QIMR Berghofer
Medical Research Institute

D-Health

The D-Health Trial

Clinical Trial Protocol
Version 16: 15 March 22

Name of Sponsor:	**QIMR Berghofer Medical Research Institute (QIMR Berghofer)** 300 Herston Rd Herston, QLD 4006
QIMR Berghofer Reference:	**P1519**
Project Coordinator:	Dr Rachel Neale
Sponsor:	QIMR Berghofer Medical Research Institute, Brisbane
Funding:	National Health and Medical Research Council, Project Grant 1046681
Duration:	2013-2022 (note: funding is currently available for 5 years – the project timeline is 10 years)

Revision No.	Section	Details	Initials/Date
1.1	1.8	Supplier of investigational product added	REN 16/4/13
1.2	9.2	Information about formulation including excipients added	REN 16/4/13
1.2	9.3	Label altered to include QIMR address, number of tablets, date	REN 22/4/13
2	Multiple	QIMR changed to QIMR Berghofer throughout	REN 21/8/13
2	1.8	Specify that laboratory where serum vitamin D testing will occur will not be chosen until 2015.	REN 21/8/13
2	7	Changed to specify that the Northern Territory will not be included.	REN 21/8/13
2	7.5	Number of prizes that will be drawn changed from 7 to 6 due to exclusion of the Northern Territory.	REN 21/8/13
2	8	Changed to remove the Northern Territory	REN 21/8/13
2	8.3	Information added about reminder follow-ups by email, postcard or phone for participants who do not return the baseline survey and consent form.	REN 21/8/13
2	9.3	Phone number on label changed to new 1300 number.	REN 21/8/13
3	9.3	Label changed to remove the tablet type	REN 8/11/13
3	7	Changed to specify that volunteers will be able to participate	REN 8/11/13
3	8	Changed to specify that volunteers will be able to participate	REN 8/11/13
3	8.3.1	Section added to describe process for enabling volunteers to participate in the trial	REN 8/11/13
4.1	8.1	Changed to allow VOLUNTEERS older than 79 to participate	REN 28/5/14
4.1	8.2	Exclusion criteria – osteoporosis removed	REN 28/5/14
4.1	8.3.1	Specify that we will invite people who were in the pilot trial to participate	REN 28/5/14
4.1	13.4	Specify that we will contact participants who withdraw as a result of an adverse event if the event has not resolved at the time of withdrawal	REN 28/5/14
4.1	13.4	Specify that the study physician will be asked to review AEs before the report is submitted to the DSMB and sponsor	REN 28/5/14
4.2	8.2	On request of HREC chair the sentence ‘Have any of the following medical conditions (which either preclude or require high dose vitamin D supplementation or prevent informed consent)’ has changed to ‘Have any of the following medical conditions (which either preclude or require high dose vitamin D supplementation) or which prevents informed consent’	REN 19/6/14

Revision No.	Section	Details	Initials/Date
6	9.2	Updated product specifications	REN 10/4/15
6.1	9.2	Additional information about stability, date of use of new formulation, recording which batch was dispensed, analysis accounting for new batch (at the request of the HREC secretariat)	REN 1/5/15
6.1	10	Additional information to specify that sensivity analyses will be performed to assess the effect of changing the formulation	REN 1/5/15
6.2	14.2	Information about statistical analyses to account for the change in formulation	REN 26/5/15
7	9.6	Updated to accommodate future use of samples	REN 23/6/15
7.1	9.6	Subsections 9.6.1, 9..6.2 and 9.6.3 added in response to comments from the CTPC – accommodates sharing of samples/data for studies of vitamin D and health and future use of samples	REN 13/7/15
7.2		Study physician changed	REN 30/7/15
7.2	9.6.3	This section has been removed. Participants will not be asked to consent to future unspecified use of samples.	REN 30/7/15
8	10	Additional information included to specify that cognition will be measured using a telephone interview.	REN 13/1/16
8.1	10	Additional information added about sample size for cognition surveys	REN 29/1/16
9	9.6.1	Modification of section on 25(OH)D assays to provide more flexibility in who does the testing	REN 15/2/16
10	4	Additional information about falls included	REN 15/6/16
10	10.1	Information about administration of falls diaries included	REN 15/6/16
10	8.4	Changes to allow participants who have had a temporary high calcium or parathyroid hormone to remain in the trial.	REN 15/6/16
10	13.4	Modified to specify that adverse events (falls) identified through falls diaries will be included in the biannual reporting to the sponsor and the HREC	REN 15/6/16
11	13.4	Changes made regarding reporting adverse events in accordance with request from the HREC	REN 3/8/16
12	4	Background information about acute respiratory infection added	REN 9/3/17
12	10.1	Methods of data collection for acute respiratory infection added	REN 9/3/17
13	9.6	Blood collection amended to include short survey	REN 20/6/17
13.1	7	Flow chart amended to refer to blood collection participants' survey	REN 6/7/17
13.1	10.1	Reference to the blood participants survey	REN 6/7/17
13.1	7.5	Information about participant engagement (newsletters and forums) added	REN 6/7/17
14	11.2	Section 11.2 added regarding selecting participants to take part in the D-Health Microbiome Project (P2365)	REN 5/3/18

Revision No.	Section	Details	Initials/Date
15	7.6	Alteration to specify that the study will be unblinded after all participants have finished taking tablets and surveys are logged, but strategies implemented to avoid study staff, analysts, and investigators becoming aware of the tablet assignment.	REN 17/12/19
16	1.8	Specifying laboratory where the telomere length analysis is occurring.	REN 15/03/22

Investigator statement and signature sheet

The D-Health Trial

Project number: P1519
Protocol date: 15 March 2022

By my signature I confirm that my staff and I have carefully read and understood the protocol and agree to comply with the conduct and terms of the study specified herein. I understand that the trial will be conducted in compliance with the Good Clinical Practice Guidelines adopted by the TGA (2000) and the National Statement (2007) and agree:

1) To obtain local ethical committee approval of the study and to advise them of any amendments to the protocol, serious adverse events and advertising associated with the study. Periodic reports will be submitted to the ethics committee as required.

2) To obtain informed consent (written or online) from each participant

3) To permit monitoring, audits, review by the sponsor, the relevant HRECs, and regulatory inspections by providing direct access to source data and trial related documents.

4) To make timely reports of serious adverse events to the sponsor.

5) To maintain confidentiality and ensure security of all documentation relating to the study including the protocol, information pertaining to participants, unpublished data and correspondence. All study documents are required to be stored securely for a period of at least 15 years following completion of the study and may not be destroyed without written permission from sponsor.

Signatures and Date:

Rachel Neale  Date: 15/3/22

Table of Contents

1 General Information

1.1 Protocol full title

The D-Health Trial

Short title: The D-Health Trial

1.2 Trial sponsor and monitor

Trial sponsor: QIMR Berghofer Medical Research Institute
300 Herston Rd, Herston 4006

Trial monitor: Clinical Network Services Pty Ltd
Level 4, 88 Jephson Street
Toowong, QLD, 4066

1.3 Authorised signatory of sponsor

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1.4 Authorised signatory for protocol and protocol amendments

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1.5 Chief investigator

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Trial site: QIMR Berghofer Medical Research Institute, 300 Herston Rd, Herston QLD 4006
Phone +61 7 3362 0222

1.6 Sponsor's independent medical monitor for the trial

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North West Academic Centre, Level 3, Western Centre for Health Research and Education
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1.7 Physician responsible for all trial-site related medical decisions

Dr Donald McLeod
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QIMR Berghofer Medical Research Institute
Department of Endocrinology and Diabetes
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Royal Brisbane & Women's Hospital
Butterfield St, Herston, QLD, 4029
Phone (04) 3557-4079 Fax +61 07 3845 3503 Email: Donald.mcleod@qimrbergofer.edu.au

1.8 Clinical laboratories, medical and technical department or institutions involved in the trial

- Datatime Services Pty Ltd, 1/318 Auburn Rd, Hawthorn VIC 3122
- Investigational product supplier
  Lipa Pharmaceuticals Ltd, 21 Reaghs Farm Road, Minto NSW 2566
- 25(OH)D testing

Centre for Metabolomics, University of Western Australia, Bayliss building (M316), 35 Stirling Highway, WA Crawley 6009

- 25(OH)D testing (using immunoassay) and other pathology testing as required
  Commercial pathology laboratories
- Telomere length testing: Telomere Length Regulation Unit, Children's Medical Research Institute, 214 Hawkesbury Rd, Westmead, NSW, 2145

1.9 Contact details for QIMR Berghofer regulatory affairs (for safety reporting)

Phone: 07 3362 0433
Email: Dept_Regulatory_affairs@qimrberghofer.edu.au
Fax: 07 3362 0109

2 Background, rationale and objectives

2.1 Background to the trial

The role of vitamin D in preventing rickets and osteomalacia in adults is well-established. More recent evidence suggests that vitamin D plays a role in many disease processes, such as mental health disorders, cardiovascular and autoimmune diseases, diabetes and cancer risk and survival.[1] In Australia, the number of vitamin D tests ordered by general practitioners increased by 10-fold from 22,670 tests in 2000 to 2.2 million tests in 2010, costing approximately $90 million annually.[2] However, there is no clear evidence that knowing a patient's serum vitamin D level (estimating by measuring circulating 25-hydroxyvitamin D (25D)) will materially improve their future health. Importantly, the level of serum 25D needed to optimise health outcomes is unknown and the source of considerable debate.[3]

