range of plausible willingness-to-pay thresholds. The probability of the telehealth intervention being cost-effective is not sensitive to the change in willingness-to-pay threshold since the intervention is cost saving and more effective compared with the control.

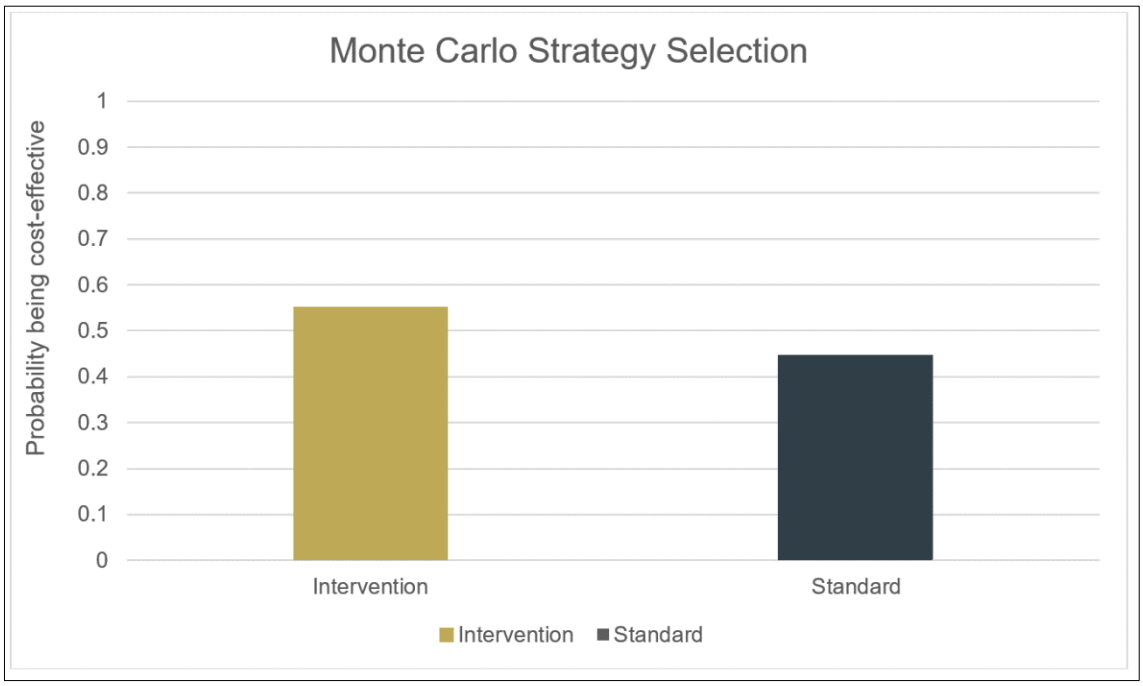

Figure 5: Probability the intervention will be cost-effective

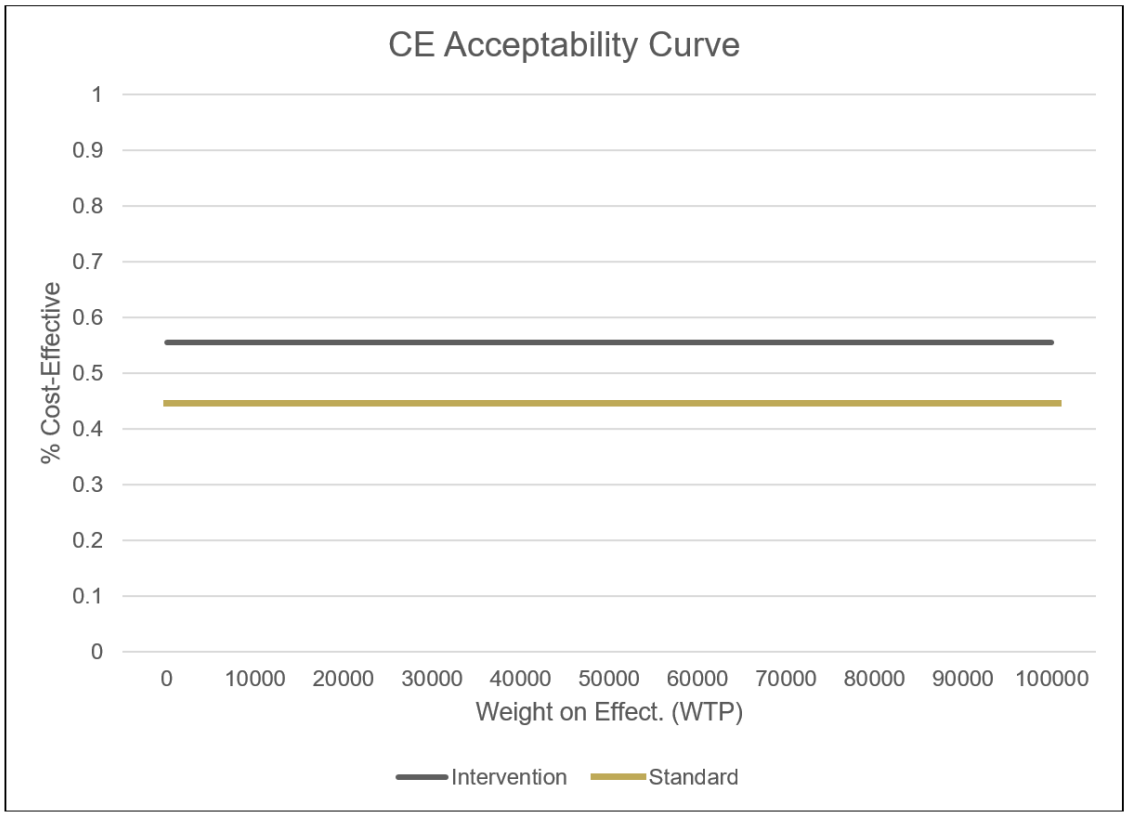

Figure 6: Cost-effectiveness acceptability curve

The expected value of reducing decision uncertainty

The EVPPI for the parameter of interest (reduction in TCL) at a willingness to pay threshold of $50,000 per QALY is $87. The population EVPPI is calculated by multiplying the EVPPI by the population expected to benefit from the results of the proposed RCT, which is $39,000,000 (i.e., $87 x 450,000). This value represents the upper bound of the expected monetary benefit of the RCT in resolving decision uncertainty. Figure 7 illustrates the change in EVPPI across a range of willingness-to-pay thresholds. The EVPPI is not sensitive to the change in willingness-to-pay because the intervention is dominant (i.e., cost saving and more effective).

