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Protocol: A Phase II randomised controlled trial of high-dose Vitamin D to prevent progression in localised prostate cancer cases with low-intermediate risk of progression (ProsD).

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Title:

Protocol: A Phase II randomised controlled trial of high-dose Vitamin D to prevent progression in localised prostate cancer cases with low-intermediate risk of progression (ProsD).

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Abstract

Introduction: Active surveillance (AS) for prostate cancer patients with low risk of PC death is an alternative to radical treatment. A major drawback of AS is the uncertainty whether a patient truly has low risk PC based on biopsy alone. Multiparametric MRI scan together with biopsy, appears useful in separating patients who need curative therapy from those for whom AS may be safe. Two small clinical trials have shown short-term high dose vitamin D supplementation may prevent prostate cancer progression. There is no substantial evidence for its long-term safety and efficacy, hence its use in the care of men with PC on AS needs assessment. This protocol describes the ProsD clinical trial which aims to determine if oral high dose vitamin D supplementation taken monthly for 2 years can prevent prostate cancer progression in cases with low-intermediate risk of progression.

Method and analysis: This is an Australian national multi-centre, 2:1 double-blinded placebo-controlled Phase II RCT of monthly oral high-dose vitamin D supplementation (50,000IU cholecalciferol), in men diagnosed with localised PC who have low-intermediate risk of disease progression and are being managed by AS. This trial will assess the feasibility, efficacy, and safety of supplementing men with an initial oral loading dose of 500,000IU cholecalciferol, followed by a monthly oral dose of 50,000IU during the 24 months of AS. The primary trial outcome is the commencement of active therapy for clinical or non-clinical reason, within 2-years of AS.

Ethics and dissemination: This trial is approved by Bellberry Ethics Committee (2016-06-459). All results will be reported in peer-reviewed journals.

Trial Registration: ACTRN12616001707459

Strengths and Limitations of this study

- This double blinded placebo controlled randomised controlled trial with stringent allocation concealment eliminates treatment and allocation bias.
- Adherence to the trial is likely high due to regular patient follow-ups and mode of delivery of intervention by mail makes this trial accessible to men in urban and rural areas.
- Blood collection at varying timepoints makes this a valuable resource but is costly.
- This is a phase 2 trial hence results will not be conclusive for the role of Vitamin D but may inform a phase 3 trial, is a limitation.
- Follow up is 2 years and therefore a benefit or lack of benefit of vitamin D may not be appreciated in this time, given the natural slow progression of prostate cancer, is a limitation.

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Introduction

Prostate cancer (PC) affects many men worldwide, with 1,276,106 new cases and 358,989 deaths estimated for 2018.[1 2] The proportion of low risk tumours diagnosed has risen since the introduction of prostate-specific antigen (PSA) testing, leading in some cases to overdiagnosis, adverse effects and unnecessary treatment.[3] Over diagnosis due to PSA-testing may be unavoidable, but overtreatment is not. Results from the Prostate Testing for Cancer and Treatment (ProtecT) suggest minimal benefits in men with *low risk* PC when managed with curative treatment, and instead recommended monitoring the course of PC with the intention of initiating curative treatment if and when the cancer progresses. Referred to as active surveillance (AS),[4] this management option has evolved as an alternative to immediate active treatment for those diagnosed with low grade disease. Consequently, AS is now the preferred management strategy for most men with low-risk PC. It aims to avoid overtreatment of clinically indolent disease by safely delaying definitive treatment until evidence of progression is evident.

The following augmented risk classification for low, intermediate and high-risk groups is used as guide to classify disease status:[5-7]

- Low risk: PSA < 10 ng/mL, and Gleason 3+3 or less, 2 or less positive biopsy cores and clinical stage T1-T2a.
- Intermediate: PSA 10 to<20 ng/mL or Gleason 7 (Gleason 3+4 or Gleason 4+3) or clinical stage T2b-c sub-divided into:
  - Favourable risk: Gleason 3+3 (with PSA 10 to <20 ng/mL or T2b-c) or Gleason 3+4.
  - Non-favourable risk: Gleason 3+4 (with PSA 10 to <20 ng/mL or T2b-c), or Gleason 4+3.
- High-risk: PSA > 20ng/mL, or Gleason 8 or greater, or clinical stage ≥T3.

The preferred management strategy that is widely adopted for most men with low risk disease is AS while curative/active treatment is widely adopted for men with intermediate to high risk disease .[8-11] There is mounting evidence that men with *favourable intermediate* risk PC may have similar mortality risk as those with *low* risk disease. These men may therefore be good candidates for AS, as a safe first-line management option, although the consensus to accurately define this sub-group of PC cases needs clarity.[4 8-12]

Prostate Cancer Diagnosis

PC is conventionally diagnosed using transrectal ultrasound (TRUS) to guide prostate biopsy (PB). As cancer cannot be imaged on ultrasound, the major limitation of this approach is non-detection of a substantial proportion of significant PC. Sampling error can lead to the misdiagnosis of clinically significant disease, which may be upgraded at repeat biopsy, referred to as reclassification, giving the perception of disease progression, subsequently leading to overtreatment. The Prostate Cancer Research International Active Surveillance Project, referred to as the PRIAS Project, estimated that

approximately 28% of PRIAS participants showed reclassification upon repeat biopsy.[13-15] The use of mpMRI, originally used for staging, is now routinely used for tumour detection and localisation, allowing image-guided targeted sampling to overcome the limitations of the traditional blind PB. mpMRI is able to detect both high-grade and larger tumours accurately, which means it may perform particularly well for detection of clinically significant disease.[16-18] It can improve the specificity of locating PC and targeting the PB. It can also differentiate low- and intermediate/high-grade PC, thereby providing more accurate risk classification of PC.

Prostate Cancer Risk and Vitamin D

Two recent clinical trials in PC patients suggest that vitamin D supplementation may prevent PC progression.[19 20] Daily supplementation of 4000IU for one year reduced the number of positive cores and Gleason grade, but did not reduce PSA levels.[19] A daily high dose of 40,000IU for only 10 weeks significantly reduced PSA levels but did not change Ki67 expression in prostate tissue. Those who received 4000IU and 10,000IU showed no significant reduction in PSA level.[20] Duration of follow-up was short in both these trials may have resulted in the lack of significant findings. Further trials of high vitamin D doses to prevent PC progression are therefore required. Trials are also needed to assess the long-term safety of vitamin D supplementation in cancer patients.

Prostate Cancer and Genome Damage

There is a strong link between the prevalence of markers of genome damage and cancer risk. Studies have shown that prevalence of chromosomal aberrations (CA) is 2.2- to 2.4-fold higher in cancer patients than in non-cancer controls, and that micronuclei (MN) formation, a marker for chromosomal instability, was associated with increased cancer incidence in a study of 6718 individuals.[21] There is also evidence to link telomeres to cancer risk.[22] Telomeres are repetitive *TTAGGG* DNA sequences that maintain genomic stability by protecting the ends of chromosomes; they shorten in length over time in normal somatic tissues due to incomplete replication of the telomere. Telomere shortening is accelerated by oxidative stress, inflammation and cell proliferation and has been linked with induction of cell senescence which guards against survival of genomically abnormal cells.[23] Evidence from prospective studies show positive associations between telomere length and various cancers, including that for low-grade (OR 1.13, 95% CI:1.01–1.27) and localised PC (OR 1.12, 95% CI:1.01–1.24) disease, possibly due to abnormal telomerase expression and telomere elongation, which enables the survival of genomically unstable cells, their unrestricted growth and their evolution into cancer.[24-26] There is evidence to show that some micronutrients are essential to prevent genome damage but the specific impact of vitamin D is only just starting to be explored.[27]

Evidence suggests that high levels of vitamin D may prevent genome damage in leukocytes by reducing prevalence of MN formation and by maintaining adequate telomere length.[28-32] There is also evidence to suggest that 1,25OHD may inhibit telomerase activity in tumour tissue in a pathway involving miRNA498, a non-coding small RNA.[33] This current trial provides an opportunity to

concurrently examine the possible role of vitamin D in the regulation of these markers of DNA damage in PC.

Rationale

The ProsD study is a 2:1 double blinded placebo controlled randomised control trial for high dose vitamin D supplementation, in a group of men with PC who have low-intermediate risk of disease progression, and are undertaking AS. There is uncertainty as to whether AS or curative therapy is best for this risk group. The protocol mandates the use of MRI-detected and targeted cancers in the inclusion criteria to reduce disease reclassification bias due to sampling error on biopsy and to assist in the diagnosis of disease progression on AS.

Objectives and outcomes

The objective of this trial is to determine if monthly oral high dose vitamin D supplementation for 2 years can prevent disease progression in PC cases with low-intermediate risk of progression.

Primary outcome:

The primary trial outcome is the time to switch from surveillance to active therapy, for clinical or non-clinical reasons, within 2-years of AS.

Secondary outcomes:

(a) Time to switch from surveillance to active therapy, specifically for clinical reasons, within 2-years of AS.
(b) Time to switch from surveillance to active therapy, specifically for non-clinical reasons, within 2-years of AS.

Tertiary outcomes:

(a) The proportion of PC patients achieving levels of total 25OHD above 75 nmol/L following vitamin D supplementation. We will also characterise those whose serum 25OHD does not increase to 75nmol/L in response to supplementation and measure levels of $1,25(OH)_2D$.
(b) Extent of DNA damage in those receiving the high dose vitamin D supplementation.
(c) The utility of mpMRI scan in detecting PC progression in cases managed on AS.

Methods: Participants, interventions, and outcomes

Participants

Trial participants will be recruited from 15 private Australian urology clinics located in Australia, with the corresponding ethics approval being obtained for all sites. Records of all patients diagnosed in the 6 months prior will be screened by urologists and clinic nurses, to identify potential participants. Those clinically eligible will be contacted, introduced to the ProsD trial, and consent obtained to forward their personal details to the trial coordinator. Each potential participant will be further screened for remaining eligibility criteria before being invited to participate. The ProsD trial will use subsets of D-Amico's classification to derive its population of interest. All eligible

participants will be mailed a Participant Information Consent Form, and those who decline will not be followed-up further.

Eligibility Criteria

All participants aged between 50 and <80 years must have results of at least one mpMRI (centrally reviewed and not limited to any PIRADS score) and one of the following:

- Gleason score = 7 (e.g. Gleason grade 3+4) or
- >2 positive biopsy core (which may include Gleason 6) or
- Clinical stage T2 (which may include Gleason 6) or
- PSA>10 ng/mL (which may include Gleason 6).

Those diagnosed with these clinical features but without a prior mpMRI scan will be requested to have a scan done for the purposes of the study. Those with a pacemaker or with metal prosthesis in their body will not be asked to have an mpMRI.

Men who were previously diagnosed with low-risk disease and whose disease has been upgraded during the preceding 6 months will be eligible to participate.

Exclusion Criteria

- Men with low risk disease:

- Gleason score 6 or less and

- PSA<10ng/mL and

- Clinical stage <T2

- Men with high risk disease:

- Gleason score 8 or more or

- PSA>20ng/mL or

- Clinical stage T3 or T4 or N/M >0.

- Daily Vitamin D supplementation more than 50% of RDI (more than 300IU/day).
- Hyperparathyroidism, hypercalcaemia, or osteomalacia.
- Glomerular filtration rate (GFR) below 30 or Stage 4 or Stage 5 kidney disease
- History of renal calculi.
- Taking orlistat, cholesterol-lowering drugs called bile acid sequestrants, such as cholestyramine and cholestipol, or other drugs known to reduce vitamin D absorption.
- Those with gastrointestinal abnormalities that may affect nutrient absorption such as inability to swallow oral medication or clinically diagnosed malabsorption

Sample size

The primary outcome for the trial is the change from AS to active therapy within 24 months from date of consuming their initial loading dose of supplements. This is currently estimated to be ~35.0% at 2 years for low-intermediate risk patients on AS. Using Simon's two-stage design, a sample size of 80 patients in the group receiving the vitamin D supplement would have > 80% power with 95% confidence to exclude a success rate of 65.0% in favour of a more interesting rate of 77.5% (i.e. active therapy rate of 22.5% rather than 35.0%).

Additionally, a futility analysis will be performed after 24 patients have received vitamin D for 24 months, and if eight or more patients in the intervention group have disease progression after 2 years of intervention, consideration will be given to modifying the intervention or stopping the study for futility. In order to obtain contemporary estimates for the control group it is proposed to randomise patients 2:1 resulting in a total sample size of 120 patients (80 vitamin D supplementation, 40 placebo controls).

Intervention

The intervention is a monthly oral dose of 50,000IU of cholecalciferol for 24 months. Participants randomised to control will take a visually identical placebo.

Initial Loading Dose

Each participant will be requested to orally consume 10 tablets within 12 hours commencing initial loading. They will be required to attend a pathology provider to have their blood and urine tested for toxicity, the following day. The pathology provider will upload the results in their results online portal which can be accessed by their treating urologist and trial coordinator to monitor for toxicity.

Follow-Up Doses

Thereafter, participants will consume 1 tablet a month (after 30 days), for the remaining 23 months. Each participant will be sent a reminder email and/or SMS to take the supplement a day before the due date and be followed-up the following week to ensure compliance. Each participant will also be asked questions on any lifestyle changes, their well-being, if they have had any falls, and be notified of the date of the next supplement follow-up. ProsD procedure is outlined in Figure 1.

Justification for Dosing Regimen

This dosing regime is similar as that proposed by the Mel-D trial (ANZMTG 02.09 Mel-D) which is a RCT of vitamin D supplementation in melanoma patients. The 500,000IU loading dose aims to achieve an early increase in 25OHD levels. This is followed by a monthly lower dose of 50,000IU to maintain high levels; the monthly dosing frequency is proposed to improve the likelihood of good compliance over the trial period. This dose has been shown to achieve average serum 25OHD levels of ~78nm/L without adverse effects.

Randomization

All supplements (placebo and active) will be packed in boxes to look similar and assigned a kit number. This information for each kit number and its corresponding content (placebo or active) will be provided to the NHMRC-CTC by the packaging company (PCI-Pharma). All staff at the coordinating site and treating urologists are blinded to the allocation.

Upon completion of baseline data collection participants will be randomised in the ratio of 2:1 using their 7-digit ID, date of birth, and diagnostic pathology status. Randomization will be performed centrally at the NHMRC Clinical Trials Centre, University of Sydney (NHMRC-CTC) to guarantee allocation concealment using an interactive voice record system (IVRS). Using the method of minimization with patients stratified by age (≤ 65 years, ≥ 65 years); Gleason score (<7, 7); upgraded to low-intermediate risk in the past 6 months (yes/no), a randomisation number will be created to generate corresponding kit numbers specific to active or placebo box of supplements. This information will be provided to the Trial Coordinator, who then mails the assigned packs of supplements, and a pathology request form (blood/urine toxicity tests) to participant, with specific instructions.

Outcomes

Primary Endpoint

The primary endpoint will be the time to active therapy for PC (Active therapy-free survival, ATFS). There will be no absolute requirements for conversion to active therapy which will be at the discretion of the treating urologist. However, as a guideline, active therapy may be considered in the following situations.

- Gleason 4+3 or greater on rebiopsy *or*
- Gleason 3+4 = 7 where pattern 4 is > 10% on rebiopsy *or*
- Any Gleason 6 or 3+4 =7 (pattern 4 < 10%) on rebiopsy where progression on mpMRI has occurred defined as (based on NCI study Frye et al ASCO GU 2016):
- increase in PIRAD score
- any increase in lesion diameter measured in the axial plane
- appearance of any new lesion
- PSA doubling time of less than 3 years

Active therapy-free survival (ATFS) is defined as men who do not undergo any active therapy (e.g. radical prostatectomy or radiotherapy) during the trial.

Secondary Endpoints

- time to active therapy for PC (ATFS) for non-cancer progression (e.g. anxiety) *or*
- time to active therapy for PC (ATFS) for clinical reasons
  - PSA doubling time (PSA doubling time <3 years is progression)
  - Increase in Gleason grade

- Increase in the percentage of involved cores
- Increase in cancer volume (total mm of cancer detected/total mm biopsied)

Tertiary Endpoints

- Proportion of patients achieving optimal serum vitamin D levels as assessed by serum 25OHD levels 75nmol/L and above
- Prevalence of lymphocytic DNA damage as assessed by markers listed above
- Re-evaluation of mpMRI scans in detecting PC progression in cases managed on AS.

Definition of Outcomes

1. Conversion to active therapy due to clinical reasons

- Gleason 4+3 or greater on rebiopsy *or*

- Gleason 3+4 =7 where pattern 4 is > 10% on re-biopsy *or*

- Any Gleason 6 or 3+4 = 7 (pattern 4 < 10%) on re-biopsy where progression on mpMRI has occurred defined as:

- increase in PIRAD score
- any increase in lesion diameter measured in the axial plane
- appearance of any new lesion

- PSA doubling time of less than 3 years

2. Conversion to active therapy due to non-clinical reasons

- Number of patients opting out of AS for non-cancer progression (e.g. anxiety)

Patient and Public Involvement

Two consumer representatives from the Prostate Cancer Support Networks (Prostate Cancer Foundation Australia), were involved in providing feedback in the conceptual development of the study, study design, purpose, and all study materials.

Methods: Data collection, and management

Data collection

Each participant will be mailed a copy of a baseline questionnaire at the start of the project, followed by a follow-up questionnaire at 12 months and 24 months. Blood specimens will also be collected at these timepoints as well as at 6 months after commencement of supplementation. Each questionnaire is anticipated to take an approximately 30 minutes to complete. Participants with incomplete responses will be followed-up.

When blood draw is complete, specimens will be collected, packed, and transported to the processing facility (CSIRO Australia) within 24 hours of collection, by the courier company (Marken Australia). Date and time of blood collection and receipt of samples will be recorded. Blood processing protocol is outlined in Appendix 1. All participants who have not had blood drawn will be followed up with a

fortnightly reminder phone call/email, for five weeks. Participants who do not respond after 5 follow-ups will be recorded as loss to follow-up.

All participants will also be mailed a MRI-request form, at 12-months and 24 months, to have this scan completed by the same provider as that during their diagnosis.

PSA and biopsy follow-up

All participants will be mailed a pathology request every three months in the first year, and every 6 months thereafter, reminding them to have their PSA test completed. Information for any follow-up biopsy is also collected from their clinic nurses.

The timeline for each participant is described in Figure 2. This figure describes from the timepoint a participant is flagged as potentially eligible, through to the completion of the trial.

Data management

All information collected and storage of study data will conform to the Australian Privacy Principles, *Guidelines under Section 95A of the Privacy Act 1988*. Data will be collected and stored in various formats during the trial, therefore appropriate methods of confidentiality and privacy will be maintained. Data will be entered into a password protected database in a de-identified manner where each participant will be allocated a unique ID number and will be archived for 10 years after the completion of the study as specified by NHMRC. All participants will be identified by their Study identification number, participants' date of birth, and date of interview. All data cleaning and preparation will be conducted by research staff that are directly involved in managing the project.

A statistical analysis plan will be prepared prior to data-lock and contain additional detail on the methods described below. All randomised participants will be eligible for inclusion in the full analysis set. Analysis of efficacy endpoints will be undertaken on participants in the full analysis set unless participants are deemed non-evaluable by the Trial Management Committee; all such decisions will be documented in the final study report. While no formal comparisons between the two groups are planned, exploratory analyses will be performed to determine the level of activity of the vitamin D supplement for the key outcomes.

Methods: Monitoring and Safety

An Independent Data Monitoring Committee (IDMC) will be established to monitor the safety of participants, to ensure the continued efficacy of the trial and compliance to the trial protocol, according to the IDMC Operations Manual. There will be 12-monthly reviews conducted by the IDMC for the purpose of monitoring the conduct of the trial and assessing participant safety.

