

**A phase II randomised controlled trial of high dose vitamin D in localised prostate cancer cases with intermediate risk of progression (ProsD).**

**PRINCIPAL INVESTIGATOR:**

Professor Howard Gurney  
Director of Clinical Trials  
Faculty of Medicine and Health Sciences  
Macquarie University  
Level 4, Suite 407  
2 Technology Place  
Macquarie University, NSW 2109  
Telephone: +61 2 9812 3561  
Email: Howard.gurney@mq.edu.au

**Principal Investigator:**



Signature: .....

Date: 24/09/18

Name: (please print):

.....Howard Gurney.....

**PROTOCOL MQ\_GUR\_ProsD1 Master VERSION: 7**

**Protocol Date: 25<sup>th</sup> September 2018**

**ETHICS STATEMENT:**

This study will be conducted in accordance with the *National Statement on Ethical Conduct in Human Research* (2007), the *CPMP/ICH Note for Guidance on Good Clinical Practice* and consistent with the principles that have their origin in the Declaration of Helsinki. Compliance with these standards provides assurance that the rights, safety and well-being of trial participants are respected.

## SYNOPSIS

### Background

Active surveillance (AS) for prostate cancer (PC) patients with low risk of PC death is an alternative to radical treatment. A major weakness of AS is the uncertainty whether a patient truly has low risk PC based on biopsy alone. Multiparametric MRI scan (mpMRI), together with biopsy, appears useful in separating patients who need curative therapy from those for whom AS may be safe. Two small US trials have shown short-term high dose vitamin D supplementation prevents PC 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.

### Aim

Primary aim is to:

- (1) Improve the Active-therapy free survival during the first two years of AS.

Secondary aims are to:

- (2) Examine if optimal levels of total 25OHD between 75 and 80nmol/L are achieved in PC patients following vitamin D supplementation and characterise those whose serum 25OHD do not increase to a level of 75nmol/L in response to supplementation.
- (3) Examine if vitamin D supplementation is able to reduce the prevalence of DNA damage.

We will also evaluate the utility of mpMRI scan in diagnosing PC progression in cases managed on AS. We will also examine if vitamin D supplementation needs to be extended for a longer period to prevent PC progression, through passive surveillance of clinical records after intervention has ceased.

### Hypothesis

**Hypothesis 1:** Monthly high dose vitamin D supplementation of 50,000IU for 24 months reduces PC progression in men with intermediate risk PC, managed by AS.

**Hypothesis 2:** Monthly high dose vitamin D supplementation of 50,000IU for 24 months will raise serum 25OHD levels optimally between 75-80nmol/L in men with intermediate risk of PC progression, receiving intervention.

**Hypothesis 3:** Monthly high dose vitamin D supplementation of 50,000IU for 24 months is able to reduce the prevalence of lymphocytic and tissue specific DNA damage in men with low to intermediate risk PC.

**Hypothesis 4:** Changes on mpMRI scan are associated with PC progression as defined by increased grade of disease and/or % core biopsy positive sequential biopsy of the prostate.

### Population and Setting

Prostate cancer cases aged between 50 and 80 years, who have an intermediate risk of disease progression, will have a:

1. mpMRI (centrally reviewed, not limited to any PIRADS score) **and**
2. Gleason score =7 (e.g. Gleason grade 3+4) **or**
3. >2 positive biopsy core (which may include Gleason 6) **or**
4. Clinical stage T2 (which may include Gleason 6) **or**
5. PSA $\geq$ 10 ng/mL (which may include Gleason 6)

All men with a histologically proven adenocarcinoma of the prostate and be willing to adhere to study protocol, will be randomised within 6 months of diagnosis.

Men who were previously diagnosed with low-risk disease and whose disease have recently been upgraded (in the past 6 months) to fit our eligibility criteria, will also be eligible to participate in our study.

## Study Design

This trial is designed as a double-blinded, placebo-controlled randomized Phase II trial.

## Intervention

Men in the intervention arm will receive an initial loading dose of vitamin D supplementation (500,000IU) followed by a monthly oral dose vitamin D supplementation (50,000IU), while controls will receive a monthly oral placebo tablet/capsule, for 2 years (24 months).

## Overview of Study Procedure

All consenting eligible men will be surveyed on their social and demographics, lifestyle, diet, mental health, and medication use, and have blood drawn, prior to randomisation. Thereafter, all participants will be randomised; all participants and study coordinators will be blinded to information on randomisation. Participants will either be supplied with vitamin D in the form of cholecalciferol (50,000IU), or placebo, as identical tablet/capsules. All men in the intervention arm will receive an initial oral loading dose of 500,000IU, which will be achieved by consuming ten tablet/capsules within a 12 hour period, followed by a monthly oral dose of 50,000IU for the remaining 23 months of AS. Those in the control arm will follow a similar protocol, but they will consume placebo tablet/capsules. Each participant will have blood and urine samples drawn, the next day, to monitor toxicity. Towards the end of the month, a message via SMS and email, will be sent to each participant, reminding them to take their monthly supplement (1 tablet/capsule). Each man will be followed-up a week later, by phone, to ensure compliance and check his well-being. This procedure will be repeated every month, for the next 22 months. Each man will be reminded to have their bloods drawn again before the 6<sup>th</sup>, 12<sup>th</sup> and 24-month supplementations are due. The trial coordinator will also be responsible for mailing out pathology forms to each participant for their routine PSA testing (and other biochemical tests), as part of their clinical care, at 3, 6, 9, 12, 18 and 24 months. Blood collections for clinical care will be coordinated to coincide with trial collections at 6, 12 and 24 months. Top-up supplementation will be mailed to participants when supply is low. In summary, each participant's blood sample will be collected at baseline (before randomisation), within 24 hours of commencing initial oral loading (and one urine sample), at 6, 12 and 24 months for the purpose of the trial, and at 3,6,9,12,18 and 24 months for routine PSA and biochemical monitoring. At 12 and 24 months, each participant will also be reminded to have a MRI scan and be surveyed.

Figure 1 illustrates the overview of ProsD study procedure.