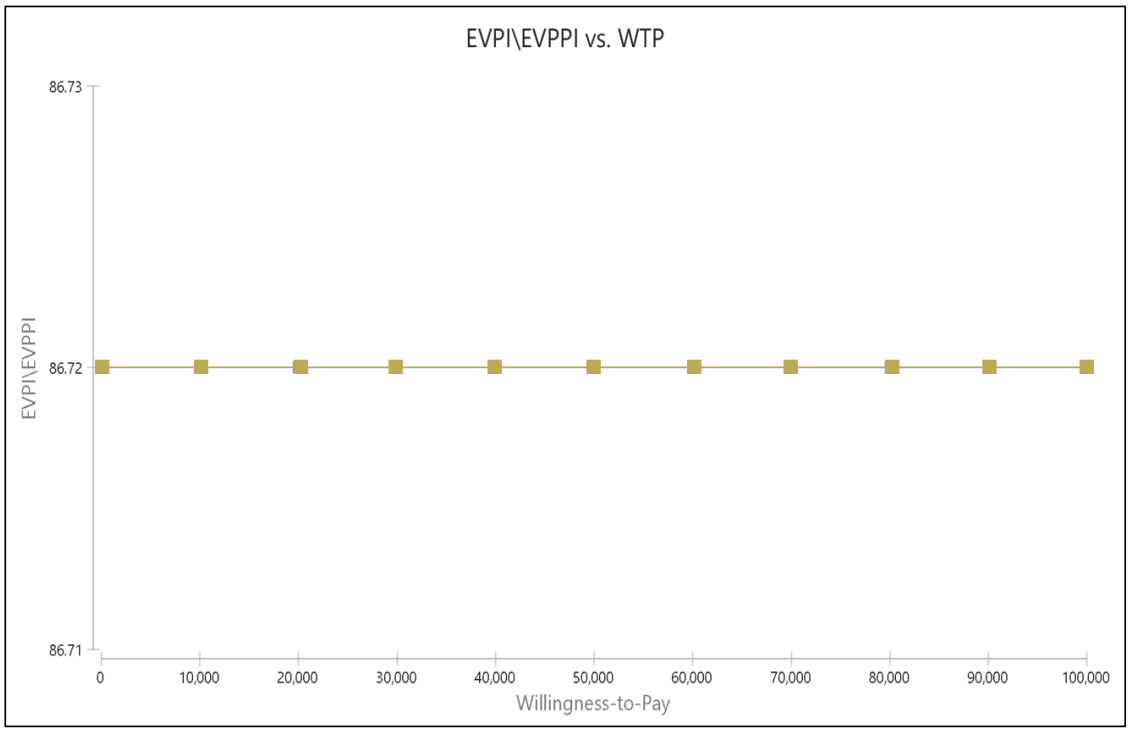

Figure 7: The expected value of perfect parameter information (EVPPI) over willingness to-pay-thresholds

The EVSI, which is the expected monetary benefit from the reduction in decision uncertainty from the RCT is presented in Fig 8. The EVSI increases as the sample size of the trial increases representing reduction in uncertainty with higher sample sizes. At the sample size planned for this RCT, which is 150 patients in each arm, the EVSI is expected to be $46; however, this estimate should be scaled up to the population expected to benefit from research outcomes. The population EVSI, for the sample size of 150 patients in each arm, is around $20,713,500 (i.e., $46*450,000).