All trial participants will be monitored by the IDMC and will be immediately removed from the study if they have:

- incidence of hypercalcaemia and hypercalcinuria, which will be measured to ensure serum and urine levels are below 2.75 mmol/L and less than 7.5 mmol/24hrs, respectively.

- a 20% fall in the estimated glomerular filtration rate, over the course of the study.
- more than two episodes of renal calculi occurring over the course of the study.

A participant who develops either hypercalcaemia or hypercalciuria will be referred to their general practitioner, for further management of their condition. A participant who develops renal calculi will be managed by their treating urologist for acute management of the stone as per normal procedures and guidelines.

Participant safety

The PI will ensure that the study is completed in accordance with the guidelines set out in the *National Statement on Ethical Conduct in Human Research* (2007) (the *National Statement*) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. Adverse event reporting will be recorded from the date of informed consent. In the case whereby there is an Adverse Event (AE), Adverse Reaction (AR), Serious Adverse Event (SAE) or Suspected Unexpected Serious Adverse Reaction (SUSAR), an assessment of seriousness will be conducted by the PI or treating urologist. An AE is defined as any untoward medical occurrence (physical, psychological, social or economic), whether mild, moderate or severe, in a trial subject related to medical management, in contrast to complications of disease. A SAE is defined as any event that results in death, is life threatening, results in hospitalisation or results in disability or incapacity (persistent or significant).

Depending on the severity of the event, a medical assessment will be completed as soon as possible. It will be left to the Principal Investigator's clinical judgment to decide whether an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he perceives as an intolerable AE. If either of these occurs, the participant will undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable. The following will be documented and recorded in the adverse event logbook:

- Record each event as separate occurrences
- Document participant identification number, date of birth, name
- Document and describe the event
- Record the start and stop times of the event
- Document the severity of the event, mild, moderate, severe, fatal

Concomitant Medications/Treatments

Concomitant medications will not be recorded during the study, except for medications used to treat adverse events or medications known to interact with the study medications. Any concomitant use of vitamin D or multi-vitamin supplements in sufficient detail to be able to estimate daily vitamin D intake from these sources (Vitamin D supplementation more than 50% of RDI). Any concomitant use

of calcium supplements, Orlistat or other drugs known to reduce vitamin D absorption will be recorded.

Informed consent process

Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial (Appendix 2). A copy of the signed Consent Form will be given to the participant to retain. The original signed form will be retained at the trial site. The right of a participant to refuse participation without giving reasons will be respected and the participant will remain free to withdraw at any time from the trial without giving reasons and without prejudicing his further treatment. The participant will be allowed as much time as wished to consider the information (within timeframe of eligibility criteria), and the opportunity to question the Investigator or other independent parties to decide whether they will participate in the trial. Potential participants will only be approached for the study if they have the full capacity to give consent and that they understand the implications of the trial. There will be no provision for alternatives to obtaining consent via the Guardianship Division within NSW Civil and Administrative Tribunal. Non-respondents will be followed up 5 times, fortnightly and will not be followed-up thereafter.

Ethics and dissemination

The protocol for the ProsD trial and all its associated documents has been reviewed and approved by the Bellberry Human Research Ethics Committee (2016-06-459-A-1), and the Macquarie University Human Research Ethics Committee (5201700188). The trial will be conducted in compliance with the approved trial protocol. Any deviations from the protocol will be firstly submitted to Bellberry HREC for review and approval. Protocol violations will be immediately reported to the ethics committee according to its standard policies and procedures.

Any deviations from the protocol will be firstly submitted to Bellberry HREC for review and approval. Protocol violations will be immediately reported to the ethics committee according to its standard policies and procedures

Study progress

Recruitment was temporarily stopped in March 2020 due to the COVID19 outbreak and was resumed in July 2020. Rate of recruitment was slow in the initial stages of the trial and hence modifications were made to the protocol to improve this rate. The original requirement to only include PC cases diagnosed in the preceding 3 months was extended to include cases diagnosed in the preceding 6 months and to also extend the maximum age cut-off from 75 years to 79 years. Changes were also made to include PC cases who were originally diagnosed with low risk disease but were later upgraded to low-intermediate risk in a follow-up biopsy. As of August 2020, the ProsD trial had recruited 120 participants, the pre-specified target number.

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Competing interest: None declared

Roles and responsibilities:

Trial sponsor: Professor Gurney from Macquarie University (MQ) contributed to study design and protocol development, interpretation of data, writing of the report and the decision to submit this report for publication.

Funder: A Movember Clinical Trials Award funded and administered through the Prostate Cancer Foundation Australia (PCFA).

Coordinating centre: Dr Nair-Shalliker and A/Prof Smith at Cancer Council NSW coordinated all aspects of this trial. They contributed to study design and protocol development, data collection, management, analysis, interpretation of results, writing of the report, and the decision to submit the report for publication.

Steering committee: Professor Gurney, Dr Nair-Shalliker, A/Prof Smith, Professor Patel, Professor Woo, Professor Gebski, Mr Espinoza, Professor Yaxley, Professor Gardiner, Professor Frydenberg and Professor Gillatt, all contributed to the study design, decision making, interpretation of data, writing of the report, and the decision to submit the report for publication.

Independent Data Monitoring and Safety Committee: Dr Hayden, A/Prof Wilcken and Dr Asher.

Radiology assessment panel: Associate Professor Richard O'Sullivan, Dr Alain Lavoipierre and Dr Lisa Tarlinton assessed the validity of the routine radiology reports on the MRI scans.

Data Management team: Dr Nair-Shalliker, A/Prof Smith, Ms Rodger and Ms Foo.

Blinding and Randomisation of participants: Professor Gebski and Mr Espinoza from the NHMRC Clinical Trials Centre setup the Interactive Voice Response System (IVRS) for blind randomisation of participants.

Blood collection, transportation and processing: All participants were requested to attend their nearest Sonic Healthcare pathology for blood sampling. Blood specimens collected to monitor PSA levels were sent to the Sonic central processing laboratory for analysis. Blood specimens collected for the purpose of the trial, were transported by Marken Australia to the processing laboratory. The Commonwealth Scientific and Industrial Research Organisation (CSIRO-Adelaide) was responsible for processing and storing all blood specimens for analysis at end of trial.

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Pharmaceutical manufacture and packaging: Vitamin D supplements and placebo were initially manufactured and packaged by API Consumer Brands (NZ). A second batch was manufactured by BioTech Pharmacal Inc (USA) and packaged by PCI Pharma (Australia).

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Figures and legends

Figure 1: Overview of the ProsD Trial

Figure 2: ProsD Trial Procedure

Appendix 1: Flow Diagram for Blood Sample Processing in ProsD Study

Appendix 2: Participant Information and Consent form

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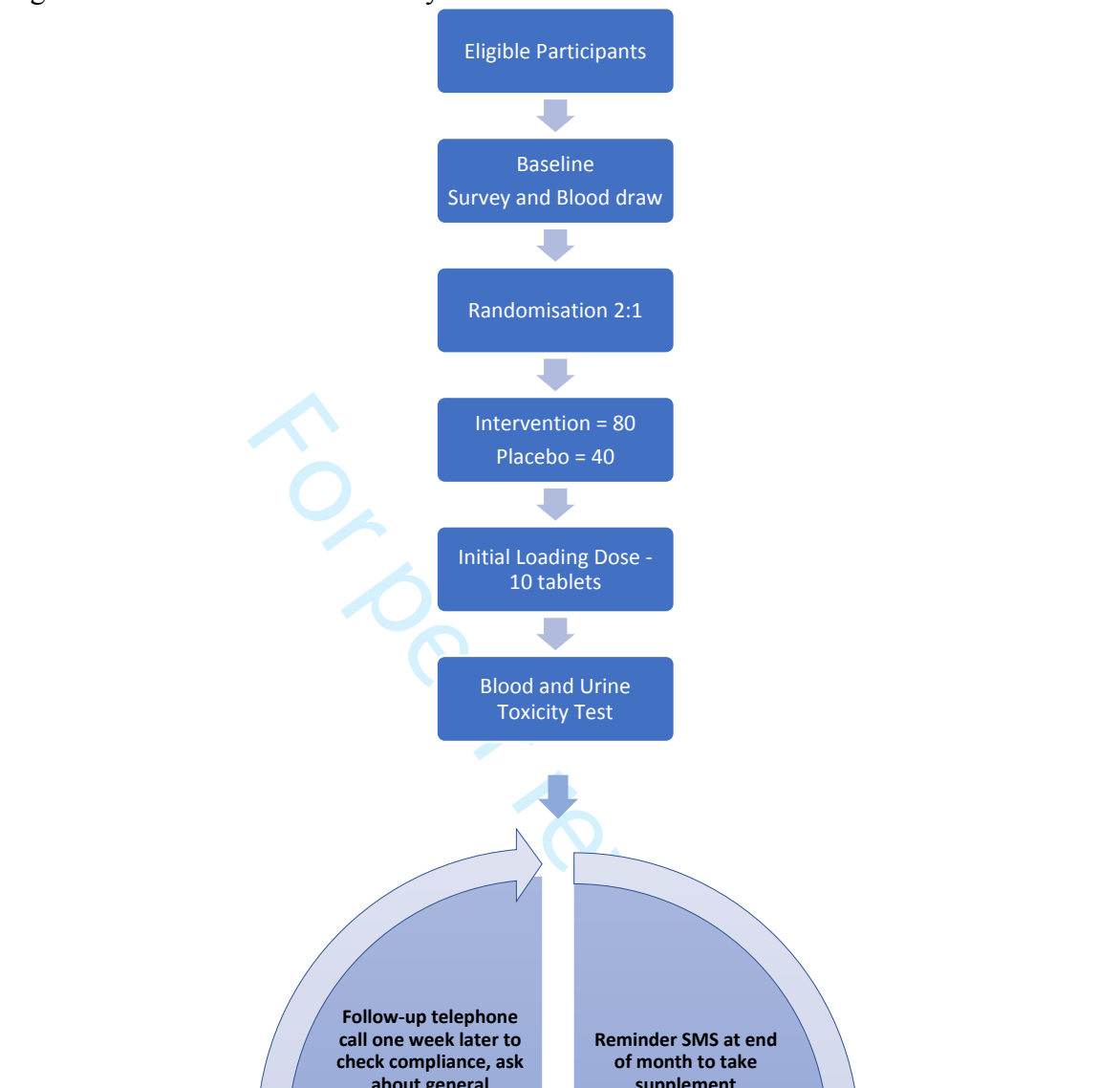
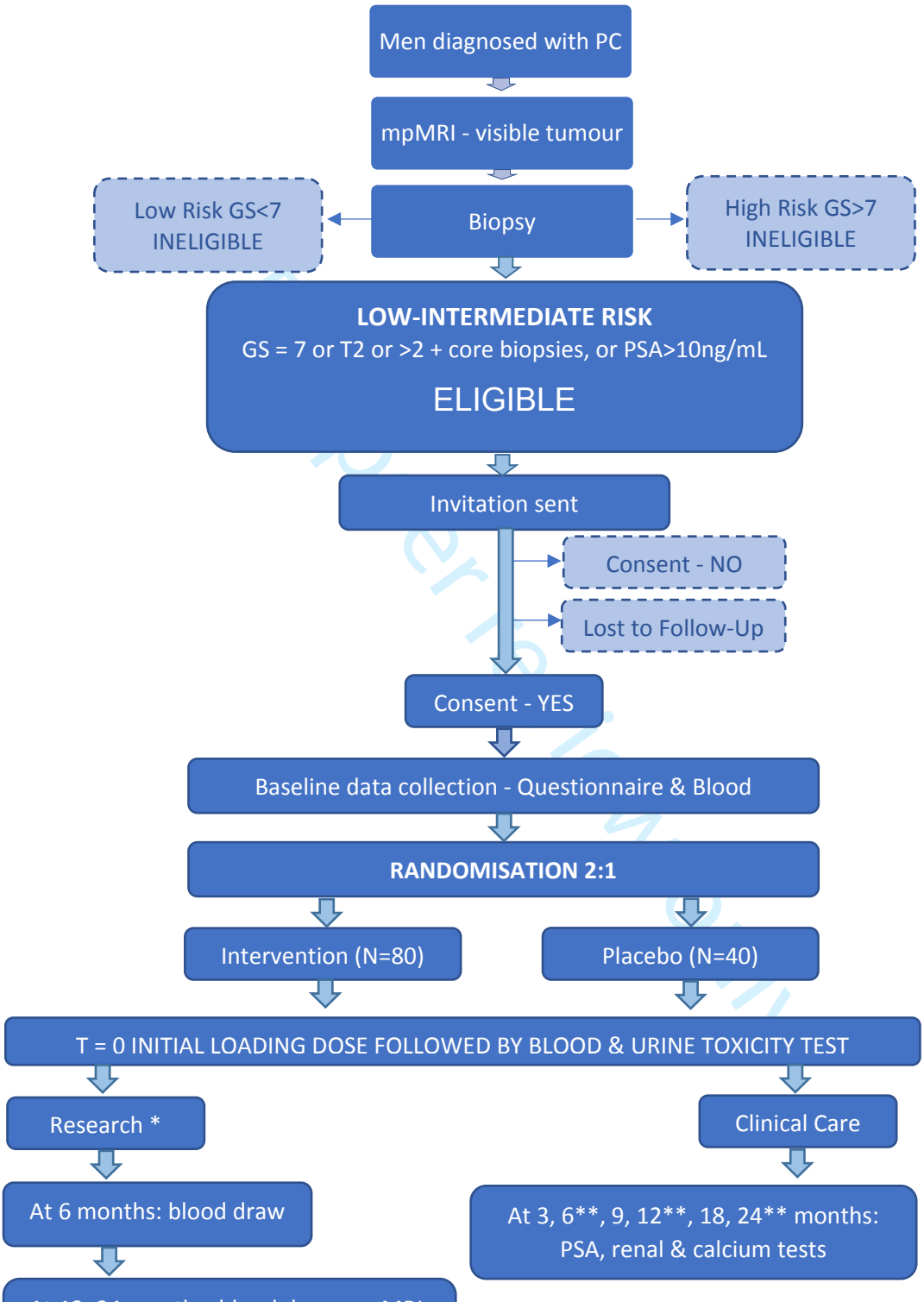
Figure 1: Overview of ProsD Study Procedure



[1] At 3,6,9,12,18,24 months: Participants will have PSA and biochemical tests (at urologists' request as in standard clinical care).
[2]At 6,12,24 months: Participants will be reminded to have a blood draw before supplementation is due.
[3]At 12 and 24 months: Participants will have to complete a questionnaire and be asked to have MRI scans.
[4]At 12 and 24 months: Repeat biopsies (at urologists' request).

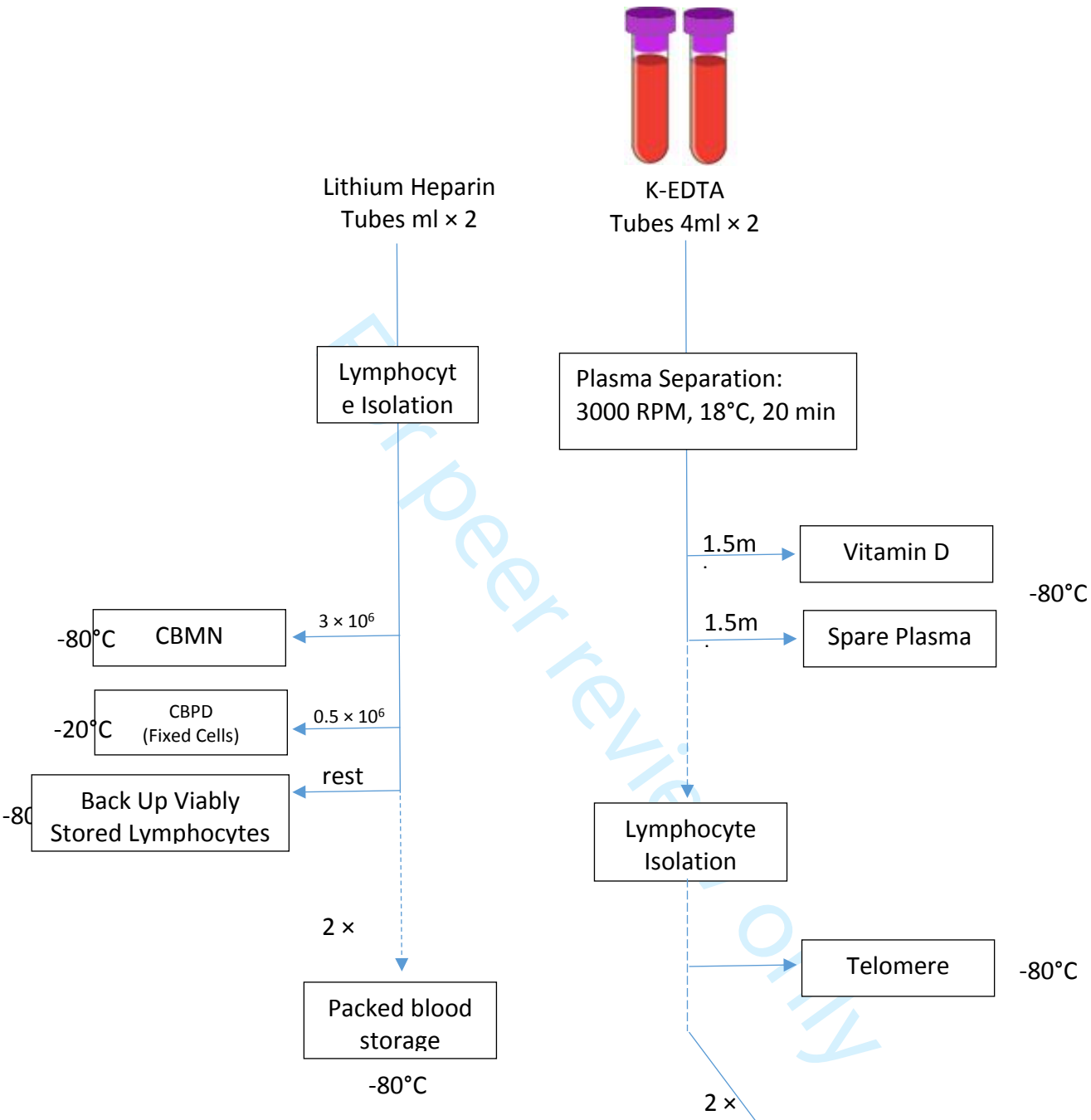
Figure 2: ProsD Trial Procedure



*All participants will be contacted monthly via email and SMS to take supplements, followed up one week later by phone to check compliance.

**The trial coordinator to coordinate all mail outs; Mail outs at 6, 12 and 24 months will include a request for a PSA test for clinical care and a request for the ProsD trial.

Appendix 1 Flow Diagram for Blood Sample Processing in ProsD Study



Appendix 2

Participant Information Sheet and Consent Form

STUDY TITLE: A PHASE II RANDOMISED CONTROLLED TRIAL OF HIGH-DOSE VITAMIN D IN LOCALISED PROSTATE CANCER CASES WITH INTERMEDIATE RISK OF PROGRESSION.

Short Title	ProsD
Protocol Number	MQ_GUR_ProsD1
Local Project Sponsor	Macquarie University
Lead Investigator	Professor Howard Gurney
Urologist	
Location	

High dose vitamin D supplementation may reduce the progression of prostate cancer. Although it is approved to treat conditions relating to vitamin D deficiency, its use is not approved to treat prostate cancer due to insufficient evidence. This is a two year clinical trial which aims to see if vitamin D can prevent disease progression in men with prostate cancer who have chosen to be on active surveillance. It also aims to also establish the safety of its use in these men.