Most studies supporting a role of vitamin D in prevention or survival from chronic disease have been observational, and inferring causality is problematic. Reverse causality and residual confounding are potential biases that are particularly relevant for interpreting studies of vitamin D, since its levels are determined by factors such as physical activity, obesity and diet, all of which are also strongly associated with numerous chronic diseases.[1] The only valid way to infer causality is through randomised trials. The literature is replete with examples of nutrients associated with disease in observational studies, but proven to have no beneficial, and sometimes even a potentially harmful effect in trials. For example, trials of beta-carotene, vitamin E and folate have all shown the potential for increased risks of cancer and mortality in those assigned to receive the active ingredient, while failing to confirm apparently beneficial effects seen in observational studies.[4]

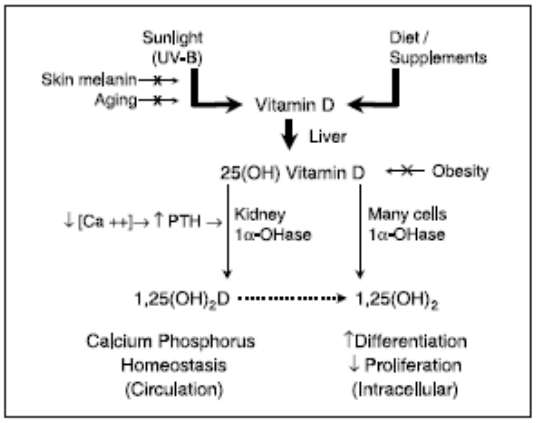
We are at the point where we need to conduct large-scale trials in the general population in order to provide rational evidence-based public health and clinical advice about vitamin D. While there are many small trials occurring in highly selected populations (for example, people with specific diseases), we know of only two other trials that are powered to address cancer and/or mortality outcomes in the general population, the Vital D Study in the United States[5] and the FIND study in Finland. The FIND study is not including all-cause mortality as a primary outcome, even though that is where the strongest existing evidence currently lies. Both of these studies, which are recruiting 20,000 (Vital D) and 18,000 (FIND) people, are being carried out in populations with vastly different ambient ultraviolet exposure. The Vital D Study population has a very different ethnic make-up as African Americans are deliberately oversampled. Any results derived from these trials may therefore not be completely applicable to Australia. Moreover, the power of any single study to analyse associations with less frequent health outcomes and to explore factors that might modify the effect of vitamin D supplementation is limited. Multiple trials are needed, and carrying one out in Australia will generate data that has direct health implications for the health of our population.

3 Name and description of the investigational product

Participants will be randomized to receive either 60,000 IU of cholecalciferol (vitamin D3) or placebo once per month, provided in a gelcap formulation.

Vitamin D_3 (cholecalciferol) is produced in the skin when ultraviolet B photons are absorbed by 7-dehydrocholesterol, present in the lipid bilayer of the plasma membrane of epidermal keratinocytes and dermal fibroblasts. It is also found in foods such as egg yolk and fatty fish. Vitamin D_3 is not biologically active. Rather it must be converted firstly in the liver to 25D and then in the kidneys or in target tissues to 1,25-dihydroxyvitamin D (1,25D), the biologically active form which attaches to cellular vitamin D receptors (figure).

The half-life of 25D is several weeks, while that of the active 1,25D is only a few hours. 1,25D production is stimulated by parathyroid hormone and decreased by calcium in processes that are tightly regulated by the kidneys. In contrast, hepatic synthesis of 25D is relatively loosely regulated, and serum levels are largely a reflection of the amount of vitamin D_3 either produced in the skin or ingested. 25D is therefore used as the marker of an individual's vitamin D status.



Definitions of what is considered 'sufficient' circulating 25D vary and are a subject of controversy.[6] Vitamin D deficiency is usually described as serum 25D below 25 nmol/L; insufficiency where 25D is between 25 and 50 nmol/L; and adequacy, where 25D is greater than 50 nmol/L. However, there is some evidence that levels of at least 75-80 nmol/L are required for maintenance of optimal health.[7]

3.1 Currently recommended vitamin D levels and intake

There is considerable debate about the optimal 25D level for human health.[8] A 2011 review by the United States Institute of Medicine concluded that the only health outcome for which a causal association has been established is bone health, and that 50 nmol/L of circulating 25D is sufficient.[9] This recommendation has been challenged on two fronts. Firstly, the level of 25D needed to minimise parathyroid hormone (PTH) (and therefore bone loss) is debatable, with a recent study confirming that 50 nmol/L is sufficient[10] but others suggesting a threshold of at least 75 nmol/L.[11] Secondly, some scientists feel that links with other chronic diseases are causally established,[12] with suggested optimal levels ranging from 75 to 110 nmol/L.

Based on a required serum 25D level of 50 nmol/L and assuming minimal vitamin D production from sun exposure, the United States Institute of Medicine (IOM) set recommended daily intakes of 600 IU for adults under 70 years and 800 IU for people aged over 70. However, to increase mean 25D levels by approximately 30 nmol/L (needed to increase the mean of most populations to 75 nmol/L) an intake of 2000 IU/day is necessary.[13]

3.2 Toxicity

Vitamin D toxicity is essentially due to hypercalcaemia, which causes psychological and gastrointestinal symptoms, and in severe cases, coma and cardiac arrest. It has been estimated that blood 25D concentrations have to be at least 250nm/L before vitamin D toxicity will occur [14]. Pharmacokinetic studies show that peak concentration after a dose of 100,000 IU is not remotely close to this level, even among people whose baseline levels are sufficient[15]. In longer term studies of 100,000 IU administered every four months no adverse events were reported[16]. A recent publication suggests a no adverse event limit of 10,000 IU/day [17] and daily dosing with 11,500 IU/day for 20 weeks did not result in any instances of hypercalcaemia among 67 participants. One randomised trial gave 500,000 IU annually - one month after dosing the median 25D level was approximately 125 nmol/L (IQ range approximately 100-150 nmol/L)[18]. We recently completed a pilot trial of vitamin D, in which we gave participants placebo, 30,000 IU or 60,000 IU/month. We reported one instance of borderline hypercalcaemia in a participant randomised to 60,000 IU but the participant's vitamin D level was well within the normal range (<75 nmol/L) suggesting that vitamin D consumption was not responsible for the hypercalcaemia.

The IOM has set a 'No adverse event level' of 10,000 IU/day, but to allow for uncertainty about chronic health outcomes the 'tolerable upper intake level' has been set at 4,000 IU/day.

4 A summary of findings from non-clinical and clinical studies that potentially have clinical significance to the trial

Sub-optimal levels of vitamin D have been implicated in the aetiology of about 30 different diseases, including some cancers, diabetes, cardiovascular disease, autoimmune diseases and mental health disorders such as depression and cognitive decline. This background concentrates on cancer, cardiovascular disease and mortality.

Cancer: Vitamin D has a range of anti-cancer activities *in vitro*, regulating cell differentiation, apoptosis, proliferation, angiogenesis and metastatic potential.[19, 20] Currently, the only cancer for which there is consistent observational evidence of a protective effect of vitamin D is colorectal, where two meta-analyses of cohort studies have both shown a relative risk of approximately 0.66 (comparing the risk in the highest versus the lowest serum 25D category for each study). [21, 22] Because colorectal cancer is strongly related to lifestyle factors such as physical activity, diet and obesity, all of which are associated with vitamin D, uncontrolled confounding may well explain the association. Data from three randomised trials do not support a protective effect of vitamin D on colorectal cancer incidence,[16, 23, 24] but the largest of these, the Women's Health Initiative (WHI) trial,[24] has been criticised on the grounds that the dose of Vitamin D was too low and compliance was inadequate.[25] The influence of vitamin D supplementation on colorectal cancer needs to be tested more rigorously in large-scale trials.

The other cancers for which there are most data, breast and prostate cancer, show inconsistent results. A meta-analysis of breast cancer shows a strong protective association of serum 25D from traditional case-control studies, but a much smaller association from nested case-control studies.[26] For prostate cancer, a meta-analysis of prospective studies found a marginally significant 14% relative **increase** in risk for each 1000 IU increase in vitamin D intake and a 4% relative increase for each 25 nmol/L increase in serum 25D.[27]

For pancreatic cancer, several[28, 29], but not all,[30] cohort studies, have shown that people with serum 25D levels over 100 nmol/L had increased risk.

Cardiovascular disease: Among the pleiotropic effects of vitamin D are effects on cardiomyocytes, the endothelium and vascular walls, renin production and the endocrine system, all of which make a role for vitamin D in influencing heart disease risk plausible. Ecological studies have reported higher rates of coronary heart disease, hypertension and diabetes with increasing distance from the equator. Several cross-sectional and longitudinal observational studies have supported these findings, showing inverse associations between sun exposure or serum vitamin D and risk of diabetes, obesity, high blood pressure, and major cardiovascular events.[31-34]. However, as with colon cancer, lifestyle is a strong predictor of cardiovascular disease, and the limited trial data do not support an association between vitamin D and cardiovascular events.[16, 35]

Total mortality: A recent meta-analysis of 11 cohort studies found that people with a serum 25D level of 75 nmol/L had a risk of dying 31% lower than those with a level of 25 nmol/L.[36] With further increases in serum 25D there was a small non-significant increase in risk. The best evidence supporting a role of vitamin D in mortality comes from a recent meta-analysis of trials ranging in size from 55 to 36,282 participants, with the majority having under 1000.[37] This analysis found a statistically significant 7% reduction in total mortality in people randomised to varying doses of vitamin D (minimum 400 IU/day). However the trials were carried out in predominantly elderly women who were mainly in institutions and total mortality was reported mostly as a secondary outcome to bone health. In some cases there was no linkage to ensure complete capture of events. In addition, the cohort studies suggest a possibly much stronger effect. Thus there is evidence that supplementing with vitamin D prolongs life, but it requires confirmation in a trial powered with mortality as a primary endpoint.