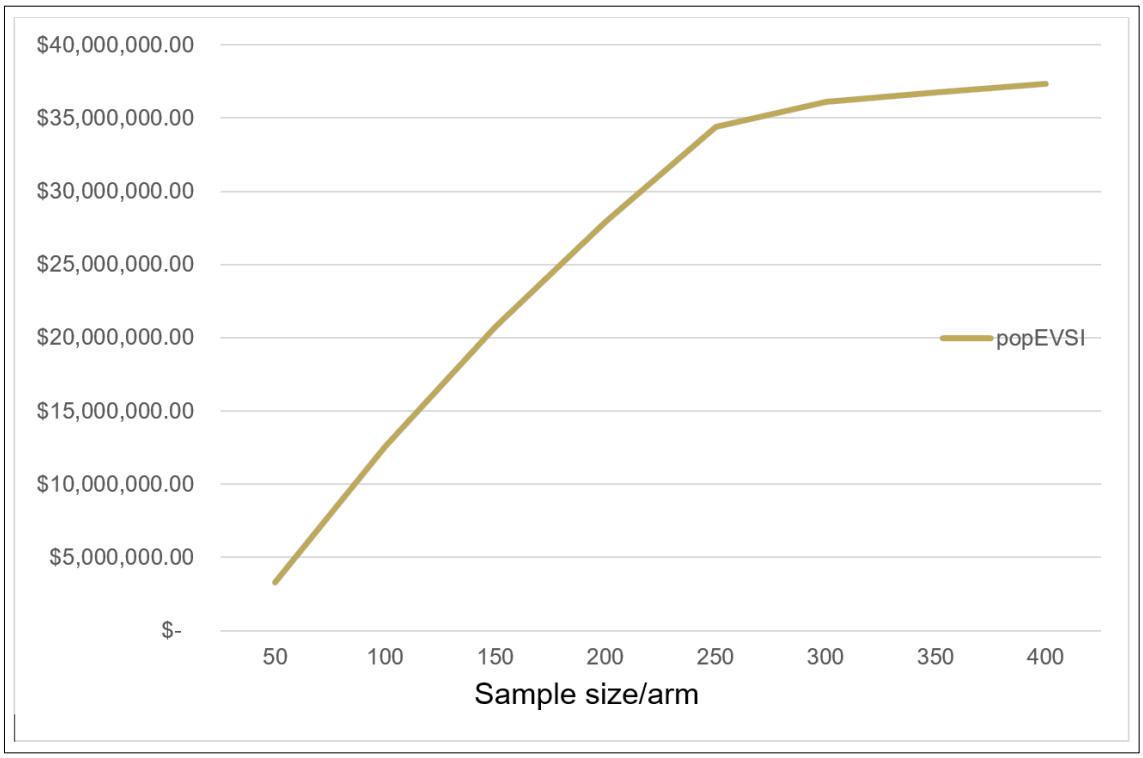

Figure 8: The expected value of sample information (EVSI)

The expected value of improved implementation

If the results of the new RCT confirm the expected benefits of the telehealth-based MNT intervention, and assuming the findings will improve implementation by 10%, the total attainable population who are expected to receive the intervention is expected to be 247,500 (i.e., a 10% increase from 225,000). The diffusion model predicts a more rapid increase in the uptake rate of the intervention during the first five years with the new RCT compared with the uptake rate if the RCT is not conducted (Figure 9).

The cumulative uptake of the intervention over time with and without the new RCT is presented in Figure 10. Because the difference between the two curves is time dependent, the average number of patients over time is used to estimate the difference in uptake improvement. The new RCT could enhance implementation with an expected improvement of 22,568 additional patients utilising the service over 10 years (178,192 versus 155,624). Multiplying this number by the INMB from the intervention (i.e., $1,750) gives us the expected value of the RCT in improving implementation, which is $39.5 million.