This trial is led by Professor Howard Gurney from Macquarie University, in conjunction with researchers at Cancer Council NSW, and a team of Australian urologists, geneticists and vitamin D experts.

This trial is funded by the Movember Clinical Trial Award (PCFA-CTA 1315) through the Prostate Cancer Foundation of Australia.

This Participant Information and Consent Form provides you information about this trial and explains all trial requirements. Knowing what is involved, will help you decide if you want to participate in this trial.

There will be no costs associated with participating in this research project. You will not be paid for participating in this trial.

Participation in this trial is voluntary. Whatever your decision, it will not affect your relationship with the staff caring for you. You will receive the best possible care whether or not you take part.

If you choose to participate, you will be kept informed of any significant new findings that may affect your willingness to continue in the trial. If you wish to withdraw from the trial once it has started, you can notify us of your decision. All information already collected will be retained.

Please read this information carefully. If you have any questions, please contact your urologist or the trial coordinator. Their contact details are provided at the end of this document.

Eligibility for trial participation

All men with prostate cancer, who have intermediate risk of disease progression, and who are being managed by active surveillance, and who have been diagnosed in the past 4 months, will be considered eligible to participate in this trial. You have been asked to participate because you appear to fit these criteria.

Intervention

We aim to recruit 120 participants to this trial. All participants will be randomly assigned to either, receive vitamin D for those in the intervention arm (total of 80 men in this group), or receive placebo (tablet with no active ingredient) tablets for those in the control arm (total of 40 men in this group). All participants and study investigators will be blinded to the content of the tablets, where neither party will be told which arm of the trial the participants are in; this ensures best scientific methods are used. This information, which will be held by the Clinical Trials Centre, will only be disclosed to the investigators at the end of the trial.

At the start of the trial, all participants will be asked to take 10 tablets over a period of 12 hours. From then on, all participants will be asked to take one tablet a month for the remaining 23 months.

Supplements for this trial have been specifically designed and manufactured for the purpose of this trial. They cannot be purchased from the pharmacy, as the doses sold at pharmacies are lower than trial dosage.

Purpose of initial loading dose at the start of trial

The initial loading dose aims to boost blood levels of vitamin D, while the monthly dose will maintain requiredlevels.

Managing side effects

Two other Australian based studies have previously used high dose Vitamin D supplements in this way. The Mel-D study which is a clinical trial in melanoma patients, and the D-Health study, which is an Australian study of ~20,000 men and women. Neither of these studies reported any unusual health effects in their participants. Nevertheless your blood and urine samples will be monitored closely for any signs of abnormalities.

Blood and urine collection

We will require your blood sample at 5 different time points, for the purpose of this trial, and that is, before commencement of intervention, and again at 6, 12 and 24 months. We will also require a blood and urine sample 24 hours after taking initial supplement. We will coordinate blood collection for the purpose of your routine clinical care, as requested by your doctor, at 3,6,9,12,18, and 24 months.

We will aim to coincide blood collection for the trial with that required by your doctor for your routine clinical care, to minimise your visits to the pathology centre. You will be given specific instructions to go to a pathology provider to have your blood drawn.

At the back of the form will be a list of pathology providers that you can choose for your convenience.

Purpose of multiple blood samples and urine sample

For the purpose of your safety and wellbeing, we will be collecting blood samples and urine to monitor renal function to ensure there are no adversities, 24 hours after commencing the trial. For the purpose of monitoring prostate specific antigen (PSA) levels, by your doctor, blood samples will be collected at 3, 6, 9, 12, 18 and 24 months; your doctor will continue to monitor your renal function to ensure there are no adversities. The results from these tests will be forwarded to your treating urologists, and a copy will be sent to the ProsD trial coordinator.

For the purpose of the trial, blood samples will also be collected at the start of the trial, and again at 6, 12, and 24 months, which will be used to determine if high levels of vitamin D are attained and also maintained thereafter. These blood samples will also be used to determine if there are overall changes to your gene profile following vitamin D supplementation.

All blood samples collected for the purpose of the trial will be stored in a -80C freezer at a laboratory specialising in specimen storage and analysis, and only be analysed at the end of the trial. These samples will be identified by a study identification number, not by name.

Prostate biopsy

You will not be required to have any additional biopsies for this trial. All biopsies that you will undertake will be according to standard clinical practice, as advised by your urologist. All pathology information that we will require for the trial will be collected from your clinical records. We will require a sample of your biopsy to assay for genome damage markers.

Tests conducted on your samples

We will analyse your blood and tissue biopsy samples for vitamin D levels, and also assess overall changes to your gene profile, from baseline to the end of the trial.

Blood test results

All test results will remain confidential. Only your doctor and the researchers will have access to any information about you. If any results have direct implications for your health, the trial team will inform your doctor and your doctor will discuss them with you.

Magnetic Resonance Imaging (MRI) scans

MRI scans take detailed pictures of your prostate and can indicate if your disease is progressing. Your diagnostic scan which would have been done before you were recruited to this trial, will establish your disease status. We will require you to have additional scans at 12 and 24 months, to determine if your disease has progressed. We will require copies of your diagnostic and follow-up scans.

We will cover all costs of these additional scans done at 12 and 24 months. We are unfortunately unable to reimburse any scans done before you were recruited into this trial.

Survey

You will be asked to complete a survey on your general health, demographic, diet, and lifestyle factors, your supplementation and medications use, and about your recent time spent outdoors, at the start of the study, and again at 12 and 24 months. We will mail you a copy of this survey which can be returned to us in a reply-paid envelope upon completion, or it can be completed online (details will be provided to you).

Changes to lifestyle

You will have to refrain from taking any vitamin D supplements while on this trial.

Benefits of taking part

We cannot guarantee that you will receive any benefits from this research. However, possible benefits may include a delay in your prostate cancer disease progression which means you will be able to remain on active surveillance longer. This may delay the uptake of more radical treatment and its possible side effects.

If this trial indicates that high dose vitamin D supplementation reduces disease progression, this will lead to a Phase III trial involving a larger group of men. If a Phase III trial is able to substantiate these findings, then results of the trial will be provided to prostate cancer organisations and policy makers at State and Territory, and Commonwealth levels to include high dose vitamin D supplementation in Australian clinical guidelines for the management of men on active surveillance.

Risks and disadvantages of taking part

High dose vitamin D supplementation is unlikely to cause significant side effects, as observed in two other Australian vitamin D based trials. There is a low risk of the blood calcium level becoming high. This will be monitored by the blood tests on the study and if it occurs, the vitamin D supplementation will be stopped. There is also a low risk of kidney stones if a high calcium level is not corrected by stopping the medication. If you do show signs of any new or unusual symptoms please do not hesitate to contact your treating urologists immediately.

Although your blood is drawn by professional health care professional, there is still a low risk of complications which may include fainting, dizziness, bruising at the puncture site, nerve injury and arterial puncture. If you have previously experienced any of these complications please bring this to the attention of the healthcare professional at time of your blood draw.

There are no proven long-term risks related to mpMRI scans and it is considered to be safe when performed at a centre with appropriate procedures. You will lie on a table inside the MRI scanner which will record information about your prostate. It will be important that you are in a comfortable position so that you can keep still. The scanner is very noisy and you may be given earphones to reduce the noise. Some people may experience symptoms of claustrophobia from lying in a confined space. If you do experience discomfort at any time during the scan, you will be able to alert staff by pressing on a call button provided to you. The magnetic field generated by the MRI will attract metal objects and therefore you will be instructed to remove all metallic belongings. This magnetic field can also pull on any metal containing object in your body such as medicine pumps and aneurysm clips, or result in overheating of some of the older style medical implants. Many new medical implants are designed to be MRI-compatible. Every MRI facility will have a comprehensive screening procedure to ensure the safe use of the MRI.

If you suffer any injury from participating in this study, the parties involved in this research project have agreed to cover any costs involved with ensuring the safety of all study participants. Any participants showing indications of any adverse event, adverse reaction or serious adverse event will be immediately withdrawn from the study and closely monitored by a clinician to ensure there are no further complications, at no cost to the study participant. If you wish to obtain a copy of the Medicines Australia compensation guidelines please contact the Trial coordinator on 1800 789 622 (FreeCall).

Access to clinical records

We will need to access your clinical records during the duration of this trial, and in the follow-up phase thereafter to determine long term effects. We will require your consent for us to access your clinical records.

De-identification of personal information

By signing the consent form you consent to your doctor and relevant trial staff collecting and using personal information about you for the research project. You will be assigned a unique identification number, and be referred to hereafter (i.e. blood sample tubes) by this unique identification number. Any identifiable information that is collected about you in connection with this study will be recoded to this identification number. It will remain confidential and will be disclosed only with your permission, or except as required by law. Only the investigators will have access to your details and results that will be held securely at Cancer Council NSW.

The results from this trial will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be presented in such a way that you cannot be identified.

Results from the trial

Individual results will not be provided to participants, as the analyses of these de-identified samples will only commence at the end of the trial, when all trial participants have completed the trial. The overall findings from this trial will be mailed to you in a newsletter.

Managing Adverse Effects

If you suffer any adverse effects, or complications as a result of this trial, you should contact your doctor as soon as possible and you will be assisted with arranging appropriate medical treatment.

Ethical review of this trial

All research in Australia involving humans is reviewed the Human Research Ethics Committee (HREC). This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies. The ethical aspects of this research project have been approved by the HRECs of Macquarie University, and Bellberry Limited, which is a national, private non-for-profit organisation providing high quality, independent scientific and ethical review of human research projects across Australia.

Utility of blood and tissue samples after the trial is complete

Your samples will be retained by the investigators for 15 years after the end of the trial. However since these samples are highly valuable, and may be extremely useful in future research, we seek your consent to retain these samples for longer than 15 years for cancer-related research in future. These samples may be used by future researchers, however no blood, tissue or health information will be released to a third party unless it is to carry out research that has been approved by a Human Research Ethics Committee.

All samples will be analysed simultaneously at the completion of this trial. All unused samples will be stored at -80^{0}C, and may be used for research projects, only with the approval of a Human

Research Ethics Committee. If you do not agree to your specimen being stored beyond 15 years, then these samples will be destroyed.

What does participation in this trial involve?

Participation in this research involves taking monthly supplements, completing surveys, giving bloods, giving us consent to access your tissue biopsy and having Magnetic Resonance Imaging (MRI) scans. In addition, the researchers would like to have access to selected medical records about your prostate cancer tests, treatment and further results to obtain information relevant to the study.

If you agree to take part in this trial then:

(i) You will agree to take 10 tablets over a period of 12 hours, at the start of the trial

(ii) You will agree to have a urine test 24 hours after taking the first dose of supplementation, at the start of the study.

(iii) You will agree to take 1 tablet every month for the remaining 23 months.

(iv) You will agree to give ~twenty millilitres (~20mL), or ~one tablespoon, of blood at time of recruitment, 24 hours after taking the first dose of supplementation, at 6, 12, and 24 months each.

(v) You will provide us consent to access your prostate cancer biopsy samples from the pathologist.

(vi) You will agree to complete a survey (either paper survey or web-survey) at time of recruitment, and again at 12 and 24 months each.

(vii) You will agree to have a MRI scan at 12 and 24 months (cost will be covered by the trial).

(viii) You will consent to the use of your personal and health information.

(ix) You will agree not to take additional vitamin D supplementation during this trial, although you can continue to take any medication as advised by your doctor

Participation in this study is voluntary. It is completely up to you whether or not you participate. Whatever your decision, it will not affect your relationship with the staff caring for you.

If you choose to participate, you will be kept informed of any significant new findings that may affect your willingness to continue in the study. If you wish to withdraw from the study once it has started, you can notify us of your decision, without having to give a reason. However all information already collected will be retained.

What to do next

If you agree to take part in this trial, please take these forms with you on your next visit to your urologist.

By signing it, you are telling us that you understand what you have read and consent to:

- taking part in this trial
- taking an initial high dose of oral vitamin D supplement
- taking a monthly dose of oral vitamin D supplements for 23 months
- giving urine and blood samples at specified time points at a pathology provider located near your residence
- Completing surveys at required time points
- having MRI scans at 12 and 24 months

- allowing researchers access your prostate biopsy samples
- allowing researchers to access your health information

You will be given a copy of this Participant Information and Consent Form to keep. Your urologist will keep one copy and return to us the third signed copy in the reply-paid envelope supplied.

After we have received your signed consent, we will send you further information about the blood collection and interview, which will be done before you are randomised to start the trial.

Remember: Participation in the study is entirely voluntary. You may withdraw at any time after you have agreed to participate.

Advice and Information

The person you may need to contact will depend on the nature of your query. If you have any medical problems which may be related to your involvement in this trial (for example any side effects) you can contact your urologist. If you want any further information concerning this project you can contact the Trial coordinator.

ProsD Study Team Contact Persons	
>Insert Urologist name<	Dr Visalini (Lini) Nair-Shalliker
Urologist	Trial Coordinator
Telephone: <Insert number>	Telephone: 1800 789 622 (FreeCall)
Email <Insert email add>	Email: enquiriesProsD@nswcc.org.au

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Bellberry Human Research Ethics Committee
HREC Executive Officer	Bellberry HREC
Telephone	(08) 8361 3222
Email	bellberry@bellberry.com.au

The Bellberry Human Research Ethics Committee has reviewed and approved this study in accordance with the National Statement on Ethical Conduct in Human Research (2007) – incorporating all updates. This Statement has been developed to protect the interests of people who agree to participate in human research studies. Should you wish to discuss the study or view a copy of the Complaint procedure with someone not directly involved, particularly in relation to matters concerning policies, information or complaints about the conduct of the study or your rights as a participant, you may contact the Committee Chair, Bellberry Human Research Ethics Committee on 08 8361 3222.

CONSENT TO PARTICIPATE IN RESEARCH

Title: A Phase II randomised controlled trial of high-dose vitamin D in localised prostate cancer cases with intermediate risk of progression

Principal Investigator: Professor Howard Gurney

Declaration by Participant

1. I understand that the researcher will conduct this study in a manner conforming to ethical and scientific principles set out by the National Health and Medical Research Council of Australia and the Good Clinical Research Practice Guidelines of the Therapeutic Goods Administration.
2. I acknowledge that I have read, or have had read to me the Participant Information Sheet relating to this study. I acknowledge that I understand the Participant Information Sheet. I acknowledge that the general purposes, methods, demands and possible risks and inconveniences which may occur to me during the study have been provided to me by the Trial Coordinator and I, being over the age of 18 acknowledge that I understand the general purposes, methods, demands and possible risks and inconveniences which may occur during the study.
3. I acknowledge that I have been given time to consider the information and to seek other advice.
4. I acknowledge that refusal to take part in this study will not affect the usual treatment of my condition.
5. I acknowledge that I am volunteering to take part in this study and I may withdraw at any time.
6. I acknowledge that this research has been approved by the Bellberry Human Research Ethics Committee.
7. I acknowledge that I have received the Participant Information Sheet and a copy of this consent form, which I have signed.
8. I acknowledge that regulatory authorities may have access to my medical records relevant to this study to monitor the research in which I am agreeing to participate. However, I understand my identity will not be disclosed to anyone else or in publications or presentations.

Name of Participant (PRINT) _____

Signature _____ Date _____

Declaration by Study Doctor:

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor (PRINT) _____

Signature _____ Date _____

PARTICIPANT TO KEEP THIS FOR THEIR RECORDS

CONSENT TO PARTICIPATE IN RESEARCH

Title: A Phase II randomised controlled trial of high-dose vitamin D in localised prostate cancer cases with intermediate risk of progression

Principal Investigator: Professor Howard Gurney

Declaration by Participant

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Signature _____ Date _____

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I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor (PRINT) _____

Signature _____ Date _____

DOCTOR TO KEEP THIS FOR THEIR RECORDS

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Signature _____ Date _____

Declaration by Study Doctor:

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Name of Study Doctor (PRINT) _____

Signature _____ Date _____

PLEASE SIGN AND RETURN IN REPLY PAID ENVELOPE

BMJ Open

Protocol: A Phase II randomised controlled trial of high-dose Vitamin D supplementation to prevent progression in localised prostate cancer cases with low-intermediate risk of progression on active surveillance (ProsD).

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044055.R1
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Primary Subject Heading:	Urology
Secondary Subject Heading:	Oncology
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Title:

Protocol: A Phase II randomised controlled trial of high-dose Vitamin D supplementation to prevent progression in localised prostate cancer cases with low-intermediate risk of progression on active surveillance (ProsD).

Trial registration

ACTRN12616001707459

Protocol Version:

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Abstract

Introduction: Active surveillance (AS) for prostate cancer patients with low risk of PC death is an alternative to radical treatment. A major drawback of AS is the uncertainty whether a patient truly has low risk PC based on biopsy alone. Multiparametric MRI scan together with biopsy, appears useful in separating patients who need curative therapy from those for whom AS may be safe. Two small clinical trials have shown short-term high dose vitamin D supplementation may prevent prostate cancer progression. There is no substantial evidence for its long-term safety and efficacy, hence its use in the care of men with PC on AS needs assessment. This protocol describes the ProsD clinical trial which aims to determine if oral high dose vitamin D supplementation taken monthly for 2 years can prevent prostate cancer progression in cases with low-intermediate risk of progression.

Method and analysis: This is an Australian national multi-centre, 2:1 double-blinded placebo-controlled Phase II RCT of monthly oral high-dose vitamin D supplementation (50,000IU cholecalciferol), in men diagnosed with localised PC who have low-intermediate risk of disease progression and are being managed by AS. This trial will assess the feasibility, efficacy, and safety of supplementing men with an initial oral loading dose of 500,000IU cholecalciferol, followed by a monthly oral dose of 50,000IU during the 24 months of AS. The primary trial outcome is the commencement of active therapy for clinical or non-clinical reason, within 2-years of AS.

Ethics and dissemination: This trial is approved by Bellberry Ethics Committee (2016-06-459). All results will be reported in peer-reviewed journals.

Trial Registration: ACTRN12616001707459

Strengths and Limitations of this study

- This double blinded placebo controlled randomised controlled trial with stringent allocation concealment eliminates treatment and allocation bias.
- Adherence to the trial is likely high due to regular patient follow-ups and mode of delivery of intervention by mail makes this trial accessible to men in urban and rural areas.
- Blood collection at varying timepoints makes this a valuable resource but is costly.
- This is a phase 2 trial hence results will not be conclusive for the role of Vitamin D but may inform a phase 3 trial, is a limitation.
- Follow up is 2 years and therefore a benefit or lack of benefit of vitamin D may not be appreciated in this time, given the natural slow progression of prostate cancer, is a limitation.

Introduction

Prostate cancer (PC) affects many men worldwide, with 1,276,106 new cases and 358,989 deaths estimated for 2018.[1 2] The proportion of low-risk tumours diagnosed has risen since the introduction of prostate-specific antigen (PSA) testing, leading in some cases to overdiagnosis, adverse effects and unnecessary treatment.[3] Over diagnosis due to PSA-testing may be unavoidable, but overtreatment is not. Results from the Prostate Testing for Cancer and Treatment (ProtecT) suggest minimal benefits in men with low-risk PC when managed with curative treatment, and instead recommended monitoring the course of PC with the intention of initiating curative treatment if and when the cancer progresses. Referred to as active surveillance (AS), this management option has evolved as an alternative to immediate active treatment for those diagnosed with low grade disease.[4] Consequently, AS is now the preferred management strategy for most men with low-risk PC. It aims to avoid overtreatment of clinically indolent disease by safely delaying definitive treatment until evidence of progression is evident.