***Falls*:** There have been many meta-analyses of vitamin D supplementation and falls. Two of these are described in detail below: (1) The most recent meta-analysis that included all available trials of vitamin D supplementation and falls;[38] (2) A meta-analysis that focused specifically on high-dose intermittent supplementation.[39]

Bolland and colleagues found non-significant protective effects of vitamin D alone or vitamin D plus calcium on the risk of falling (see figure below).[38] There were no interactions with duration of the trial, baseline 25(OH)D, residential status or whether falls was a primary or secondary endpoint. They did not analyse the data separately for trials using high-dose intermittent supplementation.

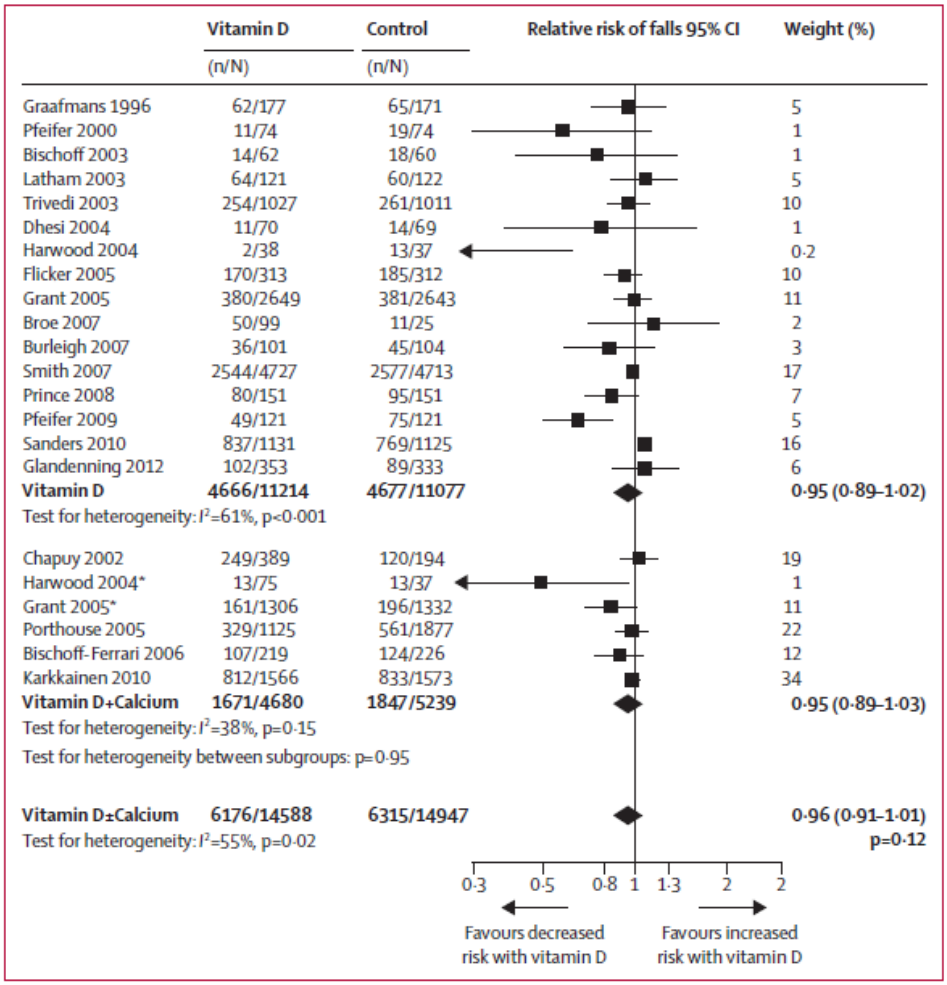


***Figure 1*: Random effects meta-analyses of the effect of supplementation with vitamin D, vitamin D with calcium, and vitamin D with or without calcium on falls**
*Multi-arm or factorial studies permitting a separate comparison of vitamin D with calcium versus controls or calcium.

Zheng and colleagues restricted their meta-analysis to trials that had used intermittent high-dose supplementation and found no effect on the risk of falls.[39] However, most of the trials included used ergocalciferol (vitamin D2) so these results cannot necessarily be extrapolated to vitamin D3 supplementation. Of the three trials included in the meta-analysis that used vitamin D3 (marked with asterisks in the figure below), the Trivedi study used 100,000 IU every 4 months, the Sanders study used 500,000 IU annually and the Glendenning study used 150,000 IU every 3 months combined with calcium. There was no protective effect observed in any of these studies and the Sanders study showed an increased risk.

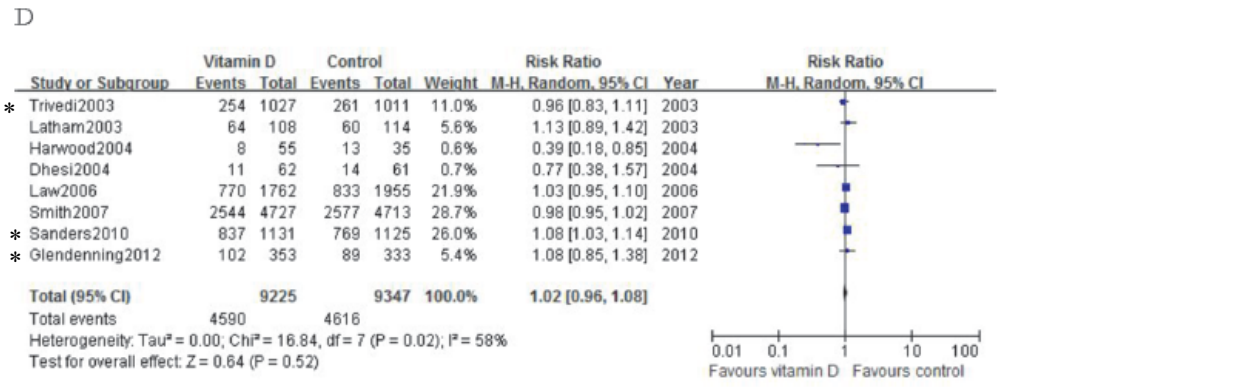


Figure 2. Meta analysis of overall mortality (A), hip fracture (B), non-vertebral fracture (C), fall (D) in participants treatment with high dose, intermittent vitamin D compare with control.

Since the publication of these meta-analyses another paper has been published in which people at high risk of falling were randomised to 60,000 IU of cholecalciferol, 24,000 IU cholecalciferol + 300µg of calcifediol (2-3 times more potent liver metabolite of vitamin D) or 24,000 IU cholecalciferol per month.[40] Falls was a secondary endpoint. Higher proportions of those in the two higher-dose groups fell during the 12-month trial period (67% and 66%) than in the lower dose group (48%; p<0.048 for the three group comparison). When the 60,000 IU vs 24,000 IU results are combined with those of the three studies included in the above meta-analysis, the pooled estimate was not significant: 1.07 (95% CI 0.97-1.19) but with moderate heterogeneity (I^2=45%).

In light of these findings a more in-depth assessment of falls in the D-Health Trial is important. In our annual surveys we currently ask participants to report whether or not they have fallen in the previous month and also if they have fallen in the past year. While our question that restricts the time frame to the previous month is likely to be reasonably accurate, and the proportion that reports falling is consistent with that reported in other studies, the gold standard for falls studies is to use a falls diary to aid recall.

Acute respiratory infections

Case-control and cohort studies conducted in diverse settings report consistent independent associations between low circulating 25(OH)D concentrations and susceptibility to acute respiratory infections (ARI). However, randomised controlled trials (RCTs) of vitamin D supplementation for the prevention of ARI have yielded conflicting results. Five aggregate data meta-analyses incorporating data from up to 15 such studies have been conducted to date, of which 2 report protective effects [41, 42] and 3 report no such effect.[43-45] All but one of these aggregate data meta-analyses reported significant heterogeneity of effect between trials.

An individual patient data meta-analysis has recently been published which concluded that vitamin D supplementation reduces the risk of ARI (odds ratio=0.80; adjusted incidence rate ratio=0.91).[46] There was significant heterogeneity across studies, and giving a bolus dose (less frequently than weekly) did not have the same benefit as daily or weekly dosing. However, several bolus dosing studies used 2- or 3-monthly dosing, and it has been suggested that monthly is the maximum dosing interval that maintains a physiological

state. Further, 25% of the adult participants came from the pilot D-Health trial which used a suboptimal method of measuring the incidence of ARI – this would have biased the results towards the null. More studies are therefore needed to explore whether vitamin D supplementation of adults using a bolus dosing regimen influences risk of ARI.

5 Summary of the known potential risks and benefits

The potential benefits are improved bone health and reduced mortality. While vitamin D toxicity can occur and causes hypercalcaemia, the risks are negligible at the proposed doses. Longer-term negative consequences are unclear, but a meta-analysis of trials with a mean of 5.7 years follow-up showed a significant reduction in mortality so longer-term negative consequences are unlikely.