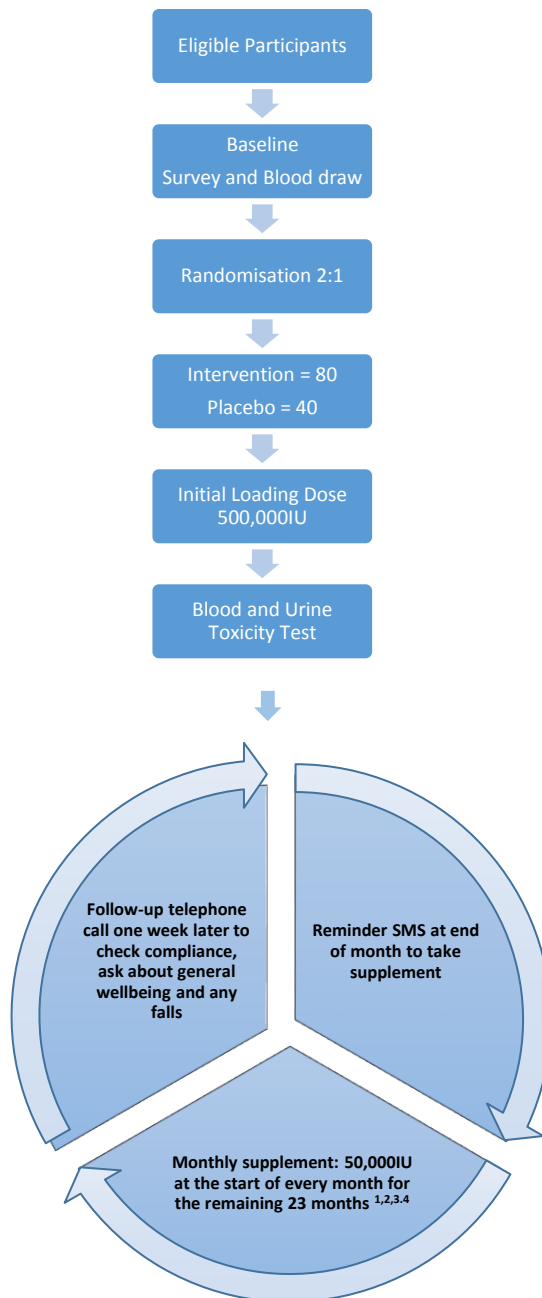
## Statistical Considerations

The primary outcome for the trial is the change from AS to active therapy by 24 months. This is currently estimated to be ~35% at 2 years for 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% in favour of a more interesting rate of 77.5% (i.e. active therapy rate of 22.5% rather than 35%). **If 8 of the first 24 (33.3%) patients in the intervention group have progressed after 2 years of therapy**, 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).

## Significance

This trial will determine the activity of using high dose vitamin D supplementation in preventing disease progression in men with intermediate risk of progression and would inform the need for a Phase III trial.

Figure 1: Overview of ProsD Study Procedure



Intervention complete at 24 months and participants followed up passively thereafter for 3 years

<sup>1</sup> At 3,6,9,12,18,24 months: Participants will have PSA and biochemical tests (at urologists' request as in standard clinical care).

<sup>2</sup>At 6,12,24 months: Participants will be reminded to have a blood draw before supplementation is due.

<sup>3</sup>At 12 and 24 months: Participants will have to complete a survey and be asked to have MRI scans.

<sup>4</sup>At 12 and 24 months: Repeat biopsies (at urologists' request).

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## LIST OF ABBREVIATIONS

|          |                                              |
|----------|----------------------------------------------|
| AE       | Adverse Event                                |
| AR       | Adverse Reaction                             |
| AS       | Active Surveillance                          |
| ATFS     | Active therapy-free survival                 |
| BN cells | Binucleate cells                             |
| CA       | Chromosomal Aberrations                      |
| CBMN     | Cytokinesis-block micronucleus cytome        |
| CCNSW    | Cancer Council NSW                           |
| CI       | Co-Investigator                              |
| CTC      | Clinical Trials Centre                       |
| DRE      | Digital Rectal Examination                   |
| HREC     | Human Research Ethics Committee              |
| IDMC     | Independent Data Monitoring Committee        |
| MN       | Micronuclei                                  |
| mpMRI    | Multiparametric magnetic resonance imaging   |
| NHMRC    | National Health and Medical Research Council |
| PB       | Prostate biopsy                              |
| PC       | Prostate cancer                              |
| PI       | Principal Investigator                       |
| PSA      | Prostate-Specific Antigen                    |
| RCT      | Randomised Controlled Trial                  |
| SAE      | Serious Adverse Event                        |
| SUSAR    | Suspected Serious Adverse Reaction           |
| SPI      | Site Principal Investigator                  |
| SSA      | Site Specific Assessment                     |
| TL       | Telomere length                              |
| TMC      | Trial Management Committee                   |
| TRUS     | Transrectal Ultrasound Scan                  |

## KEY TRIAL CONTACTS

### Principal Investigator (PI)

PI – Professor Howard Gurney

### Co-Investigators (CI)

- CIA - Doctor Visalini Nair-Shalliker - Epidemiologist (NSW)
- CIB - Associate Professor David Smith - Epidemiologist (NSW)
- CIC - Professor Val Gebski - Biostatistician (NSW)
- CID - Associate Professor Manish Patel - Urological Cancer Surgeon (NSW)
- CIE - Professor Mark Frydenberg - Urologist (VIC)
- CIF - Professor Robert 'Frank' Gardiner - Academic Urologist (QLD)
- CIG - Professor Michael Kimlin – Radiation Epidemiologist (QLD)
- CIH - Professor Michael Fenech – Geneticist (SA)
- CII - Professor David Gillatt – Urologist (NSW)

### Associate Investigators

Professor Bruce Armstrong - Epidemiologist  
Mr John Goodall - Consumer  
Mr Con Casey - Consumer  
Doctor David Malouf - Urologist (NSW)  
Doctor John Yaxley - Urologist (QLD)  
Doctor Krishan Rasiah - Urologist (NSW)  
Doctor Venu Chalasani - Urologist (NSW)  
Doctor Henry Woo – Urologist (NSW)  
Mr Sam Egger – Statistician (NSW)

### Coordinating Centres: Macquarie University and Cancer Council NSW

Professor Howard Gurney  
Faculty of Medicine and Health Sciences  
Macquarie University  
Level 4, Suite 407  
2 Technology Place  
Macquarie University, NSW 2109  
Telephone: + 61 2 9812 3561      Fax: + 61 2 9812 3600  
Email: [howard.gurney@mq.edu.au](mailto:howard.gurney@mq.edu.au)

Dr Visalini Nair-Shalliker  
Research Fellow  
Cancer Research Division  
Cancer Council NSW  
PO Box 572  
Kings Cross, NSW 1340  
Telephone: + 61 2 9334 1410      Fax: + 61 2 8302 3500  
Email: [visalini@nswcc.org.au](mailto:visalini@nswcc.org.au)

## Ethics Committees

1. Macquarie University Ethics Committee  
Ethics Secretariat Research Office  
Level 3, C5C Building  
Macquarie University, NSW 2109  
Telephone: +61 2 9850 7850 Fax: N/A  
Email: [ethics.secretariat@mq.edu.au](mailto:ethics.secretariat@mq.edu.au)
2. Bellberry Limited  
129 Glen Osmond Road  
Eastwood, SA 5063  
Telephone: + 61 8 8361 3222 Fax: + 61 8 8361 3322  
Email: [bellberry@bellberry.com.au](mailto:bellberry@bellberry.com.au)
3. Western Sydney Local Health District  
Westmead Research Office  
Westmead Hospital  
PO Box 533  
Wentworthville, NSW 2145  
Telephone: + 61 2 9845 0007 Fax: + 61 2 9845 9636  
Email: [wslhd-researchoffice@health.nsw.gov.au](mailto:wslhd-researchoffice@health.nsw.gov.au)