The following augmented risk classification for low, intermediate and high-risk groups is used as guide to classify disease status:[5-7]

- Low risk: PSA < 10 ng/mL, and Gleason 3+3 or less, 2 or less positive biopsy cores and clinical stage T1-T2a.
- Intermediate: PSA 10 to<20 ng/mL or Gleason 7 (Gleason 3+4 or Gleason 4+3) or clinical stage T2b-c sub-divided into:
  - Favourable risk: Gleason 3+3 (with PSA 10 to <20 ng/mL or T2b-c) or Gleason 3+4.
  - Non-favourable risk: Gleason 3+4 (with PSA 10 to <20 ng/mL or T2b-c), or Gleason 4+3.
- High-risk: PSA > 20ng/mL, or Gleason 8 or greater, or clinical stage ≥T3.

The preferred management strategy that is widely adopted for most men with low-risk disease is AS while curative/active treatment is widely adopted for men with intermediate to high risk disease .[8-11] There is mounting evidence that men with *favourable intermediate* risk PC may have similar mortality risk as those with *low* risk disease. These men may therefore be good candidates for AS, as a safe first-line management option, although the consensus to accurately define this sub-group of PC cases needs clarity.[4 8-12]

Prostate Cancer Diagnosis

PC is conventionally diagnosed using transrectal ultrasound (TRUS) to guide prostate biopsy (PB). As cancer cannot be imaged on ultrasound, the major limitation of this approach is non-detection of a substantial proportion of significant PC. Sampling error can lead to the misdiagnosis of clinically significant disease, which may be upgraded at repeat biopsy. Referred to as reclassification, this gives the perception of disease progression, subsequently leading to overtreatment. The Prostate Cancer Research International Active Surveillance Project, referred to as the PRIAS Project, estimated that

approximately 28% of PRIAS participants showed reclassification upon repeat biopsy.[13-15] The use of mpMRI, originally used for staging, is now routinely used for tumour detection and localisation, allowing image-guided targeted sampling to overcome the limitations of the traditional blind PB. mpMRI is able to detect both high-grade and larger tumours accurately, which means it may perform particularly well for detection of clinically significant disease.[16-18] It can improve the specificity of locating PC and targeting the PB. It can also differentiate low- and intermediate/high-grade PC, thereby providing more accurate risk classification of PC.

Prostate Cancer Risk and Vitamin D

Two recent clinical trials in PC patients suggest that vitamin D supplementation may prevent PC progression.[19 20] Daily supplementation of 4000IU for one year reduced the number of positive cores and Gleason grade, but did not reduce PSA levels.[19] A daily high dose of 40,000IU for only 10 weeks significantly reduced PSA levels but did not change Ki67 expression in prostate tissue. Those who received 4000IU and 10,000IU showed no significant reduction in PSA level.[20] Duration of follow-up was short in both these trials and may have resulted in the lack of significant findings. Further trials of high vitamin D doses to prevent PC progression are therefore required. Trials are also needed to assess the long-term safety of vitamin D supplementation in cancer patients.

Prostate Cancer and Genome Damage

There is a strong link between the prevalence of markers of genome damage and cancer risk. Studies have shown that prevalence of chromosomal aberrations (CA) is 2.2- to 2.4-fold higher in cancer patients than in non-cancer controls, and that micronuclei (MN) formation, a marker for chromosomal instability, was associated with increased cancer incidence in a study of 6718 individuals.[21] There is also evidence to link telomeres to cancer risk.[22] Telomeres are repetitive *TTAGGG* DNA sequences that maintain genomic stability by protecting the ends of chromosomes; they shorten in length over time in normal somatic tissues due to incomplete replication of the telomere. Telomere shortening is accelerated by oxidative stress, inflammation and cell proliferation and has been linked with induction of cell senescence which guards against survival of genomically abnormal cells.[23] Evidence from prospective studies show positive associations between telomere length and various cancers, including that for low-grade (OR 1.13, 95% CI:1.01–1.27) and localised PC (OR 1.12, 95% CI:1.01–1.24) disease, possibly due to abnormal telomerase expression and telomere elongation, which enables the survival of genomically unstable cells, their unrestricted growth and their evolution into cancer.[24-26] There is evidence to show that some micronutrients are essential to prevent genome damage but the specific impact of vitamin D is only just starting to be explored.[27]

Evidence suggests that high levels of vitamin D metabolites (25(OH)D and $1,25(OH)_2D$) may prevent genome damage in leukocytes by reducing prevalence of MN formation and by maintaining adequate telomere length.[28-32] There is also evidence to suggest that $1,25(OH)_2D$ may inhibit telomerase activity in tumour tissue in a pathway involving miRNA498, a non-coding small RNA.[33] This current trial

provides an opportunity to concurrently examine the possible role of vitamin D in the regulation of these markers of DNA damage in PC.

Rationale

The ProsD study is a 2:1 double blinded placebo controlled randomised control trial for high dose vitamin D supplementation, in a group of men with PC who have low-intermediate risk of disease progression, and are undertaking AS. There is uncertainty as to whether AS or curative therapy is best for this risk group. The protocol mandates the use of MRI-detected and targeted cancers in the inclusion criteria to reduce disease reclassification bias due to sampling error on biopsy and to assist in the diagnosis of disease progression on AS.

Objectives and outcomes

The objective of this trial is to determine if monthly oral high dose vitamin D supplementation for 2 years can prevent disease progression in PC cases with low-intermediate risk of progression. We will assess the feasibility and safety of an initial oral loading dose of 500,000IU followed by a monthly oral dose of 50,000IU of cholecalciferol, for 2 years of AS.

Primary outcome:

The primary trial outcome is the switch from AS to active therapy, for clinical or non-clinical reasons, within 2-years of AS.

Secondary outcomes:

(a) Switch from AS to active therapy, specifically for clinical reasons, within 2 years of AS.
(b) Switch from AS to active therapy, specifically for non-clinical reasons, within 2 years of AS.

Tertiary outcomes:

(a) The proportion of PC patients achieving levels of total 25(OH)D above 75 nmol/L following vitamin D supplementation. We will also characterise those whose serum 25(OH)D does not increase to 75nmol/L in response to supplementation and measure levels of $1,25(OH)_2D$.
(b) Extent of DNA damage in those receiving the high dose vitamin D supplementation.
(c) The utility of mpMRI scan in detecting PC progression in cases managed on AS.

Methods: Participants, interventions, and outcomes

Participants

Trial participants will be recruited from 15 private Australian urology clinics located in Australia, with the corresponding ethics approval being obtained for all sites. Records of all patients diagnosed in the 6 months prior will be screened by urologists and clinic nurses, to identify potential participants. Those clinically eligible will be contacted, introduced to the ProsD trial, and consent obtained to forward their personal details to the trial coordinator. Each potential participant will be further screened for remaining eligibility criteria before being invited to participate. The ProsD trial will use subsets of D-Amico's classification to derive its population of interest. All eligible

participants will be mailed a Participant Information Consent Form, and those who decline will not be followed-up further. All consenting participants will be assigned a 7-digit identification number.

Eligibility Criteria

All participants aged between 50 and <80 years must have results of at least one mpMRI (centrally reviewed and not limited to any PIRADS score) and one of the following:

- Gleason grade 3+4 or
- >2 positive biopsy cores (which may include Gleason 6) or
- Clinical stage T2 (which may include Gleason 6) or
- PSA>10 ng/mL (which may include Gleason 6).

Those diagnosed with these clinical features but without a prior mpMRI scan will be requested to have a scan done for the purposes of the study. Those with a pacemaker or with metal prosthesis in their body will not be asked to have an mpMRI.

Men who were previously diagnosed with low-risk disease and whose disease has been upgraded during the preceding 6 months will be eligible to participate.

Exclusion Criteria

- Men with low-risk disease:

- Gleason score 6 or less and

- PSA<10ng/mL and

- Clinical stage <T2

- Men with high-risk disease:

- Gleason score 8 or more or

- PSA>20ng/mL or

- Clinical stage T3 or T4 or N/M >0.

- Consuming daily Vitamin D supplementation more than 50% of RDI (more than 300IU/day).
- Hyperparathyroidism, hypercalcaemia, or osteomalacia.
- Glomerular filtration rate (GFR) below 30 or Stage 4 or Stage 5 kidney disease
- History of renal calculi.
- Taking orlistat, cholesterol-lowering drugs called bile acid sequestrants, such as cholestyramine and cholestipol, or other drugs known to reduce vitamin D absorption.
- Those with gastrointestinal abnormalities that may affect nutrient absorption such as inability to swallow oral medication or clinically diagnosed malabsorption

Sample size

The primary outcome for the trial is the conversion from AS to active therapy within 24 months from date of consuming their initial loading dose of supplements. This is currently estimated to be ~35.0% at 2 years for low-intermediate risk patients on AS. Using Simon's two-stage design, a sample size of 80 patients in the group receiving the vitamin D supplement would have > 80% power with 95% confidence to exclude a success rate of 65.0% in favour of a more interesting rate of 77.5% (i.e. active therapy rate of 22.5% rather than 35.0%).

Additionally, a futility analysis will be performed after 24 patients have received vitamin D for 24 months, and if eight or more patients in the intervention group have disease progression after 2 years of intervention, consideration will be given to modifying the intervention or stopping the study for futility. In order to obtain contemporary estimates for the control group it is proposed to randomise patients 2:1 resulting in a total sample size of 120 patients (80 vitamin D supplementation, 40 placebo controls).

Intervention

The intervention is a monthly oral dose of 50,000IU of cholecalciferol for 24 months. Participants randomised to control will take a visually identical placebo.

Initial Loading Dose

Each participant will be requested to orally consume 10 tablets within 12 hours commencing initial loading. They will be required to attend a pathology provider to have their blood and urine tested for toxicity the following day. They will be assessed for incidence of hypercalcaemia and hypercalcinuria, which will be measured to ensure serum and urine levels are below 2.75 mmol/L and less than 7.5 mmol/24hrs, respectively, and to ensure the average estimated glomerular filtration rate is within normal range. All results will be uploaded onto the pathology providers' online results portal which will be accessed by the treating urologist and trial coordinator.

Follow-Up Doses

Thereafter, participants will consume 1 tablet a month (after 30 days), for the remaining 23 months. Each participant will be sent a reminder email and/or SMS to take the supplement a day before the due date and be followed-up the following week to ensure compliance. Each participant will also be asked questions on any lifestyle changes, their well-being, if they have had any falls, and be notified of the date of the next supplement follow-up. At the completion of intervention period, all participants will be requested to destroy all remaining supplements. ProsD procedure is outlined in Figure 1.

Justification for dosing regimen

This dosing regime is similar as that proposed by the Mel-D trial (ANZMTG 02.09 Mel-D) which is a RCT of vitamin D supplementation in melanoma patients. The 500,000IU loading dose aims to achieve an early increase in 25(OH)D levels. This is followed by a monthly lower dose of 50,000IU to maintain high levels; the monthly dosing frequency is proposed to improve the likelihood of good

compliance over the trial period. This dose has been shown to achieve average serum 25(OH)D levels of ~78nm/L without adverse effects.[34]

Randomization

All supplements (placebo and active) will be packed in boxes to look similar and assigned a kit number. This information for each kit number and its corresponding content (placebo or active) will be provided to the NHMRC Clinical Trials Centre, University of Sydney (NHMRC-CTC-by the packaging company (PCI-Pharma). All staff at the coordinating site and treating urologists are blinded to the allocation.

Upon completion of baseline data collection, participants will be randomised in the ratio of 2:1 using their 7-digit ID, date of birth, and diagnostic pathology status. Randomization will be performed centrally at the-NHMRC-CTC to guarantee allocation concealment using an interactive voice record system (IVRS). Using the method of minimization with patients stratified by age (≤ 65 years, ≥ 65 years); Gleason score (<7, 7); upgraded to low-intermediate risk in the past 6 months (yes/no), a randomisation number will be created to generate corresponding kit numbers specific to active or placebo box of supplements. This information will be provided to the Trial Coordinator, who will then mails the assigned boxes of supplements, and a pathology request form (for blood/urine toxicity tests) to participant, with specific instructions.

Endpoints

Primary Endpoint

The primary endpoint will be the proportion of participants opting for active therapy for PC (Active therapy-free survival, ATFS). There will be no absolute requirements for conversion to active therapy which will be at the discretion of the treating urologist. However, as a guideline, active therapy may be considered in the following situations.

- Gleason 4+3 or greater on rebiopsy *or*
- Gleason 3+4 = 7 where pattern 4 is > 10% on rebiopsy *or*
- Any Gleason 6 or 3+4 =7 (pattern 4 < 10%) on rebiopsy where progression on mpMRI has occurred defined as (based on NCI study Frye et al ASCO GU 2016):
- increase in PIRAD score
- any increase in lesion diameter measured in the axial plane
- appearance of any new lesion
- PSA doubling time of less than 3 years

Active therapy-free survival (ATFS) is defined as men who do not undergo any active therapy (e.g. radical prostatectomy or radiotherapy) during the trial.

Secondary Endpoints

- proportion of participants opting for active therapy for PC for non-cancer progression (e.g. anxiety) *or*
- proportion of participants opting for active therapy for PC for clinical reasons
  - PSA doubling time (PSA doubling time <3 years is progression)
  - Increase in Gleason grade
  - Increase in the percentage of involved cores
  - Increase in cancer volume (total mm of cancer detected/total mm biopsied)

Tertiary Endpoints

- Proportion of participants achieving optimal serum vitamin D levels as assessed by serum 25OHD levels 75nmol/L and above
- Prevalence of lymphocytic DNA damage as assessed by markers listed above
- Re-evaluation of mpMRI scans in detecting PC progression in cases managed on AS.

Definition of Outcomes

1. Conversion to active therapy due to clinical reasons

- Gleason 4+3 or greater on rebiopsy *or*

- Gleason 3+4 =7 where pattern 4 is > 10% on re-biopsy *or*

- Any Gleason 6 or 3+4 = 7 (pattern 4 < 10%) on re-biopsy where progression on mpMRI has occurred defined as:

- increase in PIRAD score
- any increase in lesion diameter measured in the axial plane
- appearance of any new lesion

- PSA doubling time of less than 3 years

2. Conversion to active therapy due to non-clinical reasons

- Number of patients opting out of AS for non-cancer progression (e.g. anxiety)

Patient and Public Involvement

Two consumer representatives from the Prostate Cancer Support Networks (Prostate Cancer Foundation Australia), were involved in providing feedback in the conceptual development of the study, study design, purpose, and all study materials.

Methods: Data collection, and management

Data collection

Each participant will be mailed a copy of a baseline survey at the start of the project, followed by a follow-up survey at 12 months and 24 months (Appendix 1). Blood specimens will also be collected at these timepoints as well as at 6 months after commencement of supplementation. Each

questionnaire is anticipated to take an approximately 30 minutes to complete. Participants with incomplete responses will be followed-up.

For the purpose of research, blood will be collected into one heparin tube (10mL) to perform the cytokinesis-block micronucleus cytome (CBMN) assay in lymphocytes, and one EDTA tube (10mL) for vitamin D assay. Participants will not be required to fast before blood collection. Collection will be undertaken and coordinated by Douglass Hanly Moir Pathology (DHM) in NSW, Sullivan and Nicolaides Pathology in Queensland, and Dorevitch Pathology in Victoria. All tubes will be labelled with the 7-digit study identification number, participants' date of birth, date of blood draw, and time of blood draw. Participants' names will not appear on these tubes. When blood draw is complete, specimens will be collected, packed, and transported to the processing facility (Commonwealth Scientific and Industrial Research Organisation, CSIRO, Australia) within 24 hours of collection, by the courier company (Marken Australia). Date and time of blood collection and receipt of samples will be recorded. Blood processing protocol is outlined in Appendix 2. All participants who have not had blood drawn will be followed up with a fortnightly reminder phone call/email, for five weeks. Participants who do not respond after 5 follow-ups will be recorded as loss to follow-up.

All participants will also be mailed a MRI-request form, at 12-months and 24 months, to have this scan completed, preferably, by the same provider as that during their diagnosis.

Blood Processing

All blood specimens will be processed by CSIRO laboratory (South Australia). The heparin tubes will be processed for fresh lymphocytes, and EDTA tubes will be processed to separate the plasma and buffy coats, which will be stored in 1mL aliquots at –80°C. All tubes will be identified by their 7-digit study identification number, participants' date of birth, date of blood draw, and time of blood draw.

Measurements in Blood

Vitamin D Assays: All vitamin D plasma assays will be carried by DHM Laboratory, at the end of the trial. The assay for 25(OH)D will be carried out using LC-MSMS, which is specifically set up to exclude the detection of epimers. We will re-assay 20% of these samples using the DiaSorin® Liaison semi-automated chemiluminescence assay (DiaSorin; DEQAS accredited). Internal and external vitamin D standards will be included in each batch of analysed samples. Levels for $1,25(OH)_2D$ will be measured by using the Liaison (Diasorin) platform. Mean levels for each metabolite will be measured at baseline, 6-, 12- and at 24- months for each arm of the trial.

Genome Damage Markers: The CBMN assay will be performed using the isolated lymphocyte culture protocol described elsewhere.[35] Biomarkers in the CBMN assay include formation of micronuclei (MN) within binucleated cells (BN) which originate from lagging chromosome fragments or whole chromosomes during mitosis; thus the frequency of BN cells with MN (designated BN-MN) is an index of chromosome breakage and loss. Nuclear division index (NDI), a measure of mitogenic response, which is useful as a biomarker of immune function will also be assayed. Prevalence of DNA damage will be evaluated for each marker as percent change from baseline to 12-months and 24 months.

PSA and biopsy follow-up

All participants will be mailed a pathology request every three months in the first year, and every 6 months thereafter, reminding them to have their PSA test completed. All participants are requested to have at least one repeat biopsy during the 24 months of follow-up. Information for any follow-up biopsy will be collected from their treating urologist. The timeline for blood collection for each participant is described in Figure 2. This figure describes from the timepoint a participant is flagged as potentially eligible, through to the completion of the trial, after which all participants will continue to be followed-up passively, from their clinical records obtained from their treating urologists.

Tissue Biopsy analysis

Paraffin-embedded biopsy tissue will be collected and stored in licensed premises in accordance with the Human Tissue Act 1983 (NSW). We will liaise with pathologists to have slides prepared from 5µm section from biopsy tissues (diagnosis and follow-up biopsies) and assayed for Ki67 activity. Change in Ki67 proliferation from baseline biopsy to follow-up biopsy will be reported.

Data management

All information collected and storage of study data will conform to the Australian Privacy Principles, *Guidelines under Section 95A of the Privacy Act 1988.* Data will be collected and stored in various formats during the trial, therefore appropriate methods of confidentiality and privacy will be maintained. Data will be entered into a password protected database in a de-identified manner where each participant will be allocated a unique 7-digit ID number and will be archived for 10 years after the completion of the study as specified by NHMRC. All participants will be identified by their Study identification number, participants' date of birth, and date of interview. All data cleaning and preparation will be conducted by research staff that are directly involved in managing the project.

A statistical analysis plan will be prepared prior to data-lock and contain additional detail on the methods described below. All randomised participants will be eligible for inclusion in the full analysis set. Analysis of efficacy endpoints will be undertaken on participants in the full analysis set unless participants are deemed non-evaluable by the Trial Management Committee; all such decisions will be documented in the final study report. While no formal comparisons between the two groups are planned,

exploratory analyses will be performed to determine the level of activity of the vitamin D supplement for the key outcomes.

Methods: Monitoring and Safety

An Independent Data Monitoring Committee (IDMC) will be established to monitor the safety of participants, to ensure the continued efficacy of the trial and compliance to the trial protocol, according to the IDMC Operations Manual. There will be 12-monthly reviews conducted by the IDMC for the purpose of monitoring the conduct of the trial and assessing participant safety.