6 Trial Objectives

To conduct a randomised placebo-controlled trial to assess the impact of vitamin D supplementation of Australians aged 60-79 years on the following health outcomes:

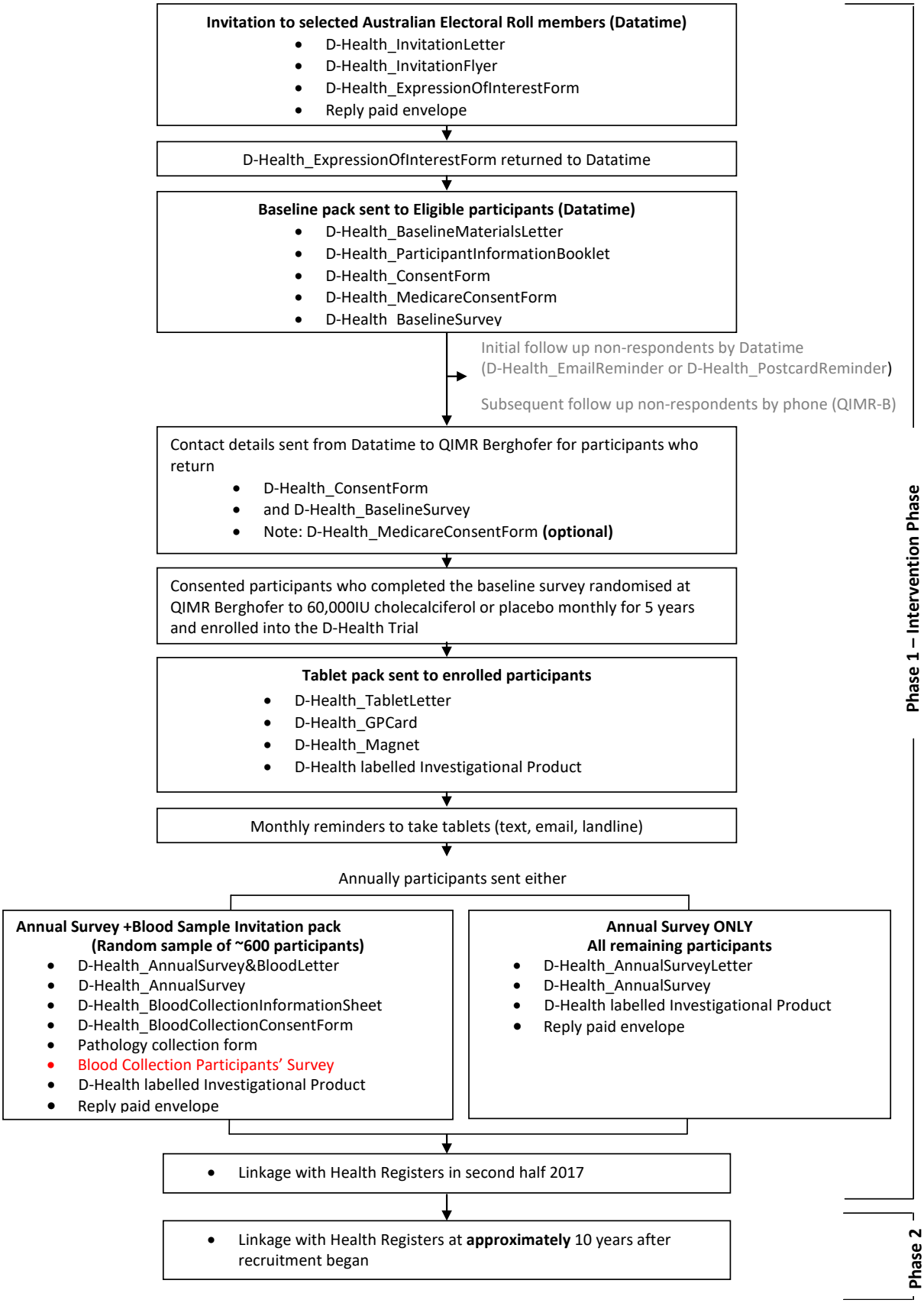
1. Primary: All cause mortality
2. Secondary: Total cancer incidence, colorectal cancer incidence.
3. Tertiary: Total cardiovascular events, depression, upper respiratory illnesses, exacerbations of asthma or chronic obstructive pulmonary disease, hyper- or hypothyroidism, diabetes, high blood pressure, falls, fractures, arthritis, use of anti-inflammatories, use of antibiotics, cognitive decline, overall self-reported health status, muscle aches and pains.

7 Trial design

This study is designed as a randomised placebo-controlled double-blind trial with participants randomised into one of two arms: placebo or 60,000 IU, each taken once a month for 5 years. The trial will be conducted in the whole of Australia (with the exception of the Northern Territory). Participants will be selected from the Australian Electoral Roll and invited to participate by post. Volunteers will also be allowed to participate in the trial. The power calculations suggest a required sample size of 25,000 people. Due to the recruitment strategy it is possible that a small number of extra participants will be recruited. The upper limit will be 27,000 people. An overview of the recruitment and follow-up is shown in the figure below and further described in the following sections.

Participant flow through D-Health

(including documents used)



7.1 Overall duration of the trial

Minimum 15 years: 5 years per participant of supplementation, a minimum of 5 years per participant of passive follow-up and approximately 5 years of data analysis and publication.

7.2 Duration of recruitment

We anticipate that recruitment will take approximately 12 months from initiation.

7.3 Duration of participation

Participants will be actively involved in the trial for approximately 5 years (phase 1), after which there will be no additional active involvement but we will obtain information from health registers for a minimum of a further 5 years (phase 2).

7.4 Nature of participation

1. Completion of baseline consent and survey
2. Randomisation to monthly vitamin D or placebo, with monthly reminders
3. Annual surveys
4. Potential selection for blood sample collection: this is for monitoring differences in serum 25D between the two arms of the trial. A random sample of 600 participants will be selected each year – participation in this aspect of the trial will be optional.

7.5 Participant incentive and engagement

For each year that participants are in the trial they will be given the opportunity to win one of six Coles Group and Myer gift cards valued at $200 each (one for each state. ACT will be considered part of NSW). The first draw will occur approximately 14 months after the first participants are recruited. Assuming recruitment takes 12 months as planned, this ensures that those recruited at the end of the recruitment period have been in the study for several months before they go into the draw.

The winner will be selected by grouping participants according to state, and then using computer-generated random numbers to pick one winner from each state. The winner will be notified by email, phone or in writing.
Newsletters: We will send newsletters one to two times per year.
Question and Answer Forums: We aim to run forums in capital cities during which we will give a short presentation, participants will be given the opportunity to ask questions and we will have informal discussions over morning tea. If participation in the first forum is low (fewer than 30 participants) subsequent forums will not occur.

7.6 Randomisation and breaking of codes

Participants will be randomised into one of the two groups. Tablets will be supplied to QIMR Berghofer by an external company that will meet good manufacturing practice (GMP) standards, labelled as A and B. The code will be held by the tablet manufacturing company and a delegate from QIMR Berghofer. When a participant is recruited a QIMR Berghofer staff member will upload the participant ID number into the online randomisation system which will generate the code. Participants will be notified of their tablet allocation after all participants have finished taking tablets and survey collection has been closed. Strategies will be put into place to ensure that study staff, investigators, analysts, and students will not be aware of the study arm tablet assignment until after the primary outcomes have been analysed. The strategy is described in the document: Unblinding Process:_V1 3 December 2019.

The investigators will follow the trial's randomisation and will ensure that the code is broken only in accordance with the protocol. It is recognised that, in the course of clinical practice, it may be necessary for the treating physician to have knowledge of the treatment assignment to ensure the safety of a study subject. This circumstance is extraordinary and will likely impact a minor fraction of the enrolled subjects. In this

situation, the project team will ask the DSMB secretary to provide the treatment assignment to the treating doctor. Any participant who is unblinded will be withdrawn from the study. The DSMB, in the first instance, will monitor all episodes requiring unblinding very carefully and will notify the sponsor of all events.

If adverse event reporting suggests differences in the rate of serious adverse events, the DSMB may request adverse event data that is unblinded.

7.7 The identification of any data to be recorded directly on the CRFs

Data that will be included directly on the electronic CRF will be:

- Randomisation code
- Dates tablets sent
- Dates study documents are sent and returned (consent forms, surveys)
- Adverse events
- Withdrawals (including date, reason for withdrawal)

8 Description of the population to be studied

Residents of Australia (with the exception of the Northern Territory) aged between 60 and 79 years will be selected at random from the Commonwealth Electoral Roll. Selection will be stratified by region, age (in 5-year age bands) and sex to ensure an approximately equal region, age- and sex-distribution. Volunteers will be able to participate in the trial and their region, age- and sex- distribution will be monitored to inform the selection from the electoral roll. We aim to recruit 25,000 participants.

8.1 Inclusion criteria

- Aged 60 to 79 years old (randomly selected electors). Aged 60 to 84 years old (volunteers)
- Enrolled to vote
- Do not have any of the health conditions listed below and are not cognitively impaired
- Are not taking vitamin D at doses >500 IU/day

8.2 Exclusion criteria

People will be excluded if they are unable to give consent or to communicate well enough in English to understand study materials or if they indicate in an initial screening form that they:

- Have any of the following medical conditions (which either preclude or require high dose vitamin D supplementation or which prevents informed consent: hyperparathyroidism, sarcoidosis, osteomalacia, a history of renal calculi, a history of high calcium.
- Are taking vitamin D at doses > 500 IU/day
- Cognitive impairment
- Do not have a telephone (landline or mobile)

8.3 Approach to potential participants/ obtaining consent

The initial approach to participants will be outsourced to Datatime Services Pty Ltd (Datatime). They will send an invitation to potential participants, enclosing an 'Expression of Interest' (EOI) form on which people who express an interest in taking part will be asked to answer several questions to determine eligibility and to provide full contact details. Those eligible will be posted a full information booklet, a trial consent form, a Medicare consent form, a baseline survey and a reply-paid envelope. Once the trial consent form and baseline survey are returned (either by mail or online – see below) participants will be formally entered into the trial and randomised. The Medicare consent form is optional.

If potential participants do not return their baseline survey and consent form within approximately two weeks of mailing, Datatime will send a reminder email (for those who provided an email address on the EOI) or

postcard (for those people with no email address). Those who do not contact the study team or return the forms within approximately two weeks of the reminder being sent will be followed up by telephone by members of the study team at QIMR Berghofer.

8.3.1 Volunteer recruitment

Volunteers will be able to participate in the D-Health Trial. If a volunteer contacts the study via telephone an EOI form will be completed over the telephone and subsequently entered in the database. If the participant is eligible they will be asked if they would prefer to do the consent and baseline survey online or via paper. If the former, the link to the website (with study ID and password) will be emailed to the participant. If they would prefer to complete the paper consent form/s and survey their details will be provided to Datatime who will manage their recruitment in the same way as those selected from the electoral roll. If a volunteer emails the study we will ask them to provide us with a telephone number so that we can contact them to undertake this process.