## Independent Data Monitoring Committee

Dr Amy Hayden (Radiation Oncologist - Westmead Hospital)

A/Prof Nicholas Wilcken  
Director of Medical Oncology  
Westmead Hospital  
PO Box 533 Wentworthville, NSW 2145  
Telephone: + 61 2 9845 5200 Fax + 61 2 9845 6391  
Email: [nicholas.wilcken@sydney.edu.au](mailto:nicholas.wilcken@sydney.edu.au)

Dr Rebecca Asher (NHMRC Clinical Trials Centre)  
NHMRC Clinical Trials Centre  
The University of Sydney  
Telephone: +612 9562 5020  
Email: [rebecca.asher@ctc.usyd.edu.au](mailto:rebecca.asher@ctc.usyd.edu.au)

## Trial Management Committee

Professor Howard Gurney (NSW)  
Doctor Visalini Nair-Shalliker (NSW)  
Associate Professor David Smith (NSW)  
Professor Val Gebiski  
Professor David Gillatt (NSW)  
Associate Professor Manish Patel (NSW)  
Professor Mark Frydenberg (Vic)  
Professor Henry Woo (NSW)  
Professor John Yaxley (Qld)  
Professor Robert 'Frank' Gardiner (QLD)

## Outcomes Assessment Committee

TBA

## Independent Radiologist Panel

Associate Professor Richard O'Sullivan

Director Bridge Road Imaging

84 Bridger Road

Richmond, VIC 3121

Telephone: + 61 3 9242 4888

Fax: + 61 3 9242 4830

Email: Richard.osullivan@healthcareimaging.com.au

Dr Alain Lavoipierre

Epworth Freemasons Medical Imaging

117 Albert Street

East Melbourne, VIC 3002

Telephone: +61 3 9483 3377

Fax: + 61 3 9483 3399

Email: alain.lavoipierre@epworthmedicalimaging.com.au

## Trial Sponsorship and Funding

The Prostate Cancer Foundation of Australia: Movember Clinical Trial Award (PCFA-CTA 1315)

Dr Miranda Xhilaga

Director Research Programs

Prostate Cancer Foundation of Australia

Level 5

437 St Kilda Road

Melbourne, VIC 3004

Telephone: + 61 3 9948 2070

Fax: + 61 3 9948 2090

## KEY TRIAL SUPPORT/ORGANISATIONAL CONTACTS

### Blood Processing, Storage and Assay Laboratories

1. **CSIRO**

Professor Michael Fenech  
CSIRO Preventative Health Flagship  
PO Box 10041  
Adelaide BC, 5000  
Telephone: + 61 8 8303 8880  
Email: Michael.fenech@csiro.au

2. **Pathology Providers**

(1) SONIC HEALTHCARE

*Douglass Hanly Moir (NSW)*  
*Barratt and Smith Pathology (NSW)*  
*Southern IML Pathology (NSW)*  
*Sullivan and Nicolaides (QLD)*

Lisa Crawford (Manager Pathology Services)  
14 Giffnock Avenue  
Macquarie Park, NSW 2113  
Telephone: + 61 2 9855 5423 Fax: + 61 2 9855 5646  
Email: lcrawford@dhm.com.au

(2) DOREVITCH PATHOLOGY (QLD)

Tanya Vassallo (Commercial Contracts Manager)  
Dorevitch Pathology  
18 Banksia Street  
Heidleberg, VIC 3084  
Telephone: + 61 3 9244 0292 Fax: + 61 3 9244 0432  
Email: tanya.vassallo@dorevitch.com.au

3. **Marken**

Bronwen Medley (Branch Manager)  
4/23 Bowden Street  
Alexandria, NSW 2015  
Telephone: +61 2 9318 1777 Fax: + 61 2 9319 1700  
Email: Bronwen.medley@marken.com

### Clinical Trials Centre

Professor Val Gebski  
NHMRC Clinical Trials Centre  
ABN 15 211 513 464  
Locked Bag 77  
Camperdown, NSW 1450  
Telephone: + 61 2 9562 5000 Fax: + 61 2 9565 1863  
Email: [val@ctc.usyd.edu.au](mailto:val@ctc.usyd.edu.au)

Pharmaceutical Manufacturer/Trials Pharmacist

API Consumer Brands (NZ)  
14-16 Norman Spencer Drive  
PO Box 76 401  
Manukau City 2105  
Auckland, New Zealand  
Telephone: + 64 9 279 7979  
NZ Freephone: 0508 776 746  
Email: sales@api.net.nz

Fax: + 64 9 279 7999

BioTech Pharmacal Inc (USA)  
Box 1927  
Fayetteville, AR  
USA  
Telephone: + 1-479-443-9148  
Email: customerservice@bio-tech-pharm.com

## 1. Background

### 1.1 Prostate Cancer and Active Surveillance

Prostate Cancer (**PC**) affects many men worldwide, with over 900 000 diagnoses and 258,000 deaths from the disease in 2008.<sup>1</sup> Since the introduction of prostate-specific antigen (**PSA**) testing, the proportion of low risk tumours diagnosed has risen, leading to overtreatment and potential negative side effects. It is anticipated that by 2017 there will be 185,700 to 201,700 Australian men diagnosed and living with PC as a consequence of early detection and overdiagnosis.<sup>2</sup> Recommendations from some peak bodies to test men's PSA from the age of 40 will result in an even higher prevalence of men living with this disease, both pre- and post-treatment. Over diagnosis due to PSA-testing may be unavoidable, but overtreatment is not. Results from the Prostate Cancer Intervention vs Observation Trial (**PIVOT**) suggest minimal benefits in men with **low risk** PC when managed with curative treatment, and instead recommends monitoring the course of PC with the intention of initiating curative treatment if PC progresses. This is referred to as active surveillance (**AS**) and has evolved as an alternative to immediate active treatment, for those diagnosed with low grade disease. The D'Amico risk classification for low, intermediate and high risk groups is used as guide to classify disease status as follows (<https://www.auanet.org/education/guidelines/prostate-cancer.cfm>):

- **Low risk:** Have a PSA less than or equal to 10ng/mL, and Gleason score less than or equal to 6, or clinical stage T1-2a.
- **Intermediate risk:** Have PSA between 10 and 20ng/mL, or a Gleason score of 7, or clinical stage T2b

**High-risk:** Have a PSA more than 20ng/mL, or a Gleason score equal or larger than 8, or clinical stage T2c-3a. (UCSF 2011) There is mounting evidence that men with favourable **intermediate** risk PC, who are usually referred for curative treatment as an initial treatment, have similar 10-year mortality risk as those with **low** risk disease.<sup>3</sup> Klotz et al recently reported a favourable outcome in a 15-year follow up of 993 men with intermediate-risk PC on AS, suggesting that these men as well may benefit from AS.<sup>4</sup>

### 1.2 Prostate Cancer Diagnosis

PC is conventionally diagnosed using transrectal ultrasound (TRUS) to anatomically guide prostate biopsy (PB). As cancer cannot be imaged on ultrasound, the major weakness of this approach is non-detection of a substantial proportion of significant PC, thus making detection of clinically significant PC a challenge. 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. Approximately 28% of the participants in PRIAS showed reclassification upon repeat biopsy.<sup>5</sup> The use of mpMRI, which was originally used for staging purposes, is now used for detection and tumour 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.<sup>6</sup> It can improve the specificity of locating PC and targeting the PB,<sup>7</sup> and be able to differentiate low- and intermediate/high-grade PC.