All trial participants will be monitored by the IDMC and will be immediately removed from the study if they have:

- incidence of hypercalcaemia and hypercalcinuria, which will be measured to ensure serum and urine levels are below 2.75 mmol/L and less than 7.5 mmol/24hrs, respectively.
- a 20% fall in the estimated glomerular filtration rate, over the course of the study.
- more than two episodes of renal calculi occurring over the course of the study.

A participant who develops either hypercalcaemia or hypercalciuria will be referred to their general practitioner, for further management of their condition. A participant who develops renal calculi will be managed by their treating urologist for acute management of the stone as per normal procedures and guidelines.

Participant safety

The Principal Investigator will ensure that the study is completed in accordance with the guidelines set out in the *National Statement on Ethical Conduct in Human Research* (2007) (the *National Statement*) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. Adverse event reporting will be recorded from the date of informed consent. In the case whereby there is an Adverse Event (AE), Adverse Reaction (AR), Serious Adverse Event (SAE) or Suspected Unexpected Serious Adverse Reaction (SUSAR), an assessment of seriousness will be conducted by the PI or treating urologist. An AE is defined as any untoward medical occurrence (physical, psychological, social or economic), whether mild, moderate or severe, in a trial subject related to medical management, in contrast to complications of disease. A SAE is defined as any event that results in death, is life threatening, results in hospitalisation or results in disability or incapacity (persistent or significant).

Depending on the severity of the event, a medical assessment will be completed as soon as possible. It will be left to the Principal Investigator's clinical judgment to decide whether an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he perceives as an intolerable AE. If either of these occurs, the participant will undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable. The following will be documented and recorded in the adverse event logbook:

- Record each event as separate occurrences
- Document participant identification number, date of birth, name
- Document and describe the event
- Record the start and stop times of the event
- Document the severity of the event, mild, moderate, severe, fatal

Concomitant Medications/Treatments

Concomitant medications will not be recorded during the study, except for medications used to treat adverse events or medications known to interact with the study medications. Any concomitant use of vitamin D or multi-vitamin supplements in sufficient detail to be able to estimate daily vitamin D intake from these sources (Vitamin D supplementation more than 50% of RDI). Any concomitant use of calcium supplements, Orlistat or other drugs known to reduce vitamin D absorption will be recorded.

Informed consent process

Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial (Appendix 3). A copy of the signed Consent Form will be given to the participant to retain. The original signed form will be retained at the trial site. The right of a participant to refuse participation without giving reasons will be respected and the participant will remain free to withdraw at any time from the trial without giving reasons and without prejudicing his further treatment. The participant will be allowed as much time as wished to consider the information (within timeframe of eligibility criteria), and the opportunity to question the Investigator or other independent parties to decide whether they will participate in the trial. Potential participants will only be approached for the study if they have the full capacity to give consent and that they understand the implications of the trial. There will be no provision for alternatives to obtaining consent via the Guardianship Division within NSW Civil and Administrative Tribunal. Non-respondents will be followed up 5 times, fortnightly and will not be followed-up thereafter.

Ethics and dissemination

The protocol for the ProsD trial and all its associated documents has been reviewed and approved by the Bellberry Human Research Ethics Committee (2016-06-459-A-1), and the Macquarie University Human Research Ethics Committee (5201700188). The trial will be conducted in compliance with the approved trial protocol. Any deviations from the protocol will be firstly submitted to Bellberry HREC for review and approval. Protocol violations will be immediately reported to the ethics committee according to its standard policies and procedures.

Any deviations from the protocol will be firstly submitted to Bellberry HREC for review and approval. Protocol violations will be immediately reported to the ethics committee according to its standard policies and procedures

Study progress

Recruitment was temporarily stopped in March 2020 due to the COVID19 outbreak and was resumed in July 2020. Rate of recruitment was slow in the initial stages of the trial and hence modifications were made to the protocol to improve this rate. The original requirement to include PC cases diagnosed in the preceding 3 months was revised to include cases diagnosed in the preceding 6 months, to extend the maximum age cut-off from 75 years to 79 years, and to include PC cases who were originally diagnosed with low-risk disease but were later upgraded to low-intermediate risk in a follow-up biopsy. Additionally, the original requirement to have biopsies at 12- and 24-months was changed to have *at least one biopsy* in the 24 months of follow-up. As of August 2020, the ProsD trial had recruited 123 participants, bypassing the pre-specified target number.

Acknowledgements

The authors would like to acknowledge the following members for their contribution to the ProsD trial: Patient/Consumer representatives Mr Goodall and Mr Casey for their feedback in the development of this trial, to all participating urologists for enabling recruitment, the secretariat at the NHMRC Clinical Trial Centre Ms Cochrane, trial coordination by Ms Rodger and Ms Foo, and for the research assistance by Ms Willis and Ms Ozersky. The authors thank all the men participating in the ProsD trial.

Competing interest: None declared

Contributors: HG is the principal investigator of ProsD. VNS, MF and BKA conceived the initial concept of this trial and in conjunction with HG, DS, MP, JY, MF, DG, RFG and MK developed the rationale for this trial. VNS and HG led the development of the trial protocol and drafted this manuscript. VNS and DS were involved in coordinating all aspects of this trial, data collection, and management. VG and DE were responsible for the statistical design of the trial, protocol development and setup the IVRS system for blinding and randomising participants. MF was responsible for the processing of all blood specimens and undertaking the genome damage assays. MP, MF, JY, DG, HW, KR, NA and JS contributed to recruiting high volume of participants to this trial. All authors have contributed to the development of the study protocol and this manuscript.

Roles and responsibilities:

Trial sponsor: Professor Gurney from Macquarie University (MQ) contributed to study design and protocol development, interpretation of data, writing of the report and the decision to submit this report for publication.

Funding: This work was funded by the Movember Clinical Trials Award and administered through the Prostate Cancer Foundation Australia (PCFA).

Coordinating centre: Dr Nair-Shalliker and A/Prof Smith at Cancer Council NSW coordinated all aspects of this trial. They contributed to study design and protocol development, data collection, management, analysis, interpretation of results, writing of the report, and the decision to submit the report for publication.

Steering committee: Professor Gurney, Dr Nair-Shalliker, A/Prof Smith, Professor Patel, Professor Woo, Professor Gebski, Mr Espinoza, Professor Yaxley, Professor Gardiner, Professor Frydenberg and Professor Gillatt, all contributed to the study design, decision making, interpretation of data, writing of the report, and the decision to submit the report for publication.

Independent Data Monitoring and Safety Committee: Dr Hayden, A/Prof Wilcken and Dr Asher.

Radiology assessment panel: Associate Professor Richard O'Sullivan, Dr Alain Lavoipierre and Dr Lisa Tarlinton assessed the validity of the routine radiology reports on the MRI scans.

Data Management team: Dr Nair-Shalliker, A/Prof Smith, Ms Rodger and Ms Foo.

Blinding and Randomisation of participants: Professor Gebski and Mr Espinoza from the NHMRC Clinical Trials Centre setup the Interactive Voice Response System (IVRS) for blind randomisation of participants.

Blood collection, transportation and processing: All participants were requested to attend their nearest Sonic Healthcare pathology for blood sampling. Blood specimens collected to monitor PSA levels were sent to the Sonic central processing laboratory for analysis. Blood specimens collected for the purpose of the trial, were transported by Marken Australia to the processing laboratory. The Commonwealth Scientific and Industrial Research Organisation (CSIRO-Adelaide) was responsible for processing and storing all blood specimens for analysis at end of trial.

Pharmaceutical manufacture and packaging: Vitamin D supplements and placebo were initially manufactured and packaged by API Consumer Brands (NZ). A second batch was manufactured by BioTech Pharmacal Inc (USA) and packaged by PCI Pharma (Australia).

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Figures and legends

Figure 1: Overview of the ProsD Trial

Figure 2: ProsD Trial Procedure

Appendix 1: Surveys conducted at baseline, 12 months and 24 months.

Appendix 2: Flow Diagram for Blood Sample Processing in ProsD Study

Appendix 3: Participant Information and Consent form

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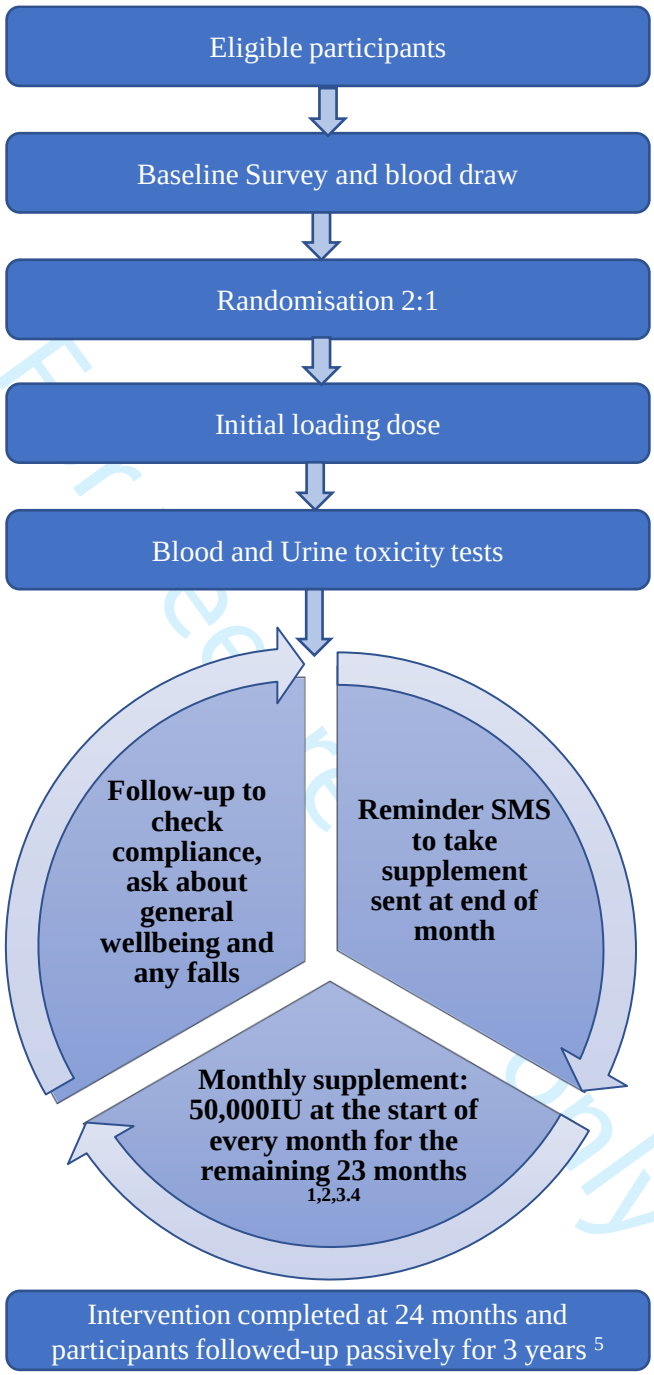
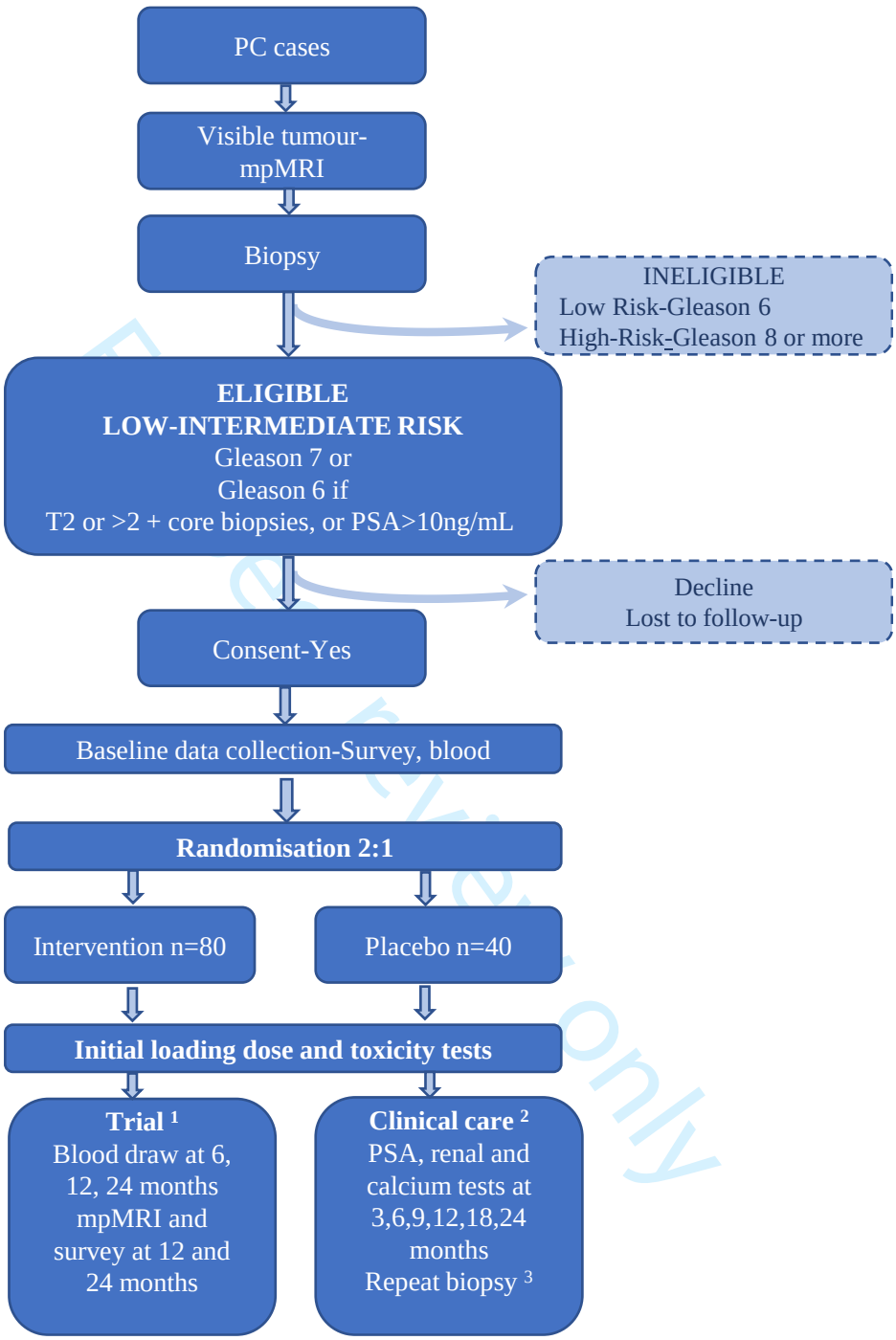
Figure 1. Overview of the ProsD trial



[1] At 3,6,9,12,18,24 months: Participants will have PSA and biochemical tests (at urologists' request as in standard clinical care).
[2]At 6,12,24 months: Participants will be reminded to have a blood draw before supplementation is due.
[3]At 12 and 24 months: Participants will have to complete a questionnaire and be asked to have MRI scans.
[4]At least one repeat biopsy during the 24 months of follow-up (at urologists' request).
[5] Follow-up from clinical records

Figure 2. ProsD Trial Procedure



[1]All participants will be contacted monthly via email and SMS to take supplements, followed up one week later by phone to check compliance.
[2]The trial coordinator will coordinate all mail outs to ensure blood requests for clinical care coincide with that for ProsD trial requirement.
[3] At least one repeat biopsy during the 24 months of follow-up

Baseline SURVEY- start of trial Study ID: **PROSDXXXX**

Appendix 1

A Randomised Control Trial of Vitamin D Supplementation in Prostate Cancer Cases (PROSD)

This randomised control trial aims to see if oral vitamin D supplementation can prevent prostate cancer progression. This survey covers a range of questions on factors that may, or may not, be connected with your cancer and how you cope with it. Your answers are important to us, so please answer every question. If you are not sure of the right dates or ages, your best guess is better than leaving it blank.

The information that we collect is confidential. Please be assured, that all the information collected from this study will be stored in a secure place and your name will be removed from it and it will not be used for any purpose other than for this study.

We thank you for your cooperation in completing this survey.

You can complete this survey online by going to https:\\webmail.nswcc.prosD.xxxxxx

Instructions on how to complete this survey.

- Please answer **ALL** questions about yourself and your own experience by placing a cross (X) in the appropriate box(es) that is adjacent to your choice of response.
- Please write clearly using BLACK or BLUE ink.
- Please write numbers in appropriate boxes e.g. 2nd Dec 1942--0 2 /1 2 /1 9 4 2
- If you make a mistake or change your mind please draw a line through that answer and write the correct answer next to it e.g. ~~25~~ 36

Index of Questions Page no.

Baseline SURVEY- start of trial Study ID: **PROSDXXXX**

PERSONAL DETAILS

Today's date: ☐☐/☐☐/☐☐☐☐

Family Name: _____

First Given name: _____

Other Given names: _____

Date of birth: ☐☐/☐☐/☐☐☐☐

Address

Street no: _____

Street name: _____

Suburb: _____

State: _____

Post code: ☐☐☐☐

Medicare Number: ☐☐☐☐ ☐☐☐☐☐ ☐

Confirm contact details:

- Home telephone_____
- Work telephone_____
- Mobile_____
- Email_____

Baseline SURVEY- start of trial Study ID: **PROSDXXXX**

GENERAL QUESTIONS ABOUT YOU

Q1 How tall are you without shoes (please give to the nearest centimetre or inch)?

- Feet: _____ Inches:_____ **or**
- Meters: _____ Centimetres:_____

Q2 How much do you currently weigh?

- _ _ _ kg **or**
- _ _ _ stones **or**
- _ _ _ pounds

Q3 What is the highest qualification you have completed? (please put one cross (X) in the most appropriate box)

- ❑ No school certificate or other qualifications
- ❑ School or intermediate certificate (or equivalent)
- ❑ Higher school or leaving certificate (or equivalent)
- ❑ Trade/apprenticeship (e.g. hairdresser, chef)
- ❑ Certificate/diploma (e.g. child care, technician)
- ❑ University degree or higher

Q4 What is your current work status? (you can cross more than one box)

- ❑ In full time paid work/self-employed
- ❑ In part time paid work/doing unpaid work
- ❑ Completely retired/pensioner
- ❑ Partially retired looking after home/family
- ❑ Disabled/sick/unemployed
- ❑ Other

Q5 What best describes your current situation? (please cross one box)

- ❑ Single
- ❑ Married
- ❑ De facto/living with a partner
- ❑ Widowed
- ❑ Divorced
- ❑ Separated

Baseline SURVEY- start of trial Study ID: **PROSDXXXX**

Q6 Which of the following do you have? (excluding Medicare)

- ❑ Private health insurance – with extras
- ❑ Private health insurance – without extras
- ❑ Department of Veterans' Affairs white or gold card
- ❑ Health care concession card
- ❑ None of these

Q7 Do you currently smoke cigarettes, cigars, pipes or any other tobacco products:

- ❑ Daily
- ❑ At least weekly (not daily)
- ❑ Less often than weekly
- ❑ Not at all

Q8 Over your lifetime would you have smoked at least 100 cigarettes or a similar amount of tobacco?

- ❑ Yes
- ❑ No

QUESTIONS ABOUT HEALTH

The following are general questions related to your health.

Q9 Have any of your first degree relatives ever been diagnosed with prostate cancer? By ` first degree relative', I mean your father, son or brother.