We will invite those participants who took part in the pilot trial, **and who said they would have been willing to continue** if the trial had continued.

8.3.2 Online consent protocol

1. DataTime will send a letter of invitation to selected potential participants (selected at random from the Australian Electoral Roll), enclosing an "Expression of Interest" (EOI) form. Participants can choose to complete this form online by entering their study ID into the online EOI.
2. Participants who meet the eligibility requirements will be directed to the online information booklet. They will be asked to confirm that they have read the information booklet, and will then be directed to the consent form.
3. The participant will be asked to fill in all the required details, type their name into the signature field and insert the date that the form was signed.
4. A second consent form will appear, asking for consent for release of Medicare data. The participant will be asked to complete necessary fields for Medicare, and to click a button confirming consent. The Medicare consent is not required for participation in the study.
5. An email will be generated automatically and sent to the participant ("Acknowledgment of Consent"); a pdf copy of the consent form/s will be attached. A copy of the form/s will also be sent to the D-Health email address.
6. After completing the consent forms, the participant will be taken straight to the survey page.
7. The "Acknowledgment of Consent" email will also contain a link to the survey page so that the participant can access this at a later time.
8. The participant will click on the link and complete the survey online.
9. Once completed another email will be generated and sent to the participant acknowledging completion.

The online database will meet stringent security standards (see appendix 1).

8.4 Participant withdrawal

Participants can withdraw from the study, defined as stopping the intervention, by informing us in writing or by telephone or email. Participants who cease taking tablets will be invited to continue completing surveys. Unless specifically requested in writing, we will link all participants to health registers during routine linkages. Participants do not have to give a reason for their withdrawal. Information already collected will be destroyed at their request.

Participants will be withdrawn at the time of notification if they are diagnosed with kidney stones or sarcoidosis or experience a suspected unexpected serious adverse reaction (SUSAR). Patients diagnosed with hypercalcaemia or hyperparathyroidism will also be withdrawn unless a cause has been identified and treated

and the serum levels of calcium and PTH have returned to normal. A decision about whether to withdraw the participant will be made in consultation with the study physician. . While we would prefer that participants not take more than 500 IU of off trial vitamin D per day, once enrolled they will only be withdrawn if they take vitamin D supplements at greater than 2000 IU/day as (if they are in the intervention arm) this will cause them to exceed the safe upper intake level of 4000 IU/day.

The following information will be captured in the D-Health Trial database for all participants who withdraw/ are withdrawn from the study:

- Date of withdrawal
- Reason for withdrawal: (including an option for no reason given)
- Willing to keep completing surveys: yes / no
- Willing for us to keep information already collected: yes / no (details if any caveats)
- Willing for us to obtain information in the future: yes / no (details if any caveats)

No withdrawn participants will be replaced.

9 Trial Treatment and Processes

9.1 Dose and dosage regimen

Participants will randomised to take either 60,000 IU of cholecalciferol or placebo orally each month for 5 years.

9.2 Formulation

Gelcaps packed in blister packs of 12

1. Active tablet: The vitamin D used in the D-Health Trial will be cholecalciferol, 60,000 IU taken as a single tablet once per month. It will be supplied in blister packs. It is stable at room temperature. Formulation is as follows:

   Cholecalciferol: From Vitamin D3 1.0 m IU/g (ARTG No 1335) 60mg (equivalent to vitamin D3, 60,000 IU). 20% overage.

   Other ingredients: soya oil (181.6mg), DL-alpha tocopheryl acetate (16.4mg), softgel capsule (glycerol, gelatin, titanium dioxide, purified water)

2. Placebo: soya oil (253.6mg), DL-alpha tocopheryl acetate (16.4mg), softgel capsule (glycerol, gelatin, titanium dioxide, purified water)

Note: The addition of alpha tocopheryl acetate is to increase the stability. Lipa pharmaceuticals manufactured the placebo and vitamin D3 (cholecalciferol) gel capsules for the D-Health Trial. The starting content of the vitamin D tablets was ~72,000 IU cholecalciferol. There has been a decreasing trend and by 12 months the content was ~47,000 IU cholecalciferol. Lipa investigated the content of the tablets using HPLC methods and concluded that the vitamin D3 has isomerised to pre-vitamin D3. They used a formula from the British Pharmacopoeia to determine that the pre-vitamin D3 equivalent quantity is 23,677 IU and that the total vitamin D per capsule is 70,467 IU. Nevertheless the product is being remanufactured using a formula previously shown to be stable in the D-Health Pilot Trial (P1294) and will be dispensed from June, 2015.

The dispense module of the D-Health database is designed such that the batch of tablets being dispensed is recorded in the participant record.

9.3 Packaging and labelling

One blister pack containing 12 gelcaps will be supplied at the beginning of the trial and every 12 months thereafter for the duration of the trial. Participants will be asked to take one gelcap each month, and will be sent automated reminders (telephone, text or email). All product will be labelled:

D-Health Study Capsules
For Clinical Trial Use Only

ID Number _____

Name _____

Dose: Swallow **one** tablet each month

These capsules contain placebo or cholecalciferol (vitamin D3) (60,000 IU). Store at room temperature
QIMR Berghofer Medical Research Institute P1519, Locked Bag 2000, Royal Brisbane Hospital, Q 4029
In emergency contact 1300 735 920

Use By: / /

Keep out of reach of children
Batch # No of tablets: 12 Date

9.4 Description of and Justification for the route of administration, dosage, dosage regimen and treatment periods

The D-Health pilot trial showed that 60,000 IU / month was needed to shift the population distribution to a mean of 75 nmol/L. This equates to an intake of 2000 IU/day which is well within the tolerable upper intake level of 4000 IU / day set by the IOM.

Evidence suggests that patients prefer intermittent rather than daily dosing, and that this may lead to higher compliance [47]. A pharmacokinetic study of a single dose of 100,000 IU in people with mean baseline 25D of 67 nmol/L found that serum levels remained above 80 nmol/L for more than 2 months [15]. A comparison of the same average daily dose (1,500 IU) given daily, weekly or monthly found that dosing monthly was as effective as daily dosing in maintaining serum levels [48]. We have therefore selected oral monthly dosing as the most cost-effective way of maximising compliance.

We have chosen an intervention period of 5-years. While there is no concrete data on which to base a decision about the length of the intervention, it appears likely that vitamin D contributes to disease processes later in life. The mean trial size-adjusted intervention period in the meta-analysis of trials with mortality as an outcome was 5.7 years.

9.5 Monitoring participant compliance

Participants will be sent surveys annually. In the surveys participants will be asked to report the number of tablets taken, and whether they have started taking off-label vitamin D supplements. If participants do not return the survey we will follow-up by telephone. If the participant indicates that they do not plan to complete the survey, we will attempt to obtain information about compliance over the telephone and enter this directly into the D-Health Trial database.

9.6 Blood collection

We will obtain blood samples (8ml tube) from approximately 600 participants (300 from each of the study arms), selected at random each year. Each month approximately 3% of participants (to allow for non-

participation) will be selected (by computer-generated random number). With their annual survey they will be sent an invitation to donate blood, a blood PICF, a short one-page survey (D-Health Blood Collection Participants' Survey), and a request form to take to a participating pathology laboratory to have blood drawn. Participants will be provided with a copy of the consent form to keep. The blood will be returned to QIMR Berghofer for processing. If the consent form does not arrive, we will telephone the participant and ask for it to be returned. If the participant is not able to return the form for some reason we will obtain verbal consent over the telephone. This will be witnessed by another QIMR Berghofer staff member.

Blood will be processed and stored in a -80°C freezer..

9.6.1 Serum vitamin D measurement

One serum aliquot will be used for estimation of serum 25D – testing will be performed by a laboratory that is taking part in international standardisation program or by a commercial clinical pathology laboratory.

The laboratory will provide results to an independent statistician who will provide a summary report (mean, median, range, interquartile range) for each group, without group labels attached. To ensure the laboratory remains blinded, the study group label provided to the laboratory will differ each year (eg year 1 will be A and B; year 2 will be P and Q). The statistician will provide the DSMB secretary with a list of ID numbers for participants with a serum 25D of less than 25 nmol/L (frank deficiency). S/he will access the database and send out a standard letter to these participants advising them of their low vitamin D level and recommending that they seek medical advice.

9.6.2 Studies of vitamin D and health

Samples collected, processed and stored according to the above procedures may also be used to investigate the effects of vitamin D on health factors such as cholesterol and blood sugar. If studies are conducted of factors that may have clinical significance we will ask participants if they would like to receive their results – if so, these will be communicated to their nominated general practitioner.

Samples will be stored to enable extraction of DNA that will be used to investigate the effects of vitamin D on health. For example, we may investigate the effect of vitamin D supplementation on epigenetic factors or telomere length. We may also contribute to pooled analyses investigating the effect of common polymorphisms on response to vitamin D supplementation.

The genetic research conducted will almost certainly not have any clinical relevance – results will therefore not be communicated to participants. If studies of genetic factors known to important to health are proposed consent will be sought.

Samples (with or without data) may be provided to external researchers for studies of vitamin D and health. These studies will have to be approved by the scientific advisory board, the QIMR Berghofer HREC and the institutional review board or the HREC of the institution requesting the samples. The D-Health Trial data manager will provide a dataset containing approved data items to the requesting scientist, along with approved blood samples.

9.6.3 Risks of blood collection

The risks associated with having blood collected are low but include:

- Excessive bleeding
- Fainting or feeling light-headed
- Haematoma
- Infection

We will minimise these risks by asking participants to have blood drawn at pathology collection centres who employ qualified phlebotomists.