### 1.3 Prostate Cancer and Genome Damage

There is a strong link between 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,<sup>9</sup> and that micronuclei (**MN**) formation, a marker for chromosomal instability, was associated with cancer incidence in a study of 6718 individuals.<sup>9</sup> There is also evidence

to link telomeres to cancer risk. Telomeres are repetitive DNA sequences that maintain genomic stability by protecting the ends of chromosomes; they shorten in length over time in a mechanism regulated by telomerase activity. Its shortening is accelerated by oxidative stress, inflammation and cell proliferation and this shortening has been linked with cancer risk. 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,<sup>10</sup> possibly due to an imbalance between elongation, which is regulated by telomerase, and telomere shortening to maintain a stable ‘optimal’ length for cell cycle control. There is strong evidence to show that vitamin D may prevent genome damage.<sup>8</sup>

Evidence suggests that high levels of vitamin D may prevent genome damage by reducing prevalence on MN formation and telomere length.<sup>13-16</sup> 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.<sup>17</sup> This current trial provides basis to concurrently examine the possible role of vitamin D in the regulation of these markers of DNA damage in PC.

## 1.4 Prostate Cancer Risk and Vitamin D

Two recent randomised trials suggest that vitamin D supplementation may prevent PC progression.<sup>11;12</sup> A daily supplementation of 4000IU for one year, a dose which can readily be attained by purchasing off-the shelf vitamin D supplements, reduced the number of positive cores and Gleason grade, but did not reduce PSA levels.<sup>12</sup> However a daily high dose of 40,000IU for only 10 weeks significantly reduced PSA levels but showed no identifiable difference in Ki67 expression in prostate tissue; those who received 4000IU and 10,000IU showed no significant reduction in PSA level.<sup>12</sup> The lack of significant findings from this trial was possibly due to the short trial duration. These results from this trial suggest that high vitamin D doses may prevent cancer progression.<sup>11</sup> There is, however, no substantial information regarding the long-term safety and efficacy of vitamin D supplementation; hence its use in PC needs to be assessed. It is therefore essential that we have a RCT to assess the long-term effects of vitamin D supplementation in men with PC.

## 2. Rationale for Performing the Study

The current proposal is a RCT for high dose vitamin D supplementation, in a group of PC cases who have an intermediate risk of disease progression, and are undertaking AS. There is uncertainty as to whether AS or curative therapy is best for this group of men. The current 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.

### 2.1 Aims

This trial will determine if vitamin D supplementation reduces the risk of PC progression in men with intermediate-risk disease.

Our primary objective is to:

- (1) Reduce the rate of change from active surveillance to active therapy during the first two years of AS

Our secondary objectives are to:

- (2) Examine if optimal levels of total 25OHD between 75 and 80nmol/L are achieved in PC patients following vitamin D supplementation and characterise those whose serum 25OHD do not increase to a level of 75nmol/L in response to supplementation
- (3) Examine if vitamin D supplementation is able to reduce the prevalence of DNA damage
- (4) Evaluate the utility of mpMRI scan in diagnosing PC progression in cases managed on AS

We will also examine if vitamin D supplementation needs to be extended for a longer period to prevent PC progression.

## 2.2 Hypothesis

The following hypotheses will be examined:

### Hypothesis 1:

Monthly high-dose vitamin D supplementation of 50,000IU reduces PC progression in men with intermediate risk PC, managed by AS. PC progression will primarily be defined as a decrease in active-therapy free survival during the first two years of AS. Secondary endpoints of disease progression will include an increase in Gleason grade *or* increase in % positive core involvement during periodic prostate biopsies *or* a decrease in PSA doubling time.

### Hypothesis 2:

Monthly high-dose vitamin D supplementation for 24 months will raise serum 25OHD levels optimally between 75-80nmol/L in men with intermediate risk of PC progression, receiving intervention.

### Hypothesis 3:

Monthly high-dose vitamin D supplementation for 24 months is able to reduce the prevalence of lymphocytic and tissue-specific DNA damage in men with low- to intermediate-risk PC.

### Hypothesis 4:

Changes on mpMRI scan are associated with PC progression on an AS program, as defined by increased grade of disease and/or percentage core biopsy positive sequential biopsy of the prostate.

We will characterise men whose serum 25OHD does not increase to reach a threshold level of 75 nmol/L in response to vitamin D supplementation.

## 2.3 Endpoints

### 2.3.1 Primary Endpoint

The primary endpoint will be **Active therapy-free survival (ATFS)**. There will be no absolute requirements for conversion to ATFS. This will be left to the treating urologist. However, as a guideline, ATFS may be considered in the following situations.

- i. Gleason 4+3 or greater on rebiopsy *or*
- ii. Gleason 3+4 = 7 where pattern 4 is > 10% on rebiopsy *or*
- iii. 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
- iv. PSA doubling time of less than 3 years

### 2.3.2 Secondary Endpoints:

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

### 2.3.3 Tertiary Endpoints:

- 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

## 2.4 Outcomes

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

### 2.4.1 Definition of Outcomes

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 (based on NCI study Frye et al ASCO GU 2016):
  - o increase in PIRAD score
  - o any increase in lesion diameter measured in the axial plane
  - o appearance of any new lesion
- PSA doubling time of less than 3 years

Conversion to active therapy due to non-clinical reasons

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

## 2.5 Significance

- (i) The results of this study will allow men with intermediate-risk disease to better understand how to manage their cancer, which will encourage more men to seek AS, as an initial option and consequently reduce the uptake of unnecessary active therapy
- (ii) If this trial is effective in preventing PC progression, and this intervention can be successfully administered, then the choice of seeking AS in this group of men may be a more attractive option, and avoid potential major side effects of radical treatment
- (iii) The study will give important information regarding the utility of mpMRI in AS. If mpMRI is found to be sensitive and specific for cancer progression on biopsy, there is the potential for this scan to replace invasive biopsy on surveillance protocols
- (iv) These outcomes will determine if a Phase III trial is needed

## 3. Trial Design

This is a 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 intermediate risk of disease progression, on 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 current protocol mandates the use of mpMRI-detected and targeted cancers in the inclusion criteria, to reduce disease reclassification, due to sampling error on biopsy and to assist in the diagnosis of disease progression on AS.