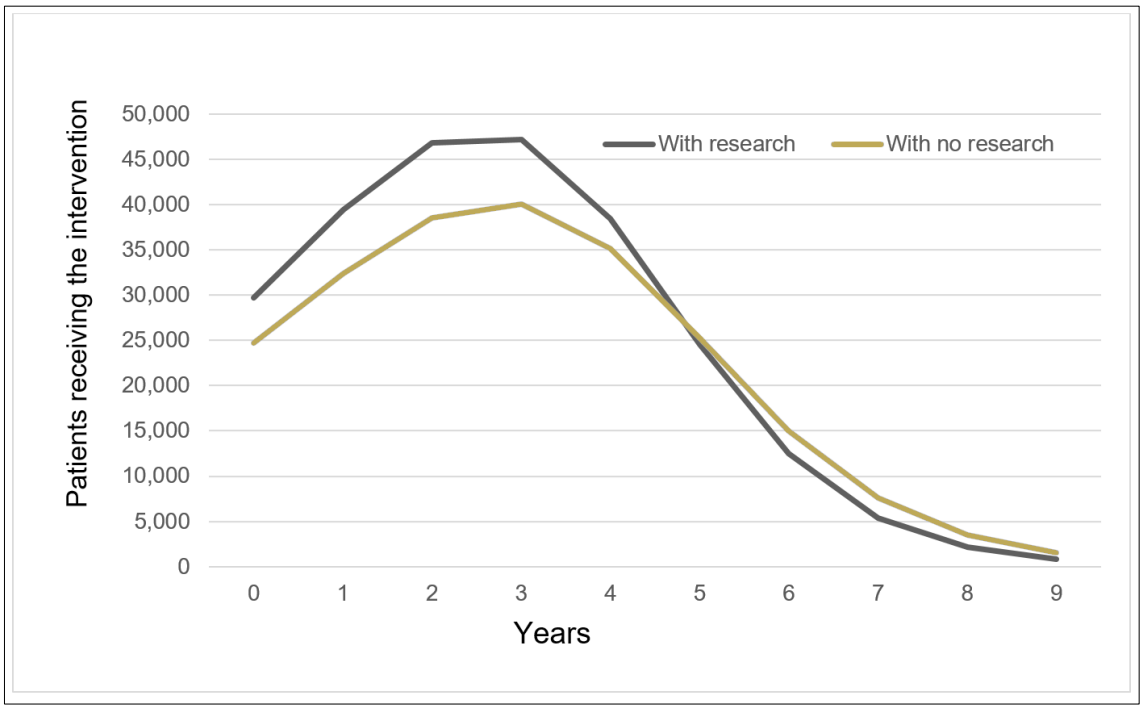

Figure 9: Number of patients using the intervention over time with and without the new RCT

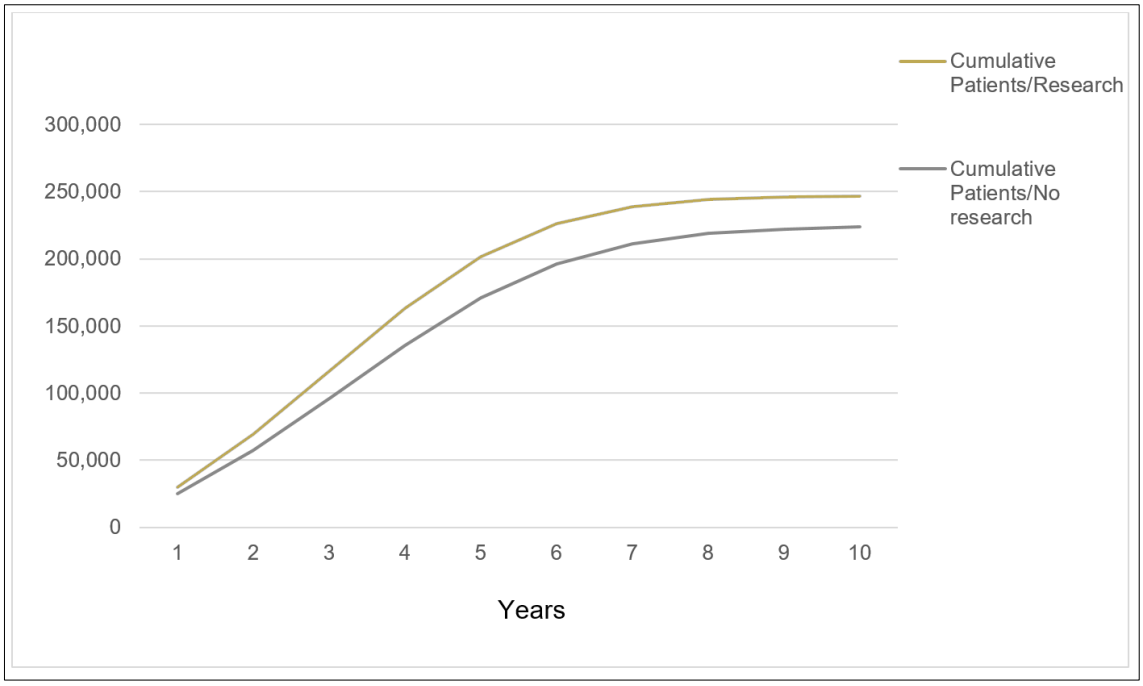

Figure 10: The cumulative number of patients using the intervention over time with and without the new RCT

Comparison of the RCT's total monetary benefits and costs

Combining both components of value, the reduction in decision uncertainty and the improved implementation is the expected value of research, which is $60,207,489 (i.e., $39,493,989 + $ 20,713,500). Compared with the budget requested, the clinical trial has an overall return on investment of (i.e., ($60,207,489 - $1,028,236)/ $1,028,236) which is around 5800%. This means that for every dollar spent on this trial the expected value of return is $58.

Scenario analyses

Table 3 shows the impact of varying key assumptions on the results of the VOI analyses. Despite the change in the base case key assumptions, the intervention remains cost-effective and the RCT has a ROI between 2800% and 7500%.