- ❑ Yes
- ❑ No
- ❑ Don't know

Q10 Has a doctor EVER told you that you have:

(Circle 'Yes" where needed)

- Cancer, other than prostate cancer (please describe type of cancer) -Yes
- Heart failure (heart failure, weak heart, enlarged heart) -Yes
- Atrial fibrillation -Yes
- High blood pressure -Yes
- Stroke -Yes

Baseline SURVEY- start of trial Study ID: **PROSDXXXX**

- Diabetes -Yes
- Blood clot (thrombosis) -Yes
- Enlarged prostate -Yes
- Asthma -Yes
- Hay fever -Yes
- Osteoarthritis -Yes
- Depression -Yes
- Anxiety -Yes
- Parkinson's disease -Yes
- **None of these** -Yes

Q11 How many times in the **LAST 4 MONTHS** have you visited your general practitioner (this does not include visits to your urologist or specialists about your prostate cancer)?

_____ Times

Q12 During the **PAST MONTH**, how many times have you fallen to the floor or ground? *(put "0" if you haven't fallen in the past month)*

_____Times

Q13 Have you had a broken/fractured bone in the last month?

- ❑ Yes
- ❑ No

QUESTIONS ABOUT YOUR PSYCHOLOGICAL DISTRESS

*The following questions are a list of comments made by men about their prostate cancer. Please **CIRCLE** the score that indicates on how frequently these comments were true for you **during the past week;***

(Scores: 0=Not at all; 1=Rarely; 2=Sometimes; 3=Often)

No.	Question	Score
14	Any reference to prostate cancer brought up strong feelings in me	**0 1 2 3**
15	Even though it's a good idea, I found that getting the PSA test scared me	**0 1 2 3**
16	Whenever I heard about a friend of public figure with prostate cancer, I get more anxious about my having prostate cancer	**0 1 2 3**

Baseline SURVEY- start of trial Study ID: **PROSDXXXX**

17	When I thought about having a PSA test, I got more anxious about my having prostate cancer	**0 1 2 3**
18	Other things kept making me think about prostate cancer	**0 1 2 3**
19	I felt kind of numb when I thought of prostate cancer	**0 1 2 3**
20	I thought about prostate cancer even though I did not mean to	**0 1 2 3**
21	I had a lot of feelings about prostate cancer, but I didn't want to deal with them	**0 1 2 3**
22	I had more trouble falling asleep because I couldn't get thoughts of prostate cancer out of my mind	**0 1 2 3**
23	I was afraid that the results from my PSA test would show that my disease was getting worse	**0 1 2 3**
24	Just hearing the words 'prostate cancer' scared me	**0 1 2 3**

*For the next three questions, please indicate how frequently these situations have **EVER** been true for you.*

(Scores: 0=Not at all; 1=Rarely; 2=Sometimes; 3=Often)

No.	Question	**Score**
25	I have been so anxious about my PSA test that I have thought about delaying it	**0 1 2 3**
26	I have been so worried about my PSA test result that I have thought about asking my doctor to repeat it	**0 1 2 3**
27	I have been so concerned about my PSA test result that I have thought about having the test repeated at another lab to make sure they were accurate	**0 1 2 3**

*The following are a number of statements concerning a person's beliefs about their own health. In thinking about the **past week**, please indicate how much you agree or disagree with each statement: strongly agree, agree, disagree, or strongly disagree. Please circle the number of your answer.*

(Scores: 0= Strongly agree; 1= Agree; 2= Disagree; 3= Strongly disagree)

No.	Question	**Score**
28	Because cancer is unpredictable, I feel I cannot plan for the future	**0 1 2 3**

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29	My fear of having my cancer getting worse gets in the way of my enjoying life	**0**	**1**	**2**	**3**
30	I am afraid of my cancer getting worse	**0**	**1**	**2**	**3**
31	I am more nervous since I was diagnosed with prostate cancer	**0**	**1**	**2**	**3**

Note: Brief Symptom Inventory (BSI18) questions (Q32-Q49) are not shown due to licencing restrictions.

QUESTION ON PHYSICAL ACTIVITY

The following questions are about any physical activities that you may have done in the ***LAST WEEK:***

Q50 In the **last week,** how many times have you **walked** continuously, for at least 10 minutes, for recreation, exercise or to get to or from places?
*(This must be **continuous** walking, i.e. for at least 10 minutes without stopping).*
_____times per week.

Q51 What do you estimate was the total time that you spent **walking** in this way in the last week?
(e.g. If you walked on Monday, how long did you spend walking? If you walked on Tuesday, how long did you spend walking?...do this for the rest of the week then add up your hours and /or minutes walked)
In hours and/or minutes
_____hours
_____minutes

The next questions exclude household chores, gardening or yard work:

Q52 In the last week, how many times did you do any **vigorous** physical activity which made you breathe harder or puff and pant?
(e.g. jogging, cycling, aerobics, competitive tennis, football (of all types), hockey, squash, cross-country skiing, cross-country hiking (i.e. rough or steep terrain), weight lifting,

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boxing, rock climbing, basketball, netball, gymnastics, using a rowing machine, martial arts, high-impact and step aerobics).

_____times

Q53 What do you estimate was the total time that you spent doing this **vigorous** physical activity in the last week?

(e.g. If you walked on Monday, how long did you spend walking? If you walked on Tuesday, how long did you spend walking?...do this for the rest of the week then add up your hours and /or minutes doing vigorous physical activity)

In hours and/or minutes

_____hours

_____minutes

Q54 In the last week, how many times did you do any other more **moderate** physical activities that you have not already mentioned?

(e.g. gentle swimming, social tennis, golf, dancing, badminton, table tennis, horseback riding, canoeing, kayaking, volleyball, cricket, baseball or softball, downhill skiing, cross-training, surfing and windsurfing).

_____times

Q55 What do you estimate was the total time that you spent doing these **moderate** activities in the last week?

In hours and/or minutes

_____hours

_____minutes

QUESTIONS ON DIETARY CHANGE

The following questions are related to possible changes you may have made to your diet. These are changes that you are **CURRENTLY** using to help with your prostate cancer and/or its side effects.

Q56 Are you **CURRENTLY** eating differently to help with your prostate cancer?

- ❑ Yes (if **YES,** please complete question 57)
- ❑ No (if **NO**, please go to question 58)

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Q57 *(please put a cross (X) for where a change in your diet was made)*

- ❑ -Increasing a particular type of fat or oil (please describe)_____
- ❑ -Increased soy products
- ❑ -Increased fruit in general
- ❑ -Increased vegetables in general
- ❑ -Increased a particular type of food (s) (please list)_____
- ❑ -Increased a particular type of drink (s)(please list)_____
- ❑ -Decreased fats, oils or fried foods (please describe)_____
- ❑ -Decreased red meat
- ❑ -Decreased processed meats, for example ham, salami, bacon
- ❑ -Decreased dairy products
- ❑ -Decreased a particular type of food (s) (please list)_____
- ❑ -Decreased a particular type of drink (s) (please list)_____
- ❑ -Special diet for example vegetarian or macrobiotic (please describe)_____
- ❑ -Other changes (please describe)_____

QUESTIONS ON YOUR SUPPLEMENT INTAKE

Q58 Did you supplement your diet with **VITAMINS/MINERALS** &/OR **HERBAL SUPPLEMENTS** during the past 16 weeks?

- ❑ YES
- ❑ NO

If **YES**, please list items consumed below:

Brand	Type	Dose (eg 5mg)	How often

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QUESTIONS ON MEDICATIONS TAKEN

Q59 Did you take any medications regularly during the past 16 weeks (prescribed or over the counter)?

- ❑ YES
- ❑ NO

If **YES**, please list below:

Medication	Dose (eg 25mg)	How Often (eg twice daily)	Condition being treated	For how long did you take them during the past 16 weeks?

QUESTIONS ON YOUR SUN SENSITIVITY

The following questions on sun sensitivity are related to your body's ability to produce vitamin D and your susceptibility to sun damage.

Q60 Which colour best describes the colour of the skin on the inside of your upper arm, that is, your skin colour without any tanning?

- ❑ Very fair
- ❑ Fair
- ❑ Light olive
- ❑ Dark olive
- ❑ Brown
- ❑ Black

Q61 What would happen to your skin if it was repeatedly exposed to bright sunlight in summer without any protection? Would it:

- ❑ Go very brown and deeply tanned
- ❑ Get moderately tanned
- ❑ Get mildly or occasionally tanned
- ❑ Get no suntan at all or
- ❑ Only get freckled

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QUESTIONS ON YOUR RECENT SUN EXPOSURE

Q62 Please tell us about the time you have spent **OUTDOORS (between 8 AM and 5 PM)** in the past 16 weeks (i.e. about 4 months). It will help if you start by writing the date 4 MONTHS AGO (just take today's date and count back to the 4th month before it), and TODAY'S DATE in the given places below.

- **Column A:** write the **first place in which you lived for 1week or more** in the past 16 weeks. Give Town or city, State if in Australia, and give name of Country if not Australia.
- **Column B:** write what your **main activity** was when you were in this location.

Eg. Working in a job, living at home, on holiday, or other (say what it was)

- **Column C:** write the first date you were in this location.
- **Column D:** write the duration of your stay in this location.
- **Columns E** and **F**: write the number of hours/day you spent outdoors, and not under any shade between 9am and 5pm while living at this place.
- Now fill in columns A and B on a new row for each time you changed **for 1week or more** the place you lived or your main activity, until you have covered the whole 16 weeks (4 month) period. If you need additional lines, you can write in the space below the table or add another sheet of paper.

Date 4 months ago: ☐☐/☐☐/☐☐☐☐

A	B	C	D	E	F
Places lived for one week or more.	**Main activity at this location**	**Approximate start date at this location**	**# weeks at this location**	**Number of hours spent outdoors at this location**	
				On week days (or working days)	**On weekend days (or days off)**
Eg. Barcelona, Spain	Working	16th Dec 15	4 weeks	Half an hour	4 hours
Eg. Fraser Island	Holiday	15th Jan 16	2 weeks	6 hours	6 hours
Eg. Sydney	At home	1st Feb 16	10 weeks	Half an hour	1 hours

Today's Date: ☐☐/☐☐/☐☐☐☐

THIS IS THE END OF THE SURVEY.

Thank you for your cooperation in answering these questions. Please return these forms in the pre-paid envelope.

SURVEY12 month follow-up Study ID: **PROSDXXXX**

A Randomised Control Trial of Vitamin D Supplementation in Prostate Cancer Cases (PROSD)

This randomised control trial aims to see if oral vitamin D supplementation can prevent prostate cancer progression. This is a follow-up survey on a range of questions for information that have previously provided us at the start of the study. Your answers are important to us, so please answer every question. If you are not sure of the right dates or ages, your best guess is better than leaving it blank.

The information that we collect is confidential. Please be assured, that all the information collected from this study will be stored in a secure place and your name will be removed from it and it will not be used for any purpose other than for this study.

We thank you for your cooperation in completing this survey.

You can complete this survey online by going to https:\\webmail.nswcc.prosD.xxxxxx

Instructions on how to complete this survey.

- Please answer ALL the questions about yourself and your own experience by placing a cross (X) in the appropriate box(es) that is adjacent to your choice of response.
- Please write clearly using BLACK or BLUE ink.
- Please write numbers in appropriate boxes e.g. 2nd Dec 1942--0 2 /1 2 /1 9 4 2
- If you make a mistake or change your mind please draw a line through that answer and write the correct answer next to it e.g. ~~25~~ 36

Please complete the following information and return to us in the pre-paid envelope.

Questions **Page no.**

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PERSONAL DETAILS

Today's date: ☐☐/☐☐/☐☐☐☐

Family Name: _____

First Given name: _____

Other Given names: _____

Date of birth: ☐☐/☐☐/☐☐☐☐

Address

Street no: _____

Street name: _____

Suburb: _____

State: _____

Post code: ☐☐☐☐

Medicare Number: ☐☐☐☐ ☐☐☐☐☐ ☐

Confirm contact details:

- Home telephone_____
- Work telephone_____
- Mobile_____
- Email_____

SURVEY12 month follow-up Study ID: **PROSDXXXX**

GENERAL QUESTIONS ABOUT YOU

Q1 How much do you currently weigh?

- ○ _ _ _ kg **or**
- ○ _ _ _ stones **or**
- ○ _ _ _ pounds

Q2 What is your current work status? (you can cross (X) more than one box)

- ❑ In full time paid work/self-employed
- ❑ In part time paid work/doing unpaid work
- ❑ Completely retired/pensioner
- ❑ Partially retired looking after home/family
- ❑ Disabled/sick/unemployed
- ❑ Other

Q3 What best describes your current situation? (please cross one box)

- ❑ Single
- ❑ Married
- ❑ De facto/living with a partner
- ❑ Widowed
- ❑ Divorced
- ❑ Separated

Q4 Which of the following do you have? (excluding Medicare)

- ❑ Private health insurance – with extras
- ❑ Private health insurance – without extras
- ❑ Department of Veterans' Affairs white or gold card
- ❑ Health care concession card
- ❑ None of these

Q5 Do you currently smoke cigarettes, cigars, pipes or any other tobacco products:

- ❑ Daily
- ❑ At least weekly (not daily)
- ❑ Less often than weekly
- ❑ Not at all

SURVEY12 month follow-up Study ID: **PROSDXXXX**

Q6 Over your lifetime would you have smoked at least 100 cigarettes or a similar amount of tobacco?

☐ Yes ☐ No

QUESTIONS ABOUT HEALTH

Q7 How many times in the **LAST 12 MONTHS** have you visited your general practitioner (this does not include visits to your urologist or specialists about your prostate cancer)?

_____ Times

Q8 During the **LAST MONTH**, how many times have you fallen to the floor or ground?

(put "0" if you have not fallen in the last month)

_____Times

Q9 Have you had a broken/fractured bone in the last month?

☐Yes ☐ No

Q10 In the **LAST 12 MONTHS**, has a doctor EVER told you that you have:

(Circle 'Yes" where needed)

- Cancer, other than prostate cancer (please describe type of cancer) -Yes
- Heart failure (heart failure, weak heart, enlarged heart) -Yes
- Atrial fibrillation -Yes
- High blood pressure -Yes
- Stroke -Yes
- Diabetes -Yes
- Blood clot (thrombosis) -Yes
- Enlarged prostate -Yes
- Asthma -Yes
- Hay fever -Yes
- Osteoarthritis -Yes
- Depression -Yes
- Anxiety -Yes
- Parkinson's disease -Yes
- **None of these** -Yes

SURVEY12 month follow-up Study ID: **PROSDXXXX**

QUESTIONS ABOUT YOUR PSYCHOLOGICAL DISTRESS

*The following questions are a list of comments made by men about their prostate cancer. Please **CIRCLE** the score that indicates on how frequently these comments were true for you **during the past week;***

(Scores: 0=Not at all; 1=Rarely; 2=Sometimes; 3=Often)

No.	Question	Score
11	Any reference to prostate cancer brought up strong feelings in me	**0 1 2 3**
12	Even though it's a good idea, I found that getting the PSA test scared me	**0 1 2 3**
13	Whenever I heard about a friend of public figure with prostate cancer, I get more anxious about my having prostate cancer	**0 1 2 3**
14	When I thought about having a PSA test, I got more anxious about my having prostate cancer	**0 1 2 3**
15	Other things kept making me think about prostate cancer	**0 1 2 3**
16	I felt kind of numb when I thought of prostate cancer	**0 1 2 3**
17	I thought about prostate cancer even though I did not mean to	**0 1 2 3**
18	I had a lot of feelings about prostate cancer, but I didn't want to deal with them	**0 1 2 3**
19	I had more trouble falling asleep because I couldn't get thoughts of prostate cancer out of my mind	**0 1 2 3**
20	I was afraid that the results from my PSA test would show that my disease was getting worse	**0 1 2 3**
21	Just hearing the words 'prostate cancer' scared me	**0 1 2 3**

*For the next three questions, please indicate how frequently these situations have **EVER** been true for you.*

(Scores: 0=Not at all; 1=Rarely; 2=Sometimes; 3=Often)

No.	Question	Score
22	I have been so anxious about my PSA test that I have thought about delaying it	**0 1 2 3**
23	I have been so worried about my PSA test result that I have thought about asking my doctor to repeat it	**0 1 2 3**

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24	I have been so concerned about my PSA test result that I have thought about having the test repeated at another lab to make sure they were accurate	**0 1 2 3**

*The following are a number of statements concerning a person's beliefs about their own health. In thinking about the **past week**, please indicate how much you agree or disagree with each statement: strongly agree, agree, disagree, or strongly disagree. Please circle the number of your answer.*

(Scores: 0= Strongly agree; 1= Agree; 2= Disagree; 3= Strongly disagree)

No.	Question	Score
25	Because cancer is unpredictable, I feel I cannot plan for the future	**0 1 2 3**
26	My fear of having my cancer getting worse gets in the way of my enjoying life	**0 1 2 3**
27	I am afraid of my cancer getting worse	**0 1 2 3**
28	I am more nervous since I was diagnosed with prostate cancer	**0 1 2 3**

Note: Brief Symptom Inventory (BSI18) questions (Q29-Q46) are not shown due to licencing restrictions.

QUESTION ON PHYSICAL ACTIVITY

*The following questions are about any physical activities that you may have done in the **LAST WEEK:***

Q47 In the **last week,** how many times have you **walked** continuously, for at least 10 minutes, for recreation, exercise or to get to or from places?

*(This must be **continuous** walking, i.e. for at least 10 minutes without stopping).*

_____times per week.

Q48 What do you estimate was the total time that you spent **walking** in this way in the last week? *(e.g. If you walked on Monday, how long did you spend walking? If you walked on Tuesday, how long did you spend walking?...do this for the rest of the week then add up your hours and /or minutes walked)*

In hours and/or minutes

_____hours _____minutes

SURVEY12 month follow-up Study ID: **PROSDXXXX**

The next questions exclude household chores, gardening or yard work:

Q49 In the last week, how many times did you do any **vigorous** physical activity which made you breathe harder or puff and pant? *(e.g. jogging, cycling, aerobics, competitive tennis, football (of all types), hockey, squash, cross-country skiing, cross-country hiking (i.e. rough or steep terrain), weight lifting, boxing, rock climbing, basketball, netball, gymnastics, using a rowing machine, martial arts, high-impact and step aerobics).*

_____times

Q50 What do you estimate was the total time that you spent doing this **vigorous** physical activity in the last week? *(e.g. If you walked on Monday, how long did you spend walking? If you walked on Tuesday, how long did you spend walking?...do this for the rest of the week then add up your hours and /or minutes doing vigorous physical activity)*

In hours and/or minutes

_____hours _____minutes

Q51 In the last week, how many times did you do any other more **moderate** physical activities that you have not already mentioned? *(e.g. gentle swimming, social tennis, golf, dancing, badminton, table tennis, horseback riding, canoeing, kayaking, volleyball, cricket, baseball or softball, downhill skiing, cross-training, surfing and windsurfing).*

_____times

Q52 What do you estimate was the total time that you spent doing these **moderate** activities in the last week?

In hours and/or minutes

_____hours _____minutes

QUESTIONS ON DIETARY CHANGE

The following questions are related to possible changes you may have made to your diet. These are changes that you are **CURRENTLY** using to help with your prostate cancer and/or its side effects.

Q53 Are you **CURRENTLY** eating differently to help with your prostate cancer?