All men will be required to complete a survey on various lifestyle, diet and demographic characteristics at baseline, 12 and 24 months and blood specimens will be collected at baseline, 6, 12 and 24 months to assess serum vitamin D status, and prevalence of genome damage, in each group. Each participant

will receive a monthly email and SMS-reminder to take their supplement (1 tablet/capsule), and be followed-up a week later, by phone, to ensure compliance and his well-being. Each participant will also be required to have (i) a blood and urine test for toxicity the day after the initial oral loading dose of 10 tablet/capsules, and (ii) 3-monthly PSA tests in the first 12 months, and 6-monthly in the remaining 12 months, as in standard clinical care. All participants will be required to have MRI scans at 12, and 24 months. All participants will be actively followed up for 24 months after recruitment to this trial. Participants' clinical information will be extracted from their clinical records for all available PSA results since baseline, biopsy (and repeat biopsies), and MRI scans. Participants will be followed-up passively for an additional 3 years after the cessation of supplementation, via their clinical records, which will allow us to assess the medium term benefits of this intervention in reducing the rate of PC progression.

### 3.1 Duration of the Trial

The study is anticipated to run over 5 complete years from 2016 to 2021. Eligible patients with localised PC with intermediate risk of progression on AS will be recruited over a period of 15 months and be randomly allocated to the intervention and control group.

## 4. Population and Setting

For the purpose of this trial we have used subsets of D-Amico's classification to derive our population of interest.

### 4.1 Inclusion Criteria

All participants aged between 50 and <80 years, diagnosed in the past 6 months, must have a mpMRI (centrally reviewed, 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 $\geq$ 10 ng/mL (which may include Gleason 6).

Those diagnosed with these clinical features but have not had a mpMRI, will be requested to have an MRI done at the cost of the study.

Men who were previously diagnosed with low-risk disease and whose disease have recently been upgraded (in the past 6 months) to fit the above-mentioned eligibility criteria, will also be eligible to participate in our study.

### 4.2 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.
- With a glomerular filtration rate (GFR) below 30 which will include those with severe loss of kidney function, and that is, to exclude anyone with Stage 4 or Stage 5 kidney disease
- History of renal calculi.
- Taking orlistat, cholesterol-lowering drug 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, those who are unable to swallow oral medication, those who have clinically diagnosed malabsorption syndrome with evidence of malabsorption, or those who have had prior surgical procedure affecting absorption.

We will also exclude those unable to comprehend study information and its requirements for intellectual reasons, or if they do not have sufficient English proficiency.

All participants will be requested to refrain from vitamin D supplementation whilst on the trial. However if they choose not to do so, their information will be recorded.

## 5. Trial Procedure

### 5.1 Summary

All participants will have had a mpMRI scan before prostate biopsy, as part of study requirement and will be actively followed up for 24 months.

1. The biopsy can be
  - a. 12 to 21 core TRUS or transperineal Biopsy + targeted biopsy of PIRADS 4 or 5 lesion (PIRADS 1 to 3 lesions will be acceptable for study inclusion but are not required to be biopsied) **or**
  - b. ≥21 core systematic TRUS or transperineal biopsy (targeted biopsy not required).
2. Eligible men will be invited to participate by their treating urologist.
3. **At baseline:** All participants, who have signed consent, will be required to complete a baseline survey, and have blood drawn. They will then be randomised.
4. **At randomisation:** All participants will be briefed on the study protocol for taking supplements.
5. **Start of intervention:** All men will be advised to take initial load dosing within 12 hours, and have blood and urine tests for toxicity, the following day. They will receive a phone call to check well-being and be given a date for their next dosing.
6. On day 29, all men will receive a monthly SMS and email reminder to take **one** supplement the **next day**. They will be recontacted, by phone, a week later to check compliance and briefly interviewed about changes to their lifestyle, wellbeing and if they had any falls. This will occur monthly (every 30 days) for the remaining 23 months.
7. All men will continue taking their monthly supplement, receive a monthly phone reminder to take supplements, and be recontacted, by phone, a week later to check compliance and briefly interviewed about their wellbeing and if they had any falls.
8. **A week prior to 3, 6, 9, 12, 18 and 24 month time points:** Participants will be mailed a pathology request form, and be reminded to visit their nearest pathology provider to have blood drawn, **before** taking their next dose of supplement. Blood specimen collected at each of these time points will be part of routine clinical care (PSA, biochemical). There will be additional blood specimens collected at 6, 12 and 24 months, for the purpose of the trial, for which separate pathology request forms will be provided. All participants who have not had a blood draw will receive a reminder phone follow-up. The trial coordinator will receive notification from the pathology provider when bloods have been drawn.
9. **A week before 12 months** – All participants also will be sent a follow-up survey, and be requested to be mpMRI scanned followed by repeat biopsy (at least 12 core); PIRADS 4 or 5 mpMRI lesions should be targeted by any means (as in standard clinical care). The requirement for the biopsy at 12 months will be determined by the treating urologist. If there is no sign of disease progression at this stage, then this follow-up biopsy can be postponed to a later date (before 24 months-end of trial).
10. Men who have chosen to opt out of AS and instead seek curative treatment will be given an alternative survey.
11. **At 24 months** – all participants will have an mpMRI scan followed by repeat biopsy if disease progression is reported. All participants will be sent a final survey.