9.7 Drug supply and distribution / accountability

The tablet manufacturing company will supply gelcaps to QIMR Berghofer in boxes labelled A or B. Blister packs will be identified with an A or B.

When a participant is randomised a letter will be generated which will be inserted into a window-faced envelope with the participant name and address displayed. A label will be generated for the blister packaging (as above). One research assistant will label the product and insert it into the envelope. A second research assistant will check that the correct product has been dispensed and appropriately labelled, and will confirm that they have checked by recording a digital signature in the database.

The D-Health Trial database will contain an up-to-date log of dispensed materials.

The IP will be held at room temperature in a secure QIMR Berghofer facility that has temperature logging enabled.

10 Measurement of outcomes

Information will be collected by surveys and data linkage with state and national health registers for up to 10 years after the intervention phase of the trial ends.

10.1 Surveys

At baseline participants will be asked about their past medical history, recent sun exposure, sensitivity of skin to the sun, intake of foods rich in or usually fortified with vitamin D, and use of nutritional supplements (with specific nomination of vitamin D). At 12 months after enrolment, each participant will be sent a survey that focuses on health events during the previous 12 months (for example but not necessarily exclusively, osteoporosis, cardiovascular disease, cardiovascular events, fracture, diabetes).

Measurement of cognition; Cognition cannot be measured using self-administered surveys. We will therefore assess this outcome as part of our annual surveys using the Telephone Interview for Cognitive Status (TICS) which is licensed by Psychological Assessment Resources Inc.

Participants will be sent a letter with their survey letting them know that we are doing an assessment of memory and thinking as part of the survey and that this will be done using a telephone interview. They will be able to opt out of this component and still participate in the trial. Unless the participant has opted out by phone, email or letter, a member of staff will telephone in the 4-6 weeks after the survey has been mailed to administer the TICS.

Measurement of cognition will be restricted to people aged over 70 years at the time of the first assessment (planned to be administered as part of the second annual survey). People who participate in the first TICS interview will be invited to take part a second time as part of their fourth or fifth annual survey.

The TICS was designed for use in epidemiological surveys and is not routinely used as a diagnostic tool. We will therefore not provide participants with their TICS score, but will advise them to seek advice from their general practitioner if they feel that they are experiencing cognitive problems. Similarly, if participants become distressed during the interview they will be reminded that the TICS is not a diagnostic tool and advised to discuss their concerns with their general practitioner.

Sample size for cognition outcome: A previous study has analysed temporal changes in TICS score. In that study, people aged 65 years and over with two long-lived parents had a decline in the TICS score of 0.14 per year; those with no long-lived parents had a decline of 0.24 - a difference of 0.1 per year. Since the prevalence of dementia doubles every five years after age 65 and we are restricting our interview to participants aged

over 70 years or older, a faster rate of decline is likely. We therefore hypothesise that a decrease of 0.3 in the TICS score per year will occur in the placebo group and that a difference of 0.2 per year in the rate of decline in the TICS score in the treatment group (i.e. a difference of 0.4 after the first two years of supplementation) would constitute a relevant difference in cognition.

Previous studies have shown that the standard deviation of the TICSm score ranges from 3.8 to 4.7.[49-51] Assuming the standard deviation will be approximately 4.5, a sample of 3976 (n=1988 per group) will result in 80% power to detect a difference of 0.4 in the TICS after two years.

Measurement of falls: The gold standard approach to measurement of falls is to ask participants to complete a falls diary. We will ask a subgroup of participants to complete falls diaries to supplement the questions we ask in our annual surveys.

Eligibility: Participants who are in the trial and are aged over 70 on the date of the selection will be eligible to participate in the falls component of the trial.

Process: We will mail an invitation to complete a falls diary, along with a falls diary, a magnet to affix the diary to a magnetic surface such as the fridge, and a reply-paid envelope. We will ask participants to contact us if they would prefer not to participate.

Participants will be asked to begin the diary on the first day of the following month and to complete the diary each day for 3 months. We will send reminders to complete the diary every 2-4 weeks using the mode/s (text, landline, email) that we currently use to send tablet reminders. At the end of the 3-month period we will remind participants to return the diary in the reply-paid envelope.

Recruitment will occur over several months to ensure capacity to manage this component of the trial.

Sample size: The sample size has been decided in consultation with the data safety monitoring board and they have approved this strategy. A sample size of 400 in each group will provide 80% power to detect a risk ratio of 1.8. We will recruit 500 people in each group to allow for loss to follow-up. If a participant declines to participate they will be replaced with another randomly selected participant of the same age group (5 year age category) and sex.

Data analysis: We will use an intention-to-treat analysis to compare: (1) the proportion of people who fall in each group; (2) the total number of falls in each group. We will use multivariate regression models (logistic and poisson), adjusted for age and sex to improve the precision of the estimates. We will categorise falls according to their severity. Due to lack of power, analyses of severity will be descriptive.

Measurement of acute respiratory infections (ARI): The gold standard approach to measurement of ARI is to ask participants to complete an ARI symptom diary. We will ask a subgroup of participants to complete symptom diaries for 8 weeks in winter/early spring to supplement the questions we ask in our annual surveys.

Eligibility: Participants who are in the trial on the date of the selection will be eligible to participate in the ARI component of the trial.

Process: We will mail an invitation to complete an ARI symptom diary, along with the diary, and a reply-paid envelope. We will ask participants to contact us if they would prefer not to participate.

Participants will be asked to begin the diary on the first day of the following month and to complete the diary each week for 8 weeks during winter. We will send reminders to complete the diary every 2-4 weeks using the mode/s (text, landline, email) that we currently use to send tablet reminders. At the end of the 8-week period we will remind participants to return the diary in the reply-paid envelope.

Sample size: A sample size of 1430 in each group will provide 80% power to detect a rate ratio of 1.8. We will recruit 1600 people in each group to allow for loss to follow-up. If a participant declines to participate

they will be replaced with another randomly selected participant of the same age group (5 year age category) and sex.

Data analysis: We will define ARI using the Jackson cold scale which takes account of both the number and severity of symptoms. We will use multivariate poisson regression models to compare the incidence of colds between the two study arms.

Blood Collection Participants' survey: 25(OH)D concentration is influenced by sun exposure, physical activity and supplementation. To enable validation of a model to predict vitamin D status (based on 25(OH)D concentration) we will ask participants providing a blood sample to complete a short one-page survey (Blood Collection Participants' survey).

10.2 Data linkage

We will link to the National Death Index to ascertain deaths and cause of death within the cohort and the National Cancer Statistics Clearing House and/or State Cancer Registers to ascertain newly diagnosed cancers. Major health events requiring hospital admission will be confirmed or identified by linkage to hospital admitted patients' registers in each State where possible within the constraints set by data custodians. Linkage to Medicare Australia will enable capture information about items such as GP consultations, medical tests and medication use. We will link towards the end of 2017 (the end of the current project grant) and approximately 10 years after recruitment began.

11 Sub-studies

11.1 D-Health sub-studies

Participants in D-Health may be invited to participate in smaller sub-studies. Some of these may require telephone or face-to-face interviews. Ethics approval will be sought for these prior to their implementation.

11.2 D-Health Microbiome Project (P2365)

Participants will be randomly selected and invited to participate in the D-Health Microbiome Project (P2365). This involves a separate consent process. Data collected as part as the D-Health Trial (P1519) will be shared with the D-Health Microbiome Project (P2365). This will include all survey and linked data. The link between the microbiome data and the D-Health data will be based on the participant identification number and no identifying information will be shared with the microbiome project.

12 D-Health Trial Database

There will be no hard copy case report forms used in D-Health. Instead, all participant information (eg randomisation code, date of randomisation, adverse events, survey return, blood sampling) will be entered directly into the custom-built D-Health Trial database.

The database will meet ICH-GCP requirements (appendix 2).

13 Assessment of safety

Adverse events monitoring and reporting will comply with QIMR Berghofer Standard Operating Procedure 13

13.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a participant or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.*

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. *All AEs judged as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means that there is evidence to suggest a possible, probable or definite causal relationship (see section 1.1 below).*

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure). *When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects which occur in a more severe form than anticipated are also considered to be unexpected.*

Serious Adverse Event (SAE) or **Serious Adverse Reaction (SAR):** any untoward medical occurrence or effect that at any dose

- Results in death
- Is life-threatening – *refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious. In this case the event is not outlined in Investigator's Brochure (IB).

13.2 Assessing Causality

The assignment of causality should be made using the definitions below.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs shortly (within 24 hours) after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

13.3 Monitoring Adverse Events

Phase 1-Intervention phase

During phase 1 of the trial (intervention phase – participants are taking the IMP) monitoring will occur as follows:

1. Participants will be provided with a wallet-sized card to show to their general practitioner or other treating physician which asks the doctor to contact the study if the participant is diagnosed with hypercalcaemia, hyperparathyroidism, kidney stones or sarcoidosis (note: vitamin D does not cause hyperparathyroidism or sarcoidosis but these are contraindications to supplementation).

2. Participants (or their families) may contact the study to let us know of an adverse event– they will be provided with a fridge magnet including the telephone number to facilitate this.

3. Each 12 months after being enrolled participants will be sent a survey in which they will be asked to report hospitalisations and the reasons for them. Participants who don't return the survey will be followed up by telephone, and if they state that they don't plan to complete the survey, we will ask if they have been diagnosed with hypercalcaemia or kidney stones (we will also ask about hyperparathyroidism or sarcoidosis – these are not adverse reactions but would be reason to withdraw the participant). We will also ask if they have been hospitalised and the reason for this.

4. Towards the end of the intervention phase we plan to link to the National Death Index which will capture deaths that have not already been reported.