Table 3: Summary of the scenario analyses

Scenario	Results
Base case analysis	
Mean incremental net benefit	$1,750
Probability the intervention is cost effective	55%
Expected value of reduced uncertainty	$20,713,500
Expected value of improved implementation	$39,493,989
Expected value of research	$60,207,489
Expected return on investment	5800%
Cost of the intervention is $300 (base case is $200)	
Mean incremental net benefit	$1,514
Probability the intervention is cost effective	56%
Expected value of reduced uncertainty	$26,900,500
Expected value of improved implementation	$34,167,942
Expected value of research	$61,068,442
Expected return on investment	6000%
Time horizon of the cost-effectiveness analysis 10 years (base case is lifetime)	
Mean incremental net benefit	$580
Probability the intervention is cost effective	56%
Expected value of reduced uncertainty	$20,713,500
Expected value of improved implementation	$13,089,436
Expected value of research	$33,802,936
Expected return on investment	3300%
Start age 65 years (base case 50 years)	
Mean incremental net benefit	$1,656

Probability the intervention is cost effective	5700%
Expected value of reduced uncertainty	$20,250,000
Expected value of improved implementation	$37,372,597
Expected value of research	$57,622,597
Expected return on investment	5600%
Prevalence of moderate-high CVD risk 10%, eligible population 225,000 (base case prevalence is 19%; eligible population 450,000)	
Mean incremental net benefit	$1,750
Probability the intervention is cost effective	55%
Expected value of reduced uncertainty	$10,350,000
Expected value of improved implementation	$18,687,500
Expected value of research	$29,037,500
Expected return on investment	2800%
Attainable population for implementation is 450,000 (base case 225,000 (50% of eligible population))	
Mean incremental net benefit	$1,750
Probability the intervention is cost effective	55%
Expected value of reduced uncertainty	$20,713,500
Expected value of improved implementation	$68,348,569
Expected value of research	$76,688,588
Expected return on investment	7500%
Improvement of implementation due to research 5% (base case 10%)	
Mean incremental net benefit	$1,750
Probability the intervention is cost effective	55%
Expected value of reduced uncertainty	$20,713,500
Expected value of improved implementation	$20,394,679
Expected value of research	$41,108,179
Expected return on investment	4000%

Discussion

Using the VOI framework to prospectively estimate the return on investment of this RCT, the report evaluates the cost-effectiveness of the MNT intervention based on existing evidence, characterises decision uncertainty of this cost-effectiveness analysis and estimates the expected value of the RCT in reducing decision uncertainty and improving the implementation in practice.

The cost-effectiveness analysis shows that the intervention is potentially cost-effective. With a mean 0.03 QALYs gained and $250 saved per patient, and at a willingness-to-pay threshold of $50,000 per QALY gained,

the incremental net monetary benefit of the intervention is $1,750 per patient, indicating that the intervention is potentially cost-effective. However, the probability of the intervention being cost-effective is only 56%, suggesting that a decision based on the results of this economic evaluation might be uncertain. The expected value of the proposed RCT (with 150 patients in each arm) in reducing decision uncertainty is estimated to be $20.70 million. If the results of the proposed RCT confirm the expected benefits of the intervention, the implementation of the intervention in practice is expected to improve. If there is only 10% improvement in the uptake of the intervention as a result of this RCT, the expected monetary benefit of improved implementation is around $39.50 million. Thus, the total expected monetary benefit of the RCT is around $60.20 million. Comparing this figure with the proposed RCT budget of $1.03 million the expected return on research investment is around 5800%.