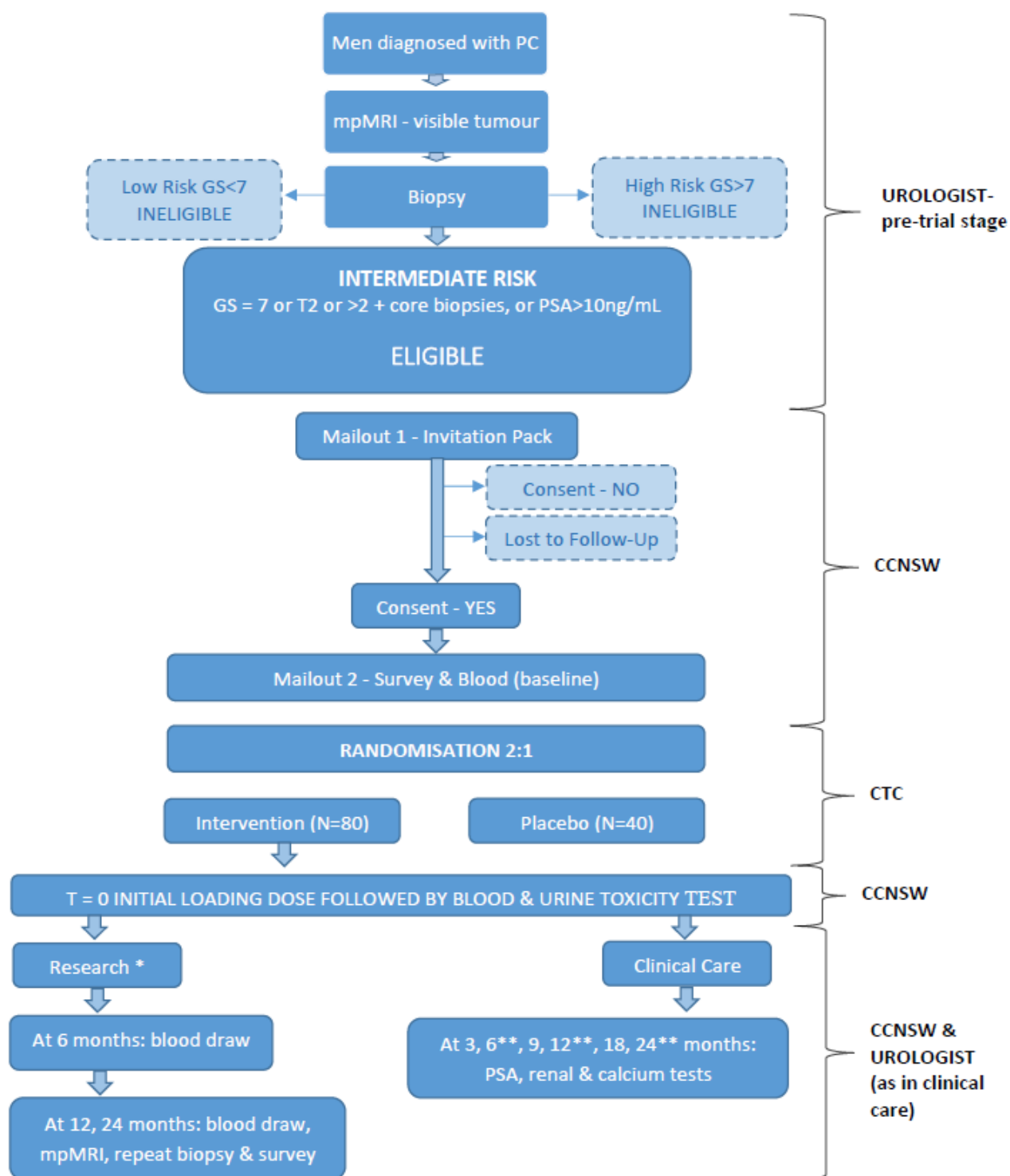
12. Closure letter to be sent to all participants.

Thereafter, participants will undergo standard AS according to the urologist's practice for 3 years. Long term data regarding progression and outcome will be collected until AS is ceased or until the patient undergoes curative treatment (surgery, radiotherapy, hormone therapy).

All participants will be managed by purpose-built tracking software, to ensure that all reminders are delivered promptly on time.

*See Figure 2: ProsD Trial procedure.*

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.

## 5.2 Recruitment

### 5.2.1 Recruitment Sites

Study participants will be identified by their treating urologist from the following high-volume centres in NSW, Victoria and Queensland:

- Macquarie University Hospital - NSW
- Westmead Private Hospital - NSW
- The Sydney Adventist (SAN) Hospital - NSW
- Royal North Shore Private Hospital - NSW
- St George Private Hospital - NSW
- Hurstville Private Hospital – NSW
- Urology Private Room, Christie Street, St Leonards - NSW
- Urology Private Room, Bungan Street, Mona Vale - NSW
- Wesley Urology Clinic - Queensland
- Australian Urological Association – Victoria
- Private room, Bairnsdale Regional Health Service - Vic
- Urology Private Room, Blacktown – NSW
- Urology Private Room, St Vincent's – NSW
- Urology Private Room, SAN Clinic – NSW
- ProsD Site Private Rooms South Coast Urology\_Chin -NSW
- Dr Wines added as a Sub-Investigator to Australian Clinical Trials - NSW
- ProsD Site Private Rooms Macarthur Urology - NSW
- ProsD Site Brisbane Urology Clinic\_Malone - QLD
- ProsD Site Private Rooms Nepean Cancer Care Centre (DRs Ko, Ferguson, Arianayagam, Canagasingham - NSW
- Site Approval Form\_Port MacQuarie - NSW
- Site Approval Form\_Westmead and MUH\_Dr\_Lau
- ProsD Site Private Rooms Darlinghurst & Riverina\_Symons
- Urology Private Room, Glen Waverly - Vic

Recruitment procedures and selection of study participants will be standardised across all sites. Each participating site will have a designated Site Principal Investigator (SPI). The SPI serves as the contact and acts on behalf of the participating site. The trial coordinator and the SPI will work together to ensure compliance with all areas of the trial.

### 5.2.2 Addition of New Recruitment Sites

The study team will initially send information letters to the Head of Urology at the treatment centres, followed up with face to face meetings to obtain support for the trial and discuss logistics. Once support is obtained and Site Specific Assessment ethical approval (SSA) has been granted for a particular site, the study team will liaise with the medical practitioners under the supervision of the treating urologists on the process of identifying eligible study participants. It is expected that the urologists review patient's medical records and identify men who meet the inclusion criteria.

### 5.2.3 Recruitment at the Urologists' Practice

Eligibility of participants will be ascertained by the treating urologist according to the following criteria:

- Diagnosed in the past 6 months **and**
- Have had a mpMRI **and,**

- Gleason score =7 (e.g. Gleason grade 3+4) or
- >2 positive core biopsies (which may include Gleason 6) or
- Clinical stage T2 (which may include Gleason 6) or
- PSA $\geq$ 10ng/mL (which may include Gleason 6)
- Age between 50 and <80 years

Men who were previously diagnosed with low-risk disease and whose disease have recently been upgraded (in the past 6 months) to fit the above-mentioned eligibility criteria, will also be eligible to participate in our study.

Potential participants will be invited to participate in this trial by their treating urologist. They will obtain a verbal consent from each participant to allow their personal details to be forwarded to the trial coordinator at the Cancer Council NSW, for further follow-up.

#### 5.2.4 Recruitment at the Cancer Council NSW

The trial coordinator will contact the urologists' practice to obtain a list of potential participants. An Invitation Pack (Mailout 1), containing an Invitation Letter and Participant Information and Consent Form (3 copies), will be mailed to each participant. All participants will be assigned a study identification number at this stage, which will appear on the consent form.

#### 5.2.5 Informed Consent Process

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the NHMRC *National Statement on Ethical Conduct in Human Research, 2007*.

Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial. A copy of the signed Consent Form will be given to the participant. 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, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial.

The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

The consent process will include the following:

- discussion between the potential participant or his legally acceptable representative and the study team or his treating urologist about the research and the nature and objectives of the trial and possible risks associated with their participation
- the presentation of written material in the Invitation Pack (e.g. Invitation Letter, Participant Information and Consent Form, which will be approved by the Lead HREC)
- the opportunity for potential participants to ask questions from both the study team and their treating urologist
- assessment of capacity. For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. A capable person will:
  - understand the purpose and nature of the research
  - understand what the research involves, its benefits (or lack of benefits), risks and burdens
  - understand the alternatives to taking part
  - be able to retain the information long enough to make an effective decision

- be able to make a free choice
- be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)
- where participants are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected

Men 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. Potential study participants who will not be considered as having this capacity include men with poor proficiency in English, affected by mental illness, dementia, intellectual disability, or impaired by drugs or alcohol. There will be no provision for alternatives to obtaining consent via the Guardianship Division within NSW Civil and Administrative Tribunal.