Phase 2-Post Intervention phase

During phase 2 of the trial (post-intervention – passive follow-up only) linkage with the National Death Index and Cancer Registers will identify people who have died or have been diagnosed with cancer. Due to the minimal ongoing contact with participants it is possible, but unlikely, that participants will voluntarily contact study staff to advise of an adverse event.

13.4 Recording and Reporting Adverse Events

Phase 1-Intervention phase

At the dose being used, vitamin D supplementation carries very low risk. Thus we plan the following processes:

1. Adverse events spontaneously reported by a participant or their doctor during the study.
   If a participant or their doctor contacts study staff to report an adverse event, an online adverse event reporting form will be completed (see appendix 3).

   If the condition hasn't resolved at time of report and the participant continues in the trial, we will contact the participant by phone or email after the next dose to ascertain outcome. If the condition hasn't resolved at the time of report and the participant withdraws, we will contact them by phone or email within the following month.

   - The chief investigator will initially assign severity (ie SAE or not) and causality. All AEs will be sent to the study physician for review. If the physician requests further information about the AE, study staff will approach the participant to obtain the necessary information. If the study physician requests changes to the AE severity or causal attribution these will be made before the AE report is submitted to the DSMB and sponsor.
   - AEs will be reported biannually to the sponsor, the HREC and the DSMB.
   - All SAEs will be reported biannually to the HREC and the DSMB.
   - SAEs that are possibly, probably or definitely related to the study medication (hypercalcaemia or kidney stones) will be reported to the sponsor within 24 hours of notification.
   - SUSARs will be reported to the HREC, the DSMB and the sponsor within 24 hours of notification

Adverse events captured through annual surveys / falls diaries

- Datatime will provide a monthly upload of survey data. Each month the survey data will be reviewed and a report provided to the sponsor of SAEs that are possibly, probably or definitely related to the study medication (hypercalcaemia or kidney stones).
- All AEs and SAEs that are unrelated or unlikely to be related to the study medication will be reported to the DSMB, the HREC and the sponsor biannually.
- All biannual reports will include an assessment of the statistical significance of any differences between the two study arms.

Adverse event reporting – phase 2 (follow-up phase)

A summary of events (cancer and death) captured through linkage will be provided annually to the HREC and the sponsor. Online adverse event reports will not be completed.

We will have limited further contact with participants during phase 2 (intermittent reports of study findings may be sent), but it is possible that some participants will contact the study to advise of adverse events. These will be managed in the same way as for events reported by participants in phase 1.

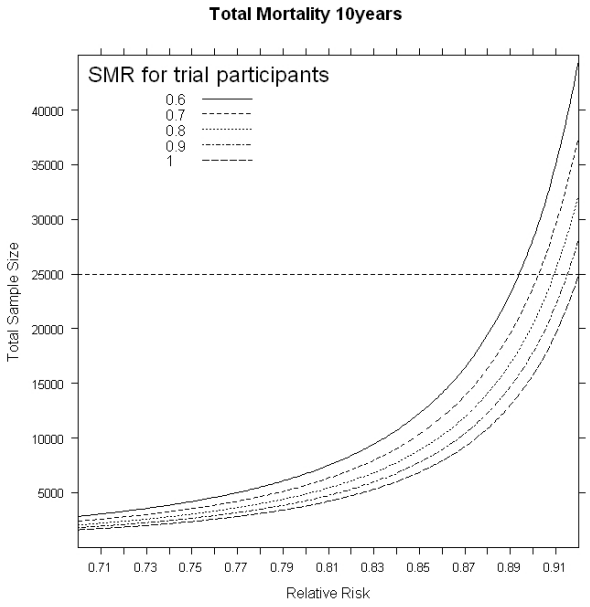
13.5 Data Safety Monitoring Board (DSMB)

We will establish a DSMB. For information see the approved D-Health DSMB Terms of Reference document.

14 Statistical considerations

14.1 Sample size

We based our sample size calculations on cumulative risk of death over a 10-year period. We used sex- and age-specific (by single year of age) death rates in the general Australian population to estimate the expected risk for trial participants. The figure shows the detectable relative risk (80% power and significance 0.05) with different sample sizes, based on a logrank test, allowing the mortality rate for the trial participants to vary between 60% and 100% of the population mortality rate (ie standardised mortality ratio (SMR) of 0.6 – 1). We have chosen a sample size of 25,000 as beyond this, there is minimal gain in power, but a substantially increased cost.



The table below shows the power to detect a range of hazard ratios (alpha=0.05) for total mortality, total cancer incidence and colorectal cancer incidence, assuming that, because of its selection, the trial cohort experiences 0.8 of the event rate of the general Australian population. Assuming 10% departure from randomised treatment in both groups, with is realistic based on the pilot trial data, the true relative risks are also given. As used here, a 10% departure corresponds to a 20% departure over the full intervention period because we assume that on average, people become non-adherent at the midpoint.

Hazard Ratio		POWER		
Observed	True	Total Mortality	Total Cancer	Colorectal Cancer
0.91	0.88	0.80	0.78	0.31
0.90	0.871	0.87	0.86	0.37
0.85	0.810	>95	>95	0.69
0.80	0.752	>95	>95	0.90
0.75	0.692	>95	>95	>95
0.70	0.634	>95	>95	>95
0.65	0.576	>95	>95	>95
0.60	0.519	>95	>95	>95

14.2 Statistical analysis

We will use intention-to-treat analyses to assess the effect of vitamin D supplementation on all endpoints. Use of the Cox proportional hazards model will allow for variable follow-up lengths and estimation of hazard ratios for mortality and other events obtained from linkage. For outcomes such as falls, fractures and nonmelanoma skin cancer where events can occur more than once, we will use Poisson or negative binomial models (depending on the distribution) to model the number of events. Endpoints that are measured on a continuous scale and that cannot be captured through passive monitoring will be assessed using linear regression models, with analyses to estimate the effects of differential loss-to-follow-up and therefore differences in patient-reported outcomes.

In exploratory analyses we will evaluate effect modification by age, sex, baseline risk factors, dietary calcium intake and predicted baseline vitamin D level (in our pilot data we were able to predict a baseline vitamin D level of less than 50 nmol/L with a C statistic of 0.7). The study has insufficient power for these stratified analyses, but we plan to pool our data with the Vital Study data (and possibly with the FIND data despite its different dose) to substantially increase the available sample size.

Interim analyses will occur after the first linkage (planned for 2017) and after subsequent linkages. Final analysis will be at approximately 5 years after the final participant has completed the intervention phase.

An analysis using Cox Proportional Hazards analysis will be conducted up to the time of change in the formulation of the tablets. This will supplement the final analysis across all time points as presently proposed. In addition, we will carry out some supplementary analyses that are not based on intention-to-treat principles. These will account for compliance and off-trial use of vitamin D (contamination), and we will incorporate time on the old versus the new formulation into these analyses.

14.3 Criteria for termination of the trial

The Sponsor, Chief Investigator, Ethics Committee (EC) and Regulatory Authorities independently reserve the right to discontinue the study at any time for safety or other reasons. This will be done in consultation with the Sponsor where practical. In the occurrence of premature trial termination or suspension, the above-mentioned parties will be notified in writing by the terminator/suspender stating the reasons for early termination or suspension (with the exception of the sponsor's responsibility for notifying the Regulatory Authorities). After such a decision, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interest. The investigator must review all participating subjects as soon as practical and complete all required records.

14.4 Reporting deviation of original statistical plan

Any deviation from the original statistical plan will be described and justified in the final report and notified to the sponsor.

15 Direct access to source data/documents

Upon request, the investigator(s)/institution(s) will permit direct access to source data/ documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by the Sponsor (or their appropriately qualified delegate) and Regulatory Authorities. Direct access includes examination, analysis, verification and reproduction of records and reports that are important to the evaluation of the trial. All data collection forms and the database will be held at the QIMR Berghofer Medical Research Institute. Copies of de-identified data may be made available to other institutions for analysis. This would require approval from the QIMR Berghofer HREC and the HREC of the receiving institution.

16 Quality Control and Quality Assurance

This study will be conducted in accordance with the NHMRC Guidelines, the Note for Guidance on Good Clinical Practice and the Declaration of Helsinki. Relevant Human Research Ethics Committee approval for the protocols and subsequent amendments will be sought prior to implementation.

Adequately trained and experienced personnel will be employed for trial-related activities. This will be documented by way of signed and dated Curriculum Vitae to be kept at QIMR Berghofer. Source Data and Essential Documents will be filed and kept for at least 15 years.

Protocol amendments will be submitted to the QIMR Berghofer HREC prior to implementation. Detected non-compliance with the approved protocol will be reported to QIMR Berghofer according to the non-compliance standard operating procedure (SOP021).

17 Ethics

The clinical trial protocol will be submitted to the QIMR Berghofer Clinical Trials Protocol Committee (QIMR Berghofer -CTPC) and the QIMR Berghofer Human Research Ethics Committee (QIMR Berghofer - HREC). QIMR Berghofer-HREC approval will be gained for the protocol and participant information and consent forms before commencement of the D-Health trial. All amendments to the trial protocol and trial documents must be approved by QIMR Berghofer-HREC before the implementation of the amendments.

The study will be conducted under the Australian Therapeutic Goods Administration Clinical Trial Notification scheme. QIMR Berghofer will provide a study monitor who will undertake monitoring for compliance with GCP, the frequency of which will be determined by QIMR Berghofer Regulatory Affairs Manager in consultation with the chief investigator.

The participants' consent to participate in the trial will be obtained after they have been provided with a comprehensive information brochure and given the opportunity to ask questions. All participants will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which they may be exposed. They will be informed of the strict confidentiality of their data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician. A contact number will be given to the participant should they wish to discuss any aspect of the trial. Participants will always be asked to sign a consent form, either in hard copy or electronically online.