It is difficult to directly compare the results presented in this report with other published studies because this is the first cost-effectiveness analysis of a telehealth-based MNT intervention in reducing CVD risk in the primary care setting in rural and regional areas in Australia. It is also the first to prospectively assess the value for money of a clinical trial to provide the necessary evidence to inform the implementation of this intervention. Nevertheless, the results can be compared with those for other lifestyle telehealth interventions addressing CVD risk. For example, Graves *et al.* evaluated the cost-effectiveness of a telephone-delivered intervention for physical activity and diet.[54] Comparing telephone counselling outcomes to existing practice, the intervention was cost-effective with an incremental cost of $29,375 per QALY gained.[54] In another study, Cheng *et al*. evaluated a population-based lifestyle intervention to promote healthy weight, nutrition and physical activity for cardiac rehabilitation.[55] They showed that the intervention was cost effective with an additional cost of $972 and 0.04 QALYs gained per patient (i.e., $2,927 per QALY). In terms of relevant VOI literature, a recent study in the Netherlands applied VOI analysis to the problem of choosing between home-tele monitoring and nurse telephone support over usual care in chronic heart failure management.[56] That study estimated the VOI at €590 million for the population in the Netherlands over 20 years. Another study from the UK evaluated the cost-effectiveness and the VOI of brief interventions to promote physical activity in primary care. At a willingness-to-pay threshold of £20,000/QALY, the base-case VOI was £97 per-person and £1.85 billion in total to the NHS Health Check population.[57] Of note, none of these VOI studies estimated the value of improved implementation, which is an important element to consider when estimating the return on research investment.

In Australia, there has been an increasing interest in estimating returns on research investments. A recent report by the Australian Clinical Trials Alliance (ACTA) evaluated 25 high-impact clinical trials across three networks:[52] the Australasian Stroke Trials Network (ASTN), the Interdisciplinary Maternal Perinatal Australasian Collaborative Trials (IMPACT) Network, and the Australian and New Zealand Intensive Care Society. The report estimated that the gross research monetary benefit would be approximately $2 billion measured through better health outcomes and reduced health service costs, assuming implementation in 11% of the eligible patient populations.[52] Furthermore, the report estimated an overall return of $5.80 for every $1 invested by the clinical networks, and $51 in return for every $1 awarded in National Health and Medical Research Council (NHMRC) grants to the 25 trials. The return on investment estimated in ACTA's report is close to the return on research investment estimated in this report (i.e., $58 for each 1$), albeit this report

estimates this return on investment prospectively using the VOI analysis framework. The ability to prospectively estimate the return on investment of clinical trials is important for investigators who wish to demonstrate value for money of their research proposals, and for research organisations to set research priorities and allocate funds to research studies that maximise return on research investment. It is worth mentioning that the other prospective quantitative approach that could have been used in this report to estimate the return on research investment is the prospective-Payback approach; however, the Payback approach considers the health and monetary benefits of new research from improving implementation in practice with no consideration to the value of research in reducing uncertainty and improving decision making. As a result, the prospective-Payback approach does not capture the full monetary benefit of research and it cannot inform optimal (i.e., efficient) trial design (e.g., sample size and follow-up duration) to maximise return on research investment.[32, 58]

The strength of the analyses presented here include the application of the comprehensive and novel value of information analyses methods to prospectively estimate the return on investment of the proposed RCT. The approach considers the existing evidence, the potential cost-effectiveness of the intervention based on that evidence, the decision uncertainty and the consequences (e.g., monetary benefits forgone) of making a wrong decision under uncertainty, the size of the population affected by research results and the value of the RCT in reducing decision uncertainty at various sample sizes. This means that even if the intervention was not found to be effective and/or cost-effective in the RCT, there would be a value from the research in terms of reducing decision uncertainty and avoiding wasting health resources on a suboptimal intervention. The approach also estimates the expected health and monetary benefits from the improvement in implementation in practice if the results show the intervention is cost-effective. Importantly, the report builds on the diffusion model to dynamically estimate the level of intervention uptake over time with and without the results of the RCT.