All men will have the opportunity to contact the study team if they have any further questions via the study FreeCall number 1800 789 622 provided on all study documents. The study team will record and log the number of calls including the date and reason for contact on the FreeCall number.

All participants will be requested to take the consent forms with them on their next visit with their treating urologist, and to clarify any uncertainties. If they consent, they will be asked to sign each of the 3 copies of this form and this will be witnessed by their urologist. Alternatively, participants who do not have an immediate follow-up appointment with their urologist (as they are on AS), can sign the consent forms and mail them to their urologist, AFTER they have discussed the trial and addressed all concerns that they may have had, with their urologist/trial coordinator by telephone or other means. They will retain (or be mailed) a signed copy for themselves and the remaining copies will be retained by the urologist and another by the staff at CCN.

Following receipt of signed-consent, the trial coordinator will confirm eligibility. All ineligible participants will be contacted, notifying them of their ineligibility but thanking them for their interest.

All non-respondents will be followed-up 5 times, fortnightly, by phone. Non-respondents will not be followed-up thereafter.

The trial coordinator will maintain detailed records on the consent process:

# of Recruitment packs sent out from each specific site and date sent

# of Invitation letters returned and date received

# of non-responders

# of Return to Sender

# of consenting participants and date of consent

# of non-consenting participants and date of non-consent; to include reasons (if any) for non-consenting participants

# of ineligible participants

# of eligible participants

### 5.2.6 Expected Participant Numbers

The primary outcome for the trial is disease progression at 24 months based on patients receiving active therapy. It is estimated that a rate of switching to active therapy for intermediate-risk patients on AS is currently ~35% at 2 years. 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% in favour of a more interesting rate of 77.5% (i.e. active therapy rate of 22.5% rather than 35%). Additionally, a futility analysis will be performed after 24 patients have received vitamin D for 12 months, and if eight or more patients in the intervention group have disease progression after 2 years of therapy, 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).

## 5.3 Post-Recruitment

### 5.3.1 Baseline data collection

Participants who consent would have agreed to follow trial requirements and, that is:

- to be randomised to either the intervention or placebo arm
- take required supplementation
- to complete 3 surveys
- to provide blood samples at various time points
- to have mpMRI scans
- to allow investigators to access their tissue biopsy samples
- to allow investigators to access their clinical records, for the duration of the trial, and
- to also allow investigators to access clinical records thereafter for passive monitoring.

All consenting participants will be mailed (Mailout 2), a copy of the baseline survey, and a pathology request form, with instructions on what is required of them.

When baseline blood draw is complete, the collection centre will notify Marken to courier the sample to CIH-Fenech's laboratory for further processing. When the trial coordinator receives notification from the pathology provider of a completed blood draw, CIH-Fenech's laboratory will immediately be notified to arrange receipt of sample,

All participants who have not had blood drawn will be followed up with a weekly reminder phone call and emails, for five weeks. We will cease to follow-up those who do not respond. Participants will be followed-up for incomplete responses to survey items.

### 5.3.2 Randomisation of Participants

After completion of baseline blood draw and survey, the trial coordinator will contact the randomisation hotline to obtain a kit number for each participant. This number will be used to randomise each participant to intervention or placebo arm.

### 5.3.4 Intervention

After receiving a kit number from the CTC Randomisation hotline, the trial coordinator will send the participant 2 packs of supplements specified by kit identification number, a pathology request form (blood/urine toxicity tests) with specific instructions to each participant (Mailout 3).

#### 5.3.4.1 Initial Loading Dose

Each participant will be requested to orally consume 10 tablet/capsules within 12 hours commencing initial loading. They can consume these 10 tablet/capsules in any way they prefer, as long as they consume all 10 tablet/capsules within 12 hours.

We will suggest a few options that they can choose to follow:

Option 1: Take all 10 tablet/capsules in one sitting OR

Option 2: Take 2 tablet/capsules at breakfast, 2 tablet/capsules at morning tea, 2 tablet/capsules at lunch, 2 tablet/capsules at afternoon tea and 2 tablet/capsules at dinner (total 10 tablet/capsules). OR

Option 3: Take 3 tablet/capsules at breakfast, 1 tablet/capsule at morning tea, 3 tablet/capsules at lunch, and 3 tablet/capsules at dinner (total 10 tablet/capsules).

Again we emphasize that participants do not have to adhere to any of these options. They can choose whatever options they prefer, as long as they consume all 10 tablet/capsules within 12 hours.

After consumption of initial loading (10 tablet/capsules), participants will be asked to visit their pathology provider to have a blood and urine test for toxicity, the following day. The pathology provider will forward the results of these tests to the treating urologist and to the trial coordinator.

After receiving notification of blood collection, the trial coordinator will follow-up each participant to check on their well-being and provide them with a date to take their next dosage.

#### *5.3.4.2 Justification for Dosing Regimen*

We are using similar dosing protocol 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.<sup>18</sup>

#### *5.3.4.3 Follow-Up Doses*

Thereafter, participants will consume 1 tablet/capsule a month later (30 days), for of the remaining 23 months. On the 29<sup>th</sup> day since consumption of supplement, the trial coordinator will send each participant a reminder email and SMS to take the supplement the next day. The trial coordinator will also follow-up each participant with a reminder phone call a week later, to ensure compliance. Each participant will also be briefly asked questions on any lifestyle changes, their well-being, if they have had any falls, and be notified of the date of his next supplement follow-up, in this phone call. This weekly reminder phone call will continue for participants who have not consumed their supplement, until compliance is met.

#### *5.3.5 Follow-Up at 6, 12 and 24 months*

All men will be reminded to have a blood draw at 6 months. They will again be reminded, at 12 months and again at 24 months:

- to have a repeat MRI with the same diagnostic provider
- repeat biopsy (as in standard clinical care)
- to have a blood draw
- complete a survey

These men will be mailed a MRI-request form to have this scan completed by the same provider as that during their diagnosis. They will also be mailed a pathology request form for the blood draw.

#### *5.3.6 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
- Taking orlistat or other drugs known to reduce vitamin D absorption

## 6. Biospecimen collection

### 6.1 Blood and Urine Collection for Toxicity Measures

Blood and urine samples will be collected 24 hours after commencing initial loading dose, to determine 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. These assays will be repeated when these men have their blood samples tested for their 3-monthly and 6-monthly PSA levels as in standard care (see section 6.3). A sample of blood specimen from each time point will be used to determine renal function by ensuring there is no greater than a 20% fall in the average estimated glomerular filtration rate, in each participant, over the course of the study.