The right of the participant to refuse to participate in the trial without giving reasons will be respected. Similarly, the participant will remain free to withdraw at any time from the trial.

This is a randomised controlled trial; therefore neither the participants nor their physicians will be able to choose the participant's treatment. Treatment will be allocated randomly using a computer-based algorithm. This is to ensure that the groups of participants receiving each of the different treatments are similar.

17.1 Compliance with the protocol, good clinical practice and the applicable regulatory requirement(s)

The study will be conducted in accordance with the following:

1. World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (with notes for clarification 2004) [52].
2. NH&MRC National Statement on Ethical Conduct in Research Involving Humans [53].
3. Notes for Guidance on Good Clinical Practice – Annotated with TGA Comments (CPMP/ICH/135/95), as adopted by the Australian Therapeutic Goods Administration (July 2000). [54]
4. Current ethics approved Clinical Trial Protocol.
5. The QIMR Berghofer Medical Research Institute's Statement on Integrity in Research Conduct [55] and Clinical Trial Code of Conduct [56].

Ethics approval will be sought from the QIMR Berghofer Medical Research Institute Human Research Ethics Committee.

17.2 Ethical considerations specific to this study

Adults aged between 60 and 79 years who are able to give informed consent (not cognitively impaired, able to speak and understand English) will be invited to participate by letter. They will be asked to complete an Expression of Interest form. Those who are interested and meet eligibility criteria will be mailed:

- An information booklet
- A consent form
- A survey

The information booklet will fully disclose all risks and benefits of taking part in the study. Participants will be provided with a D-Health helpline number so that they can ask questions about the study. They will not be randomised until their consent form is received.

The risk of taking cholecalciferol at the proposed doses are negligible. There are small risks of bruising or sepsis associated with collection of a blood sample. Blood samples for those participants taking part in this component of the study will be collected by phlebotomists at commercial pathology company collection centres who are qualified to manage any complications that arise.

18 Data Handling, Record Keeping and Reporting

All information collected from participants will be treated with strict confidentiality and data stored in a secure environment (electronic controlled access buildings and locked filing cabinets) under numerical code. Tracking data will contain participant identifying details. Data will be kept at the QIMR Berghofer Medical Research Institute (QIMR Berghofer). Only researchers involved in this study will have access to the data. Electronic data will be password protected. The database and the electronic system that will run it will comply with GCP requirements with regard to electronic trial data handling listed in Section 5.5 of the ICH-GCP guideline adopted by the TGA. Only information that is relevant to the trial will be kept. All study-related documents and records will be retained for a minimum of fifteen years after trial completion. Written agreement from the Sponsor will precede destruction of the same.

The following reports will be produced on a regular basis:

- Adverse Event Reports

- Annual Study Reports – will be submitted to the QIMR Berghofer-HREC and the funding bodies
- Protocol Deviation Report – all protocol deviations/violations will be documented in a protocol deviation summary form and notified to the sponsor and QIMR Berghofer-HREC
- Clinical Study Report – will be submitted at study completion
- Final Study Report – will be submitted to the relevant ethics committees, the funding bodies, hospitals and clinicians involved in the study

19 Financing and Insurance

The trial is funded by the National Health and Medical Research Council (Project Grant 1046681). The clinical trial insurance policy will be maintained, for the duration of the study, by QIMR Berghofer.

20 Publication policy

Publication and reporting of results and outcomes of this trial will be accurate and honest, undertaken with integrity and transparency and in accordance with QIMR Berghofer's Publication Policy. Publication of results will be subjected to fair peer-review. Authorship will be given to all persons providing significant input into the conception, design, execution or reporting of the research according to QIMR Berghofer Statement of Record Integrity. No person who is an author, consistent with this definition, will be excluded as an author without their permission in writing. Authorship will be discussed between researchers prior to study commencement (or as soon as possible thereafter) and reviewed whenever there are changes in participation. All conflicts arising through disputes about authorship will be reviewed by the QIMR Berghofer Director. Acknowledgment will be given to collaborating institutions and hospitals and other individuals and organisations providing finance or facilities. Participant confidentiality will be maintained by referring to individual participants by their identifying code used in the trial. Data will not be released publicly until the manuscript is accepted for publication. In the case of no publication, information will only be released to the public and media in accordance with QIMR Berghofer's Corporate Media Strategy Policy.

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22 Appendix 1: QIMR Berghofer Web Application Security

QIMR Berghofer hosted web applications are protected by multiple security measures, which combine to provide a high level of safety for data and infrastructure.

Security measures employed are:

Enterprise Firewall

All systems at QIMR Berghofer exist behind an enterprise grade firewall. The firewall blocks traffic that is not sent to the appropriate to specific devices in a specific manor.

Application Security Firewall

The application security firewall scans for known security exploits that target web applications. These include the OWASP top 10 security threats. The list of known exploits is automatically updated to include new variants as they identified.

Intrusion Protection

Intrusion protection systems scan traffic for known and unknown security threats. This usually operates at a lower level that the application security firewalls. As with the application security firewall, a list of known exploits is automatically updated. This solution is also provided by a different vendor to the application security firewall, providing a greater protection.

Anti-Virus

All servers hosting a web application run up-to-date antivirus software which includes on access scanning. This provides a high level of anti-virus protection

Security Patching

All servers hosting a web application are regularly patched with the latest security updates. These updates are designed to fix known vulnerabilities in operating systems and software that can host web applications.

Secure Physical Access

All servers hosting a web application have restricted physical access. Only members of the ITS department can physically access the computers.

Secure Remote Access

All servers hosting a web application have restricted remote access. Only authorized system administrators can log in to the servers to run applications or change the configuration.

23 Appendix 2: QIMR Berghofer Database Development Security Methodologies

Purpose

The purpose of this document is to highlight the security, encryption and audit trail logging that is a standard function within all clinical trial-based application delivered by the QIMR Berghofer Development Team. These development standards have been designed to meet the requirements of the Therapeutic Goods Administration (TGA) and Food and Drug Administration (FDA) guidelines.

23.1 Encryption

Application encryption is broken into 2 areas, backup encryption and identifiable data encryption at the column level;

Backup level encryption

QIMR Berghofer utilises one backup solution for all data. Any tape written by this backup solution requires the software solution used to write the tape available to restore the tape. All backup data tapes are securely transported to an undisclosed professional storage centre (vendor contracted) and are held until recalled, based on QIMR Berghofer's data retention period. To investigate our off-site tape storage company, please visit http://www.databank.com.au.

All clinical trial databases are encrypted when written to tape. The encryption type used is AES128, a method of encryption employed by QIMR Berghofer's backup software solution.

Identifiable data encryption at the column level

As part of the project's detailed requirements document, sponsors have the ability to specify the requirement for column level encryption. This can be incorporated for specified columns (usually patient identifiable data), but with the understanding that this feature limits some functionality. i.e. searching capabilities.

23.2 Security

- All clinical trial-based websites are developed with a SSL encryption layer on the website.
- Users given permission to access the website are detailed by the sponsor in the requirements document. Username and password authentication is required to access the website.
- Password complexity meets the following requirements;
    - Passwords cannot contain the user's account name or parts of the user's full name that exceed two consecutive characters.
    - Passwords must be at least six characters in length.
    - Passwords must contain characters from three of the following four categories:
        - English uppercase characters (A through Z).
        - English lowercase characters (a through z).
        - Base 10 digits (0 through 9).
        - Non-alphabetic characters (for example, !, $, #, %).

23.3 Audit data logging

The purpose of audit logging;

1. To provide a record of changes to *key* data within the application (adds, changes, deletions), including who made the change, when and from where.
2. Enable use of the system while ensuring that data entered is not deleted. i.e. A function may be available to delete a record. This function should permanently hide the record from view, not delete the data.

24 Appendix 3: D-Health Adverse Event Log

(Will be completed electronically in custom-designed database)

Participant ID:

Participant Initials:

Staff member taking the report:

Report Date (dd/mm/yy)		
Date last IMP taken (dd/mm/yy)		
Event		
Intensity (Select one)	☐ Mild ☐ Moderate ☐ Severe	Mild: discomfort noted, but no disruption to normal activities Moderate: discomfort sufficient to reduce or affect normal activities Severe: inability to work or perform normal daily activities
Start Date (dd/mm/yy)		
Duration (days)		
Did participant see a doctor?	☐ Yes ☐ No	
Treatment received?		
Has symptom resolved?	☐ Yes ☐ No	
Serious AE Criteria (Tick all that apply)	☐ NOT A SERIOUS AE ☐ Death- Fill in Date of Death ☐ Hospitalisation/prolonged hospitalisation ☐ Persistent or significant disability ☐ Life-threatening	

Causal Relationship to Study Treatment (Select one)	☐ Unrelated	There is no evidence of any causal relationship.
	☐ Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
	☐ Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs shortly (within 24 hours) after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
	☐ Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
	☐ Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Outcome (Select one)	☐ Continue in trial ☐ Review after next dose of IMP ☐ Withdrawn from Study	
Date of Death (dd/mm/yy)		

If an SAE that is possibly, probably or definitely associated with the IMP (kidney stones or hypercalcaemia), generate adverse event report immediately for submission to the sponsor, the HREC and the DSMB.

25 Appendix 4: D-Health Collaborators

Collaborator Name	Institution
Bruce Armstrong	University of Sydney
Peter Ebeling	University of Melbourne
Dallas English	University of Melbourne
Michael Kimlin	Queensland University of Technology
Rachel O'Connell	NHMRC Clinical Trials Centre - University of Sydney
Jolieke Van Der Pols	University of Queensland
Alison Venn	University of Tasmania
Penny Webb	QIMR Berghofer Medical Research Institute
David Whiteman	QIMR Berghofer Medical Research Institute