- ❑ Yes (if **YES,** please complete question 54)

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- ❑ No (if **NO**, please go to question 55)

Q54 *(please put a cross (X) for where a change in your diet was made)*

- ❑ -Increasing a particular type of fat or oil (please describe)_____
- ❑ -Increased soy products_____
- ❑ -Increased fruit in general_____
- ❑ -Increased vegetables in general_____
- ❑ -Increased a particular type of food (s) (please list)_____
- ❑ -Increased a particular type of drink (s) (please list)_____
- ❑ -Decreased fats, oils or fried foods (please describe)_____
- ❑ -Decreased red meat_____
- ❑ -Decreased processed meats, for example ham, salami, bacon_____
- ❑ -Decreased dairy products_____
- ❑ -Decreased a particular type of food (s) (please list)_____
- ❑ -Decreased a particular type of drink (s) (please list)_____
- ❑ -Special diet for example vegetarian or macrobiotic (please describe)_____
- ❑ -Other changes (please describe)_____

QUESTIONS ON YOUR SUPPLEMENT INTAKE

Q55 Did you supplement your diet with **VITAMINS/MINERALS** &/OR **HERBAL SUPPLEMENTS** during the past 16 weeks?

- ❑ YES
- ❑ NO

If **YES**, please list items consumed below:

Brand	Type	Dose (eg 5mg)	How often

QUESTIONS ON MEDICATIONS TAKEN

Q56 Did you take any medications regularly during the past 16 weeks (prescribed or over the counter)?

- ❑ YES
- ❑ NO

SURVEY12 month follow-up Study ID: **PROSDXXXX**

If **YES**, please list below:

Medication	Dose (eg 25mg)	How Often (eg twice daily)	Condition being treated	For how long did you take them during the past 16 weeks?

QUESTIONS ON YOUR SUN SENSITIVITY

The following questions on sun sensitivity are related to your body's ability to produce vitamin D and your susceptibility to sun damage.

Q57 Which colour best describes the colour of the skin on the inside of your upper arm, that is, your skin colour without any tanning?

- ❑ Very fair
- ❑ Fair
- ❑ Light olive
- ❑ Dark olive
- ❑ Brown
- ❑ Black

Q58 What would happen to your skin if it was repeatedly exposed to bright sunlight in summer without any protection? Would it:

- ❑ Go very brown and deeply tanned
- ❑ Get moderately tanned
- ❑ Get mildly or occasionally tanned
- ❑ Get no suntan at all or
- ❑ Only get freckled

SURVEY- 12 month follow-up Study ID: **PROSDXXXX**

QUESTIONS ON YOUR RECENT SUN EXPOSURE

Q59 Please tell us about the time you have spent **OUTDOORS (between 8 AM and 5 PM)** in the past 16 weeks (i.e. about 4 months). It will help if you start by writing the date 4 MONTHS AGO (just take today's date and count back to the 4th month before it), and TODAY'S DATE in the given places below.

- **Column A:** write the **first place in which you lived for 1week or more** in the past 16 weeks. Give Town or city, State if in Australia, and give name of Country if not Australia.
- **Column B:** write what your **main activity** was when you were in this location. Eg. Working in a job, living at home, on holiday, or other (say what it was)
- **Column C:** write the first date you were in this location.
- **Column D:** write the duration of your stay in this location.
- **Columns E** and **F**: write the number of hours/day you spent outdoors, and not under any shade between 9am and 5pm while living at this place.
- Now fill in columns A and B on a new row for each time you changed **for 1week or more** the place you lived or your main activity, until you have covered the whole 16 weeks (4 month) period. If you need additional lines, you can write in the space below the table or add another sheet of paper.

Date 4 months ago: ☐☐/☐☐/☐☐☐☐

A	B	C	D	E	F
Places lived for one week or more.	**Main activity at this location**	**Approximate start date at this location**	**# weeks at this location**	**Number of hours spent outdoors at this location**	
				On week days (or working days)	**On weekend days (or days off)**
Eg. Barcelona, Spain	Working	16th Dec 15	4 weeks	Half an hour	4 hours
Eg. Fraser Island	Holiday	15th Jan 16	2 weeks	6 hours	6 hours
Eg. Sydney	At home	1st Feb 16	10 weeks	Half an hour	1 hours

Today's Date: ☐☐/☐☐/☐☐☐☐

THIS IS THE END OF THE SURVEY.

Thank you for your cooperation in answering these questions. Please return these forms to us in the pre-paid envelope.

SURVEY-24 month follow-up Study ID: **PROSDXXXX**

A Randomised Control Trial of Vitamin D Supplementation in Prostate Cancer Cases (PROSD)

This randomised control trial aims to see if oral vitamin D supplementation can prevent prostate cancer progression. This is a follow-up survey on a range of questions for information that have previously provided us at the start of the study, which will be your last. Your answers are important to us, so please answer every question. If you are not sure of the right dates or ages, your best guess is better than leaving it blank.

The information that we collect is confidential. Please be assured, that all the information collected from this study will be stored in a secure place and your name will be removed from it and it will not be used for any purpose other than for this study.

We thank you for your cooperation in completing this survey.

You can complete this survey online by going to https:\\webmail.nswcc.prosD.xxxxxx

Instructions on how to complete this survey.

- Please answer ALL the questions about yourself and your own experience by placing a cross (X) in the appropriate box(es) that is adjacent to your choice of response.
- Please write clearly using BLACK or BLUE ink.
- Please write numbers in appropriate boxes e.g. 2nd Dec 1942--0 2 /1 2 /1 9 4 2
- If you make a mistake or change your mind please draw a line through that answer and write the correct answer next to it e.g. ~~25~~ 36

Please complete the following information and return to us in the pre-paid envelope.

Questions **Page no.**

SURVEY-24 month follow-up Study ID: **PROSDXXXX**

PERSONAL DETAILS

Today's date: ☐☐/☐☐/☐☐☐☐

Family Name: _____

First Given name: _____

Other Given names: _____

Date of birth: ☐☐/☐☐/☐☐☐☐

Address

Street no: _____

Street name: _____

Suburb: _____

State: _____

Post code: ☐☐☐☐

Medicare Number: ☐☐☐☐ ☐☐☐☐☐ ☐

Confirm contact details:

- Home telephone_____
- Work telephone_____
- Mobile_____
- Email_____

SURVEY-24 month follow-up Study ID: **PROSDXXXX**

GENERAL QUESTIONS ABOUT YOU

Q1 How much do you currently weigh?

- ○ _ _ _ kg **or**
- ○ _ _ _ stones **or**
- ○ _ _ _ pounds

Q2 What is your current work status? (you can cross (X) more than one box)

- ❑ In full time paid work/self-employed
- ❑ In part time paid work/doing unpaid work
- ❑ Completely retired/pensioner
- ❑ Partially retired looking after home/family
- ❑ Disabled/sick/unemployed
- ❑ Other

Q3 What best describes your current situation? (please cross one box)

- ❑ Single
- ❑ Married
- ❑ De facto/living with a partner
- ❑ Widowed
- ❑ Divorced
- ❑ Separated

Q4 Which of the following do you have? (excluding Medicare)

- ❑ Private health insurance – with extras
- ❑ Private health insurance – without extras
- ❑ Department of Veterans' Affairs white or gold card
- ❑ Health care concession card
- ❑ None of these

Q5 Do you currently smoke cigarettes, cigars, pipes or any other tobacco products:

- ❑ Daily
- ❑ At least weekly (not daily)
- ❑ Less often than weekly
- ❑ Not at all

SURVEY-24 month follow-up Study ID: **PROSDXXXX**

Q6 Over your lifetime would you have smoked at least 100 cigarettes or a similar amount of tobacco?

☐Yes ☐No

QUESTIONS ABOUT HEALTH

Q7 How many times in the **LAST 12 MONTHS** have you visited your general practitioner (this does not include visits to your urologist or specialists about your prostate cancer)?

_____ Times

Q8 In the **LAST MONTH**, how many times have you fallen to the floor or ground?

(put "0" if you have not fallen in the last month) _____Times

Q9 Have you had a broken/fractured bone in the last month?

☐Yes ☐No

Q10 In the **LAST 12 MONTHS**, has a doctor EVER told you that you have:

(Circle 'Yes" where needed)

- Cancer, other than prostate cancer (please describe type of cancer) -Yes
- Heart failure (heart failure, weak heart, enlarged heart) -Yes
- Atrial fibrillation -Yes
- High blood pressure -Yes
- Stroke -Yes
- Diabetes -Yes
- Blood clot (thrombosis) -Yes
- Enlarged prostate -Yes
- Asthma -Yes
- Hay fever -Yes
- Osteoarthritis -Yes
- Depression -Yes
- Anxiety -Yes
- Parkinson's disease -Yes
- **None of these** -Yes

SURVEY-24 month follow-up Study ID: **PROSDXXXX**

QUESTIONS ABOUT YOUR PSYCHOLOGICAL DISTRESS

*The following questions are a list of comments made by men about their prostate cancer. Please **CIRCLE** the score that indicates on how frequently these comments were true for you **during the past week;***

(Scores: 0=Not at all; 1=Rarely; 2=Sometimes; 3=Often)

No	Question	Score
11	Any reference to prostate cancer brought up strong feelings in me	**0 1 2 3**
12	Eventhough it's a good idea, I found that getting the PSA test scared me	**0 1 2 3**
13	Whenever I heard about a friend of public figure with prostate cancer, I get more anxious about my having prostate cancer	**0 1 2 3**
14	When I thought about having a PSA test, I got more anxious about my having prostate cancer	**0 1 2 3**
15	Other things kept making me think about prostate cancer	**0 1 2 3**
16	I felt kind of numb when I thought of prostate cancer	**0 1 2 3**
17	I thought about prostate cancer even though I did not mean to	**0 1 2 3**
18	I had a lot of feelings about prostate cancer, but I didn't want to deal with them	**0 1 2 3**
19	I had more trouble falling asleep because I couldn't get thoughts of prostate cancer out of my mind	**0 1 2 3**
20	I was afraid that the results from my PSA test would show that my disease was getting worse	**0 1 2 3**
21	Just hearing the words 'prostate cancer' scared me	**0 1 2 3**

For the next three questions, please indicate how frequently these situations have EVER been true for you.

(Scores: 0=Not at all; 1=Rarely; 2=Sometimes; 3=Often)

No	Question	Score
22	I have been so anxious about my PSA test that I have thought about delaying it	**0 1 2 3**
23	I have been so worried about my PSA test result that I have thought about asking my doctor to repeat it	**0 1 2 3**

SURVEY-24 month follow-up Study ID: **PROSDXXXX**

24	I have been so concerned about my PSA test result that I have thought about having the test repeated at another lab to make sure they were accurate	**0 1 2 3**

*The following are a number of statements concerning a person's beliefs about their own health. In thinking about the **past week**, please indicate how much you agree or disagree with each statement: strongly agree, agree, disagree, or strongly disagree. Please circle the number of your answer.*

(Scores: 0= Strongly agree; 1= Agree; 2= Disagree; 3= Strongly disagree)

No.	Question	Score
25	Because cancer is unpredictable, I feel I cannot plan for the future	**0 1 2 3**
26	My fear of having my cancer getting worse gets in the way of my enjoying life	**0 1 2 3**
27	I am afraid of my cancer getting worse	**0 1 2 3**
28	I am more nervous since I was diagnosed with prostate cancer	**0 1 2 3**

Note: Brief Symptom Inventory (BSI18) questions (Q29-Q46) are not shown due to licencing restrictions.

QUESTION ON PHYSICAL ACTIVITY

*The following questions are about any physical activities that you may have done in the **LAST WEEK:***

Q47 In the **last week,** how many times have you **walked** continuously, for at least 10 minutes, for recreation, exercise or to get to or from places?

*(This must be **continuous** walking, i.e. for at least 10 minutes without stopping).*

_____times per week.

Q48 What do you estimate was the total time that you spent **walking** in this way in the last week? *(e.g. If you walked on Monday, how long did you spend walking? If you walked on Tuesday, how long did you spend walking?...do this for the rest of the week then add up your hours and /or minutes walked)*

In hours and/or minutes

_____hours _____minutes

SURVEY-24 month follow-up Study ID: **PROSDXXXX**

The next questions exclude household chores, gardening or yard work:

Q49 In the last week, how many times did you do any **vigorous** physical activity which made you breathe harder or puff and pant? *(e.g. jogging, cycling, aerobics, competitive tennis, football (of all types), hockey, squash, cross-country skiing, cross-country hiking (i.e. rough or steep terrain), weight lifting, boxing, rock climbing, basketball, netball, gymnastics, using a rowing machine, martial arts, high-impact and step aerobics).*

_____times

Q50 What do you estimate was the total time that you spent doing this **vigorous** physical activity in the last week? *(e.g. If you walked on Monday, how long did you spend walking? If you walked on Tuesday, how long did you spend walking?...do this for the rest of the week then add up your hours and /or minutes doing vigorous physical activity)*

In hours and/or minutes

_____hours _____minutes

Q51 In the last week, how many times did you do any other more **moderate** physical activities that you have not already mentioned? *(e.g. gentle swimming, social tennis, golf, dancing, badminton, table tennis, horseback riding, canoeing, kayaking, volleyball, cricket, baseball or softball, downhill skiing, cross-training, surfing and windsurfing).*

_____times

Q52 What do you estimate was the total time that you spent doing these **moderate** activities in the last week?

In hours and/or minutes

_____hours _____minutes

QUESTIONS ON DIETARY CHANGE

The following questions are related to possible changes you may have made to your diet. These are changes that you are **CURRENTLY** using to help with your prostate cancer and/or its side effects.

Q53 Are you **CURRENTLY** eating differently to help with your prostate cancer?

- ❑ Yes (if **YES,** please complete question 54)
- ❑ No (if **NO**, please go to question 55)

SURVEY-24 month follow-up Study ID: **PROSDXXXX**

Q54 *(please put a cross (X) for where a change in your diet was made)*

- ❑ -Increasing a particular type of fat or oil (please describe)_____
- ❑ -Increased soy products_____
- ❑ -Increased fruit in general_____
- ❑ -Increased vegetables in general_____
- ❑ -Increased a particular type of food (s) (please list)_____
- ❑ -Increased a particular type of drink (s) (please list)_____
- ❑ -Decreased fats, oils or fried foods (please describe)_____
- ❑ -Decreased red meat_____
- ❑ -Decreased processed meats, for example ham, salami, bacon_____
- ❑ -Decreased dairy products_____
- ❑ -Decreased a particular type of food (s) (please list)_____
- ❑ -Decreased a particular type of drink (s) (please list)_____
- ❑ -Special diet for example vegetarian or macrobiotic (please describe)_____
- ❑ -Other changes (please describe)_____

QUESTIONS ON YOUR SUPPLEMENT INTAKE

Q55 Did you supplement your diet with **VITAMINS/MINERALS** &/OR **HERBAL SUPPLEMENTS** during the past 16 weeks?

☐Yes ☐No

If **YES**, please list items consumed below:

Brand	Type	Dose (eg 5mg)	How often

QUESTIONS ON MEDICATIONS TAKEN

Q56 Did you take any medications regularly during the past 16 weeks (prescribed or over the counter)?

☐Yes ☐No

If **YES**, please list:

SURVEY-24 month follow-up Study ID: **PROSDXXXX**

Medication	Dose (eg 25mg)		How Often (eg twice daily)	Condition being treated	For how long did you take them during the past 16 weeks?

QUESTIONS ON YOUR SUN SENSITIVITY

The following questions on sun sensitivity are related to your body's ability to produce vitamin D and your susceptibility to sun damage.

Q57 Which colour best describes the colour of the skin on the inside of your upper arm, that is, your skin colour without any tanning?

- ❑ Very fair
- ❑ Fair
- ❑ Light olive
- ❑ Dark olive
- ❑ Brown
- ❑ Black

Q58 What would happen to your skin if it was repeatedly exposed to bright sunlight in summer without any protection? Would it:

- ❑ Go very brown and deeply tanned
- ❑ Get moderately tanned
- ❑ Get mildly or occasionally tanned
- ❑ Get no suntan at all or
- ❑ Only get freckled

Survey- 24 month follow-up

Study ID:

QUESTIONS ON YOUR RECENT SUN EXPOSURE

Q59 Please tell us about the time you have spent **OUTDOORS (between 8 AM and 5 PM)** in the past 16 weeks (i.e. about 4 months). It will help if you start by writing the date 4 MONTHS AGO (just take today's date and count back to the 4th month before it), and TODAY'S DATE in the given places below.

- **Column A:** write the **first place in which you lived for 1week or more** in the past 16 weeks. Give Town or city, State if in Australia, and give name of Country if not Australia.
- **Column B:** write what your **main activity** was when you were in this location. Eg. Working in a job, living at home, on holiday, or other (say what it was)
- **Column C:** write the first date you were in this location.
- **Column D:** write the duration of your stay in this location.
- **Columns E** and **F**: write the number of hours/day you spent outdoors, and not under any shade between 9am and 5pm while living at this place.
- Now fill in columns A and B on a new row for each time you changed **for 1week or more** the place you lived or your main activity, until you have covered the whole 16 weeks (4 month) period. If you need additional lines, you can write in the space below the table or add another sheet of paper.

Date 4 months ago: ☐☐/☐☐/☐☐☐☐

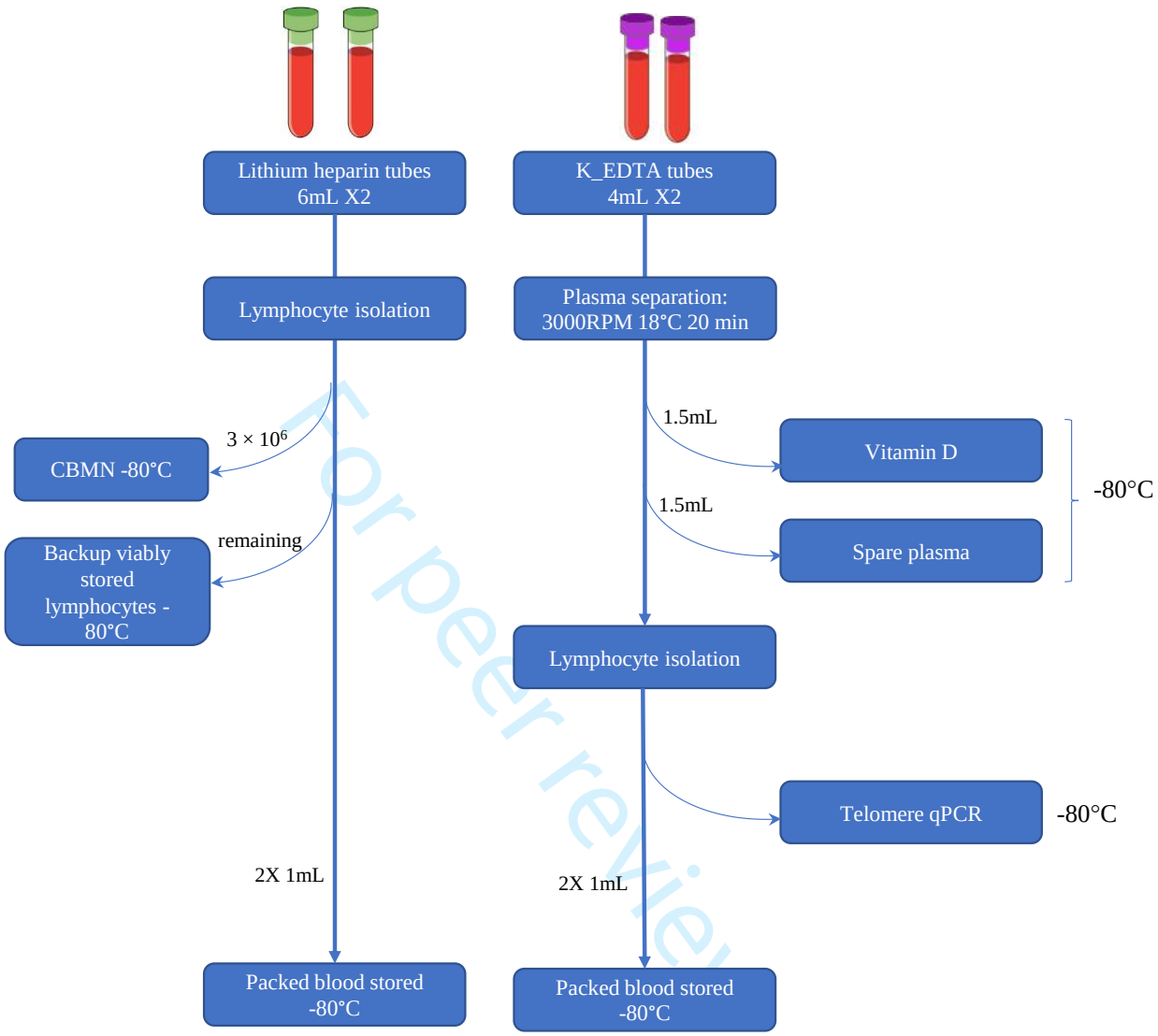
A	B	C	D	E	F
Places lived for one week or more.	**Main activity at this location**	**Approximate start date at this location**	**# weeks at this location**	**Number of hours spent outdoors at this location**	
				On week days (or working days)	**On weekend days (or days off)**
Eg. Barcelona, Spain	Working	16th Dec 15	4 weeks	Half an hour	4 hours
Eg. Fraser Island	Holiday	15th Jan 16	2 weeks	6 hours	6 hours
Eg. Sydney	At home	1st Feb 16	10 weeks	Half an hour	1 hours

Today's Date: ☐☐/☐☐/☐☐☐☐

THIS IS THE END OF THE SURVEY.