A number of assumptions have been made in the presented analysis. The model used to link the change in TCL to long-term CVD outcomes does not include all types of CVD, but rather focuses on heart attack and stroke as the two main types of CVD. Furthermore, it does not consider all treatment options and possible medications to reduce TCL or CVD (e.g., cholesterol lowering drugs or aspirin). However, this type of 'minimal-modelling' is recommended in estimating the value for money of clinical trials when an intermediate outcome is reported or when the trial comprehensively captures all effects and costs of the intervention.[28, 34, 36, 38] Other assumptions have been made regarding the size of the population, the attainable population for intervention implementation, and the rate of implementation over time. The report uses CVD risk prevalence data from the literature and from the AIHW reports. For the attainable population, the analysis is conservative in assuming that only 50% of the eligible population would be targeted and that the new RCT would result in 10% improvement in implementation. Other parameters in the Bass diffusion model (i.e., coefficient of innovation and coefficient of imitation) could have been obtained in an official expert opinion elicitation exercise; however, this would be a time and resource intensive exercise. The coefficient estimates used in the model are based on published diffusion models of health technologies.[37, 51] The extensive sensitivity and scenario analyses conducted confirm that that the proposed RCT is potentially value for money with a return ranging from $28 to $75 for each $1 requested to fund the RCT. These estimates are also conservative since these monetary benefits are related to the expected improvement in population health; however, clinical trials in rural and

regional areas may bring additional economic benefits to society in terms of improving research and workforce capacity as well as enhancing clinicians and researcher retention in those regions. Future work should focus on estimating those additional societal benefits.

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A-1 Appendix A: Value of information analysis

Assume that we have a model informing a decision on a number of interventions (*i*). The model predicts NB (*i*, θ), which is the net benefit of *i* with unknown parameters (*θ*). A probabilistic sensitivity analysis (PSA) takes K samples from the joint distribution of *θ*, and generates a corresponding set of K net benefits (NB (i, θ_1),…, NB (i, θ_K)), for each intervention. Averaging these values, the optimal decision with current information is to adopt the intervention that produces the maximum expected NB, *maxi* E_θ *NB (i, θ).* With perfect information on *θ*, the maximised NB is *maxi NB (i, θ);* however, because the true value of *θ* is unknown, averaging the maximised values gives the expected maximum NB under perfect information, E_θ *maxi NB (i, θ).* The EVPI is the difference between the expected NB of a decision with perfect information and the decision based on current information:

EVPI = E_θ maxi NB (i, θ) - maxi E_θ NB (i, θ)

Using regression methods in R software (R Foundation, Vienna, Austria) as described by Strong et al Using the PSA sample of 10,000 iterations (K=10,000), a regression model is fitted for each decision option. After that we extracted the regression-model–fitted values denoted as $\hat{g}(i,\theta_{kI})$ and calculated EVPPI by the following equation:

$$EVPPI_{\theta_I} \cong \frac{1}{K}\sum_{k=1}^{K} max_i\, \hat{g}(i,\theta^k{}_I) - max_i\, \frac{1}{K}\sum_{k=1}^{K} \hat{g}(i,\theta^k{}_I)$$

To calculate EVSI, we generated data and calculated the summary statistics D^k conditional on each sample $\theta_I{}^k$ in the PSA. Then, we fitted a regression model for each decision option and extracted the regression-model–fitted values denoted as $\hat{g}(i,D^k)$ and calculated EVSI based on the following equation:

$$EVSI \cong \frac{1}{K}\sum_{k=1}^{K} max_i\, \hat{g}(i,D^k{}_I) - max_i\, \frac{1}{K}\sum_{k=1}^{K} \hat{g}(i,D^k{}_I)$$

A-2 Appendix B: Bass model

The basic equation for the Bass model:

$p + (q/m)\, N\, (t - 1)$ is the likelihood of use by a new adopter in time period *t.*

$m - N\, (t - 1)$ is the number of consumers who have *not* previously adopted the new product by the start of time period *t*; this is the pool from which new adoptions in the current period can occur.

In its simplest form, the Bass model looks as follows:

$S\,(t) = [p + (q/m)\, N(t - 1)]\, [m - N(t - 1)]$

Where S (t) is the number of new adopters during time t.

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