Thank you for your cooperation in answering these questions. Please return these forms to us in the pre-paid envelope.

Appendix 2. Flow Diagram for Blood Sample Processing in ProsD Study



Appendix 3

Participant Information Sheet and Consent Form

STUDY TITLE: A PHASE II RANDOMISED CONTROLLED TRIAL OF HIGH-DOSE VITAMIN D IN LOCALISED PROSTATE CANCER CASES WITH INTERMEDIATE RISK OF PROGRESSION.

Short Title	ProsD
Protocol Number	MQ_GUR_ProsD1
Local Project Sponsor	Macquarie University
Lead Investigator	Professor Howard Gurney
Urologist	
Location	

High dose vitamin D supplementation may reduce the progression of prostate cancer. Although it is approved to treat conditions relating to vitamin D deficiency, its use is not approved to treat prostate cancer due to insufficient evidence. This is a two year clinical trial which aims to see if vitamin D can prevent disease progression in men with prostate cancer who have chosen to be on active surveillance. It also aims to also establish the safety of its use in these men.

This trial is led by Professor Howard Gurney from Macquarie University, in conjunction with researchers at Cancer Council NSW, and a team of Australian urologists, geneticists and vitamin D experts.

This trial is funded by the Movember Clinical Trial Award (PCFA-CTA 1315) through the Prostate Cancer Foundation of Australia.

This Participant Information and Consent Form provides you information about this trial and explains all trial requirements. Knowing what is involved, will help you decide if you want to participate in this trial.

There will be no costs associated with participating in this research project. You will not be paid for participating in this trial.

Participation in this trial is voluntary. Whatever your decision, it will not affect your relationship with the staff caring for you. You will receive the best possible care whether or not you take part.

If you choose to participate, you will be kept informed of any significant new findings that may affect your willingness to continue in the trial. If you wish to withdraw from the trial once it has started, you can notify us of your decision. All information already collected will be retained.

Please read this information carefully. If you have any questions, please contact your urologist or the trial coordinator. Their contact details are provided at the end of this document.

MACQUARIE University

Cancer Council NSW

Eligibility for trial participation

All men with prostate cancer, who have intermediate risk of disease progression, and who are being managed by active surveillance, and who have been diagnosed in the past 4 months, will be considered eligible to participate in this trial. You have been asked to participate because you appear to fit these criteria.

Intervention

We aim to recruit 120 participants to this trial. All participants will be randomly assigned to either, receive vitamin D for those in the intervention arm (total of 80 men in this group), or receive placebo (tablet with no active ingredient) tablets for those in the control arm (total of 40 men in this group). All participants and study investigators will be blinded to the content of the tablets, where neither party will be told which arm of the trial the participants are in; this ensures best scientific methods are used. This information, which will be held by the Clinical Trials Centre, will only be disclosed to the investigators at the end of the trial.

At the start of the trial, all participants will be asked to take 10 tablets over a period of 12 hours. From then on, all participants will be asked to take one tablet a month for the remaining 23 months.

Supplements for this trial have been specifically designed and manufactured for the purpose of this trial. They cannot be purchased from the pharmacy, as the doses sold at pharmacies are lower than trial dosage.

Purpose of initial loading dose at the start of trial

The initial loading dose aims to boost blood levels of vitamin D, while the monthly dose will maintain requiredlevels.

Managing side effects

Two other Australian based studies have previously used high dose Vitamin D supplements in this way. The Mel-D study which is a clinical trial in melanoma patients, and the D-Health study, which is an Australian study of ~20,000 men and women. Neither of these studies reported any unusual health effects in their participants. Nevertheless your blood and urine samples will be monitored closely for any signs of abnormalities.

Blood and urine collection

We will require your blood sample at 5 different time points, for the purpose of this trial, and that is, before commencement of intervention, and again at 6, 12 and 24 months. We will also require a blood and urine sample 24 hours after taking initial supplement. We will coordinate blood collection for the purpose of your routine clinical care, as requested by your doctor, at 3,6,9,12,18, and 24 months.

We will aim to coincide blood collection for the trial with that required by your doctor for your routine clinical care, to minimise your visits to the pathology centre. You will be given specific instructions to go to a pathology provider to have your blood drawn.

At the back of the form will be a list of pathology providers that you can choose for your convenience.

Purpose of multiple blood samples and urine sample

For the purpose of your safety and wellbeing, we will be collecting blood samples and urine to monitor renal function to ensure there are no adversities, 24 hours after commencing the trial. For the purpose of monitoring prostate specific antigen (PSA) levels, by your doctor, blood samples will be collected at 3, 6, 9, 12, 18 and 24 months; your doctor will continue to monitor your renal function to ensure there are no adversities. The results from these tests will be forwarded to your treating urologists, and a copy will be sent to the ProsD trial coordinator.

For the purpose of the trial, blood samples will also be collected at the start of the trial, and again at 6, 12, and 24 months, which will be used to determine if high levels of vitamin D are attained and also maintained thereafter. These blood samples will also be used to determine if there are overall changes to your gene profile following vitamin D supplementation.

All blood samples collected for the purpose of the trial will be stored in a -80C freezer at a laboratory specialising in specimen storage and analysis, and only be analysed at the end of the trial. These samples will be identified by a study identification number, not by name.

Prostate biopsy

You will not be required to have any additional biopsies for this trial. All biopsies that you will undertake will be according to standard clinical practice, as advised by your urologist. All pathology information that we will require for the trial will be collected from your clinical records. We will require a sample of your biopsy to assay for genome damage markers.

Tests conducted on your samples

We will analyse your blood and tissue biopsy samples for vitamin D levels, and also assess overall changes to your gene profile, from baseline to the end of the trial.

Blood test results

All test results will remain confidential. Only your doctor and the researchers will have access to any information about you. If any results have direct implications for your health, the trial team will inform your doctor and your doctor will discuss them with you.

Magnetic Resonance Imaging (MRI) scans

MRI scans take detailed pictures of your prostate and can indicate if your disease is progressing. Your diagnostic scan which would have been done before you were recruited to this trial, will establish your disease status. We will require you to have additional scans at 12 and 24 months, to determine if your disease has progressed. We will require copies of your diagnostic and follow-up scans.

We will cover all costs of these additional scans done at 12 and 24 months. We are unfortunately unable to reimburse any scans done before you were recruited into this trial.

Survey

You will be asked to complete a survey on your general health, demographic, diet, and lifestyle factors, your supplementation and medications use, and about your recent time spent outdoors, at the start of the study, and again at 12 and 24 months. We will mail you a copy of this survey which can be returned to us in a reply-paid envelope upon completion, or it can be completed online (details will be provided to you).

Changes to lifestyle

You will have to refrain from taking any vitamin D supplements while on this trial.

Benefits of taking part

We cannot guarantee that you will receive any benefits from this research. However, possible benefits may include a delay in your prostate cancer disease progression which means you will be able to remain on active surveillance longer. This may delay the uptake of more radical treatment and its possible side effects.

If this trial indicates that high dose vitamin D supplementation reduces disease progression, this will lead to a Phase III trial involving a larger group of men. If a Phase III trial is able to substantiate these findings, then results of the trial will be provided to prostate cancer organisations and policy makers at State and Territory, and Commonwealth levels to include high dose vitamin D supplementation in Australian clinical guidelines for the management of men on active surveillance.

Risks and disadvantages of taking part

High dose vitamin D supplementation is unlikely to cause significant side effects, as observed in two other Australian vitamin D based trials. There is a low risk of the blood calcium level becoming high. This will be monitored by the blood tests on the study and if it occurs, the vitamin D supplementation will be stopped. There is also a low risk of kidney stones if a high calcium level is not corrected by stopping the medication. If you do show signs of any new or unusual symptoms please do not hesitate to contact your treating urologists immediately.

Although your blood is drawn by professional health care professional, there is still a low risk of complications which may include fainting, dizziness, bruising at the puncture site, nerve injury and arterial puncture. If you have previously experienced any of these complications please bring this to the attention of the healthcare professional at time of your blood draw.

There are no proven long-term risks related to mpMRI scans and it is considered to be safe when performed at a centre with appropriate procedures. You will lie on a table inside the MRI scanner which will record information about your prostate. It will be important that you are in a comfortable position so that you can keep still. The scanner is very noisy and you may be given earphones to reduce the noise. Some people may experience symptoms of claustrophobia from lying in a confined space. If you do experience discomfort at any time during the scan, you will be able to alert staff by pressing on a call button provided to you. The magnetic field generated by the MRI will attract metal objects and therefore you will be instructed to remove all metallic belongings. This magnetic field can also pull on any metal containing object in your body such as medicine pumps and aneurysm clips, or result in overheating of some of the older style medical implants. Many new medical implants are designed to be MRI-compatible. Every MRI facility will have a comprehensive screening procedure to ensure the safe use of the MRI.

If you suffer any injury from participating in this study, the parties involved in this research project have agreed to cover any costs involved with ensuring the safety of all study participants. Any participants showing indications of any adverse event, adverse reaction or serious adverse event will be immediately withdrawn from the study and closely monitored by a clinician to ensure there are no further complications, at no cost to the study participant. If you wish to obtain a copy of the Medicines Australia compensation guidelines please contact the Trial coordinator on 1800 789 622 (FreeCall).

Access to clinical records

We will need to access your clinical records during the duration of this trial, and in the follow-up phase thereafter to determine long term effects. We will require your consent for us to access your clinical records.

De-identification of personal information

By signing the consent form you consent to your doctor and relevant trial staff collecting and using personal information about you for the research project. You will be assigned a unique identification number, and be referred to hereafter (i.e. blood sample tubes) by this unique identification number. Any identifiable information that is collected about you in connection with this study will be recoded to this identification number. It will remain confidential and will be disclosed only with your permission, or except as required by law. Only the investigators will have access to your details and results that will be held securely at Cancer Council NSW.

The results from this trial will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be presented in such a way that you cannot be identified.

Results from the trial

Individual results will not be provided to participants, as the analyses of these de-identified samples will only commence at the end of the trial, when all trial participants have completed the trial. The overall findings from this trial will be mailed to you in a newsletter.

Managing Adverse Effects

If you suffer any adverse effects, or complications as a result of this trial, you should contact your doctor as soon as possible and you will be assisted with arranging appropriate medical treatment.

Ethical review of this trial

All research in Australia involving humans is reviewed the Human Research Ethics Committee (HREC). This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies. The ethical aspects of this research project have been approved by the HRECs of Macquarie University, and Bellberry Limited, which is a national, private non-for-profit organisation providing high quality, independent scientific and ethical review of human research projects across Australia.

Utility of blood and tissue samples after the trial is complete

Your samples will be retained by the investigators for 15 years after the end of the trial. However since these samples are highly valuable, and may be extremely useful in future research, we seek your consent to retain these samples for longer than 15 years for cancer-related research in future. These samples may be used by future researchers, however no blood, tissue or health information will be released to a third party unless it is to carry out research that has been approved by a Human Research Ethics Committee.

All samples will be analysed simultaneously at the completion of this trial. All unused samples will be stored at -80^{0}C, and may be used for research projects, only with the approval of a Human

Research Ethics Committee. If you do not agree to your specimen being stored beyond 15 years, then these samples will be destroyed.

What does participation in this trial involve?

Participation in this research involves taking monthly supplements, completing surveys, giving bloods, giving us consent to access your tissue biopsy and having Magnetic Resonance Imaging (MRI) scans. In addition, the researchers would like to have access to selected medical records about your prostate cancer tests, treatment and further results to obtain information relevant to the study.

If you agree to take part in this trial then:

(i) You will agree to take 10 tablets over a period of 12 hours, at the start of the trial

(ii) You will agree to have a urine test 24 hours after taking the first dose of supplementation, at the start of the study.

(iii) You will agree to take 1 tablet every month for the remaining 23 months.

(iv) You will agree to give ~twenty millilitres (~20mL), or ~one tablespoon, of blood at time of recruitment, 24 hours after taking the first dose of supplementation, at 6, 12, and 24 months each.

(v) You will provide us consent to access your prostate cancer biopsy samples from the pathologist.

(vi) You will agree to complete a survey (either paper survey or web-survey) at time of recruitment, and again at 12 and 24 months each.

(vii) You will agree to have a MRI scan at 12 and 24 months (cost will be covered by the trial).

(viii) You will consent to the use of your personal and health information.

(ix) You will agree not to take additional vitamin D supplementation during this trial, although you can continue to take any medication as advised by your doctor

Participation in this study is voluntary. It is completely up to you whether or not you participate. Whatever your decision, it will not affect your relationship with the staff caring for you.

If you choose to participate, you will be kept informed of any significant new findings that may affect your willingness to continue in the study. If you wish to withdraw from the study once it has started, you can notify us of your decision, without having to give a reason. However all information already collected will be retained.

What to do next

If you agree to take part in this trial, please take these forms with you on your next visit to your urologist.

By signing it, you are telling us that you understand what you have read and consent to:

- taking part in this trial
- taking an initial high dose of oral vitamin D supplement
- taking a monthly dose of oral vitamin D supplements for 23 months
- giving urine and blood samples at specified time points at a pathology provider located near your residence
- Completing surveys at required time points
- having MRI scans at 12 and 24 months

- allowing researchers access your prostate biopsy samples
- allowing researchers to access your health information

You will be given a copy of this Participant Information and Consent Form to keep. Your urologist will keep one copy and return to us the third signed copy in the reply-paid envelope supplied.

After we have received your signed consent, we will send you further information about the blood collection and interview, which will be done before you are randomised to start the trial.

Remember: Participation in the study is entirely voluntary. You may withdraw at any time after you have agreed to participate.

Advice and Information

The person you may need to contact will depend on the nature of your query. If you have any medical problems which may be related to your involvement in this trial (for example any side effects) you can contact your urologist. If you want any further information concerning this project you can contact the Trial coordinator.

ProsD Study Team Contact Persons	
>Insert Urologist name<	Dr Visalini (Lini) Nair-Shalliker
Urologist	Trial Coordinator
Telephone: <Insert number>	Telephone: 1800 789 622 (FreeCall)
Email <Insert email add>	Email: enquiriesProsD@nswcc.org.au

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Bellberry Human Research Ethics Committee
HREC Executive Officer	Bellberry HREC
Telephone	(08) 8361 3222
Email	bellberry@bellberry.com.au

The Bellberry Human Research Ethics Committee has reviewed and approved this study in accordance with the National Statement on Ethical Conduct in Human Research (2007) – incorporating all updates. This Statement has been developed to protect the interests of people who agree to participate in human research studies. Should you wish to discuss the study or view a copy of the Complaint procedure with someone not directly involved, particularly in relation to matters concerning policies, information or complaints about the conduct of the study or your rights as a participant, you may contact the Committee Chair, Bellberry Human Research Ethics Committee on 08 8361 3222.

CONSENT TO PARTICIPATE IN RESEARCH

Title: A Phase II randomised controlled trial of high-dose vitamin D in localised prostate cancer cases with intermediate risk of progression

Principal Investigator: Professor Howard Gurney

Declaration by Participant

1. I understand that the researcher will conduct this study in a manner conforming to ethical and scientific principles set out by the National Health and Medical Research Council of Australia and the Good Clinical Research Practice Guidelines of the Therapeutic Goods Administration.
2. I acknowledge that I have read, or have had read to me the Participant Information Sheet relating to this study. I acknowledge that I understand the Participant Information Sheet. I acknowledge that the general purposes, methods, demands and possible risks and inconveniences which may occur to me during the study have been provided to me by the Trial Coordinator and I, being over the age of 18 acknowledge that I understand the general purposes, methods, demands and possible risks and inconveniences which may occur during the study.
3. I acknowledge that I have been given time to consider the information and to seek other advice.
4. I acknowledge that refusal to take part in this study will not affect the usual treatment of my condition.
5. I acknowledge that I am volunteering to take part in this study and I may withdraw at any time.
6. I acknowledge that this research has been approved by the Bellberry Human Research Ethics Committee.
7. I acknowledge that I have received the Participant Information Sheet and a copy of this consent form, which I have signed.
8. I acknowledge that regulatory authorities may have access to my medical records relevant to this study to monitor the research in which I am agreeing to participate. However, I understand my identity will not be disclosed to anyone else or in publications or presentations.

Name of Participant (PRINT) _____

Signature _____ Date _____

Declaration by Study Doctor:

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor (PRINT) _____

Signature _____ Date _____

PARTICIPANT TO KEEP THIS FOR THEIR RECORDS

CONSENT TO PARTICIPATE IN RESEARCH

Title: A Phase II randomised controlled trial of high-dose vitamin D in localised prostate cancer cases with intermediate risk of progression

Principal Investigator: Professor Howard Gurney

Declaration by Participant

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6. I acknowledge that this research has been approved by the Bellberry Human Research Ethics Committee.
7. I acknowledge that I have received a copy of this form and the Participant Information Sheet, which I have signed.
8. I acknowledge that regulatory authorities may have access to my medical records relevant to this study to monitor the research in which I am agreeing to participate. However, I understand my identity will not be disclosed to anyone else or in publications or presentations.

Name of Participant (PRINT) _____

Signature _____ Date _____

Declaration by Study Doctor:

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor (PRINT) _____

Signature _____ Date _____

DOCTOR TO KEEP THIS FOR THEIR RECORDS

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CONSENT TO PARTICIPATE IN RESEARCH

Title: A Phase II randomised controlled trial of high-dose vitamin D in localised prostate cancer cases with intermediate risk of progression

Principal Investigator: Professor Howard Gurney

Declaration by Participant

1. I understand that the researcher will conduct this study in a manner conforming to ethical and scientific principles set out by the National Health and Medical Research Council of Australia and the Good Clinical Research Practice Guidelines of the Therapeutic Goods Administration.
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7. I acknowledge that I have received a copy of this form and the Participant Information Sheet, which I have signed.
8. I acknowledge that regulatory authorities may have access to my medical records relevant to this study to monitor the research in which I am agreeing to participate. However, I understand my identity will not be disclosed to anyone else or in publications or presentations.

Name of Participant (PRINT) _____

Signature _____ Date _____

Declaration by Study Doctor:

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor (PRINT) _____

Signature _____ Date _____

PLEASE SIGN AND RETURN IN REPLY PAID ENVELOPE