### 6.2 Blood Collection for Research

For the purpose of research, blood will be collected at baseline, 6, 12 and 24 months, 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. Men will be requested to attend their preferred blood pathology for blood draw between Monday and Wednesday, in the morning (before 12pm). This will ensure that concurrent procedures of transportation, processing and storage can be completed by Friday. Collection will be undertaken and coordinated by Douglass Hanly Moir (DHM) in NSW, Sullivan and Nicolaides Pathology in Queensland: and Dorevitch Pathology in Victoria.

All tubes will be labelled with the Study identification number, participants' date of birth, date of blood draw, and time of blood draw. Participant's name will not appear on these tubes.

All tubes will be transported (by Marken), at 4°C, within 24 hours of blood draw, to CSIRO laboratories (CIH-Fenech) in Adelaide.

#### 6.2.1 Blood Processing

All blood specimens will be processed in CIH-Fenech's laboratory (CSIRO-SA). The heparin tubes will be processed for fresh lymphocytes, and the 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 Study identification number, participants' date of birth, date of blood draw, and time of blood draw.

Upon completion of the study, an aliquot of frozen plasma of each participant will be shipped in dry ice to CIG-Kimlin and SA Pathology, for vitamin D assays. All unused samples will be stored at -80C for future use.

#### 6.2.2 Measurements in Blood

##### 6.2.2.1 Vitamin D Assays

All vitamin D plasma assays will be carried by a laboratory to be determined at the end of the trial. The assay for 25OHD will be carried out using LC-MSMS (Thermo Scientific), which is specifically set up to exclude the detection of epimers. We will re-assay 20% of these samples in CIG-Kimlin's laboratory using the DiaSorin® Liaison semi-automated chemiluminescence assay (DiaSorin, Italy; DEQAS accredited). Internal and external vitamin D standards will be included in each batch of analysed samples 1,25OHD will be measured by using the Liaison (Diasorin) platform. This assay, using a RIA double antibody method, measures 1,25 D2 and 1,25 D3 and has a detection limit of  $\leq 2.0$  pg/mL.

#### 6.2.2.2 Genome Damage Markers

The CBMN assay will be performed using the isolated lymphocyte culture protocol described elsewhere.<sup>19</sup> 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. We will also assay for nuclear division index (NDI), a measure of mitogenic response, which is useful as a biomarker of immune function, long interspersed nuclear elements (LINE-1) methylation which is a marker for global methylation, and measure the prevalence of cyclobutane pyrimidine dimers, a marker for UV damage, and telomere length.

#### 6.3 Blood Collection for Clinical Monitoring (as part of AS Protocol)

All participants will have a PSA test every 3 months for the first 12 months, and 6-monthly testing, for the following 12 months. The blood samples will be collected at 3,6,9,12,18 and 24 months, and will be tested for PSA levels and additionally tested for calcium levels.

#### 6.4 Tissue Biopsies

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 additional slides (5µm sections) prepared and sent to CIH-Fenech's laboratory. These slides will be assayed for genome damage markers, vitamin D and Ki67.

### 7. Monitoring for Safety and Toxicity

Vitamin D toxicity can result in hypercalcaemia, and if untreated can result in coma or even cardiac arrest. It is estimated that serum levels have to reach 250nmol/L before vitamin D toxicity will occur.<sup>20</sup> Two Australian based RCTs using similar vitamin D doses to ProsD, have reported no adverse effects, and thus the likelihood of hypercalcaemia as a consequence of our dosing protocol is negligible. We will nevertheless closely monitor each participant for safety and toxicity. A sample of urine and blood will be collected for the following tests within 24 hours of commencing initial loading dose, to determine:

- incidence of hypercalcaemia and hypercalcauria, which will be measured to ensure serum and urine levels are below 2.75 mmol/L and less than 7.5mmol/24hrs, respectively.
- renal function by ensuring there is no greater than a 20% fall in the average estimated glomerular filtration rate, in each participant, over the course of the study (at baseline, 3,6, 9,12, 18 and 24 months).
- incidence of renal calculi if no more than two episodes of renal calculus occurs over the course of the study.

Blood samples collected at time of PSA testing for clinical monitoring, will also be tested for calcium levels and renal function. These results will be forwarded to the urologists and trial coordinator by the pathology provider.

The trial coordinator will then forward these results to the statistician at the CTC to determine if these adverse events are a result of the trial. Adverse results from this analysis will then be forwarded to the Independent Data Monitoring Committee (IDMC), after which the Ethics Committees will be notified.

## 8. Retrieval of Clinical Records

The study team will review men's medical and treatment records to obtain their diagnostic biochemical, MRI and biopsy results. This information will be collected at time of recruitment, and when re-biopsies are due, using a Clinical Data Collection Form.

### 8.1 Diagnostic and Follow-Up MRI Results and Scans

All results from MRI scans (at diagnosis and follow-up at 12 and 24 months) will be retrieved from the urologists' clinical records.

There will be a blinded review of all MRI scans. Each scan will be re-assessed by one member of the Independent Radiologist Panel for consistency. If both reviews are similar, then no further review will be required. However if the re-assessment differs from that at diagnosis, or at 12 months or at 24 months, then the scan will be re-assessed by a second member of the panel. There will be no further review if two out of the three scans are consistent. However if all three reviews differ, then the scan will be re-assessed at the end of the study.

The results of the independent review of the scans will be forwarded to the trial coordinator and treating urologist.

### 8.2 Diagnostic and Follow-Up PSA and Biopsy Information

The trial coordinator will collect all available PSA results and annual biopsy results from the urologists' clinical records (baseline through to 24 months). Thereafter these men will be followed-up according to their urologist's standard practice for AS. If their disease has not progressed after the first follow-up biopsy (based on ATFS), men will not be biopsied for another 36 months.

## 9. Survey

Each participant will be mailed a copy of the baseline survey at the start of the project, followed by a follow-up survey at 12 months and 24 months. The 12 month and 24 month follow-up surveys will coincide with the 12 month and 24 month blood collections. Each interview is anticipated to take a maximum of 30 minutes. All participants will have the option of completing the survey online. Those with incomplete responses will be followed-up.

### 9.1 Storage

Data from completed surveys will be entered into a database in a de-identified format and all identifying information and consent forms will be stored separately in accordance with NHMRC guidelines. All participants will be identified by their Study identification number, participants' date of birth, and date of interview.

Records of all people who have been contacted for an interview will be stored separately to avoid re-contacting people who have either participated or withdrawn from the study.

All data is stored electronically in password protected and encrypted files for a period no less than 10 years. The stored data will only include the survey responses and the respondents' IDs.

### 9.2 Data Access

Access to all survey data is limited to research staff who are directly involved in managing the project or undertaking data collection.

### 9.3 Separation of Files

Survey data (i.e. answers) will be kept separate from the database of contact information (i.e. phone numbers). It will be possible to re-link these databases using the study identification number. However, re-linking of the databases would only be undertaken in cases where participants, having completed the survey, ask for their survey answers to be deleted.

### 9.4 Data Cleaning and Preparation

All data cleaning and preparation will be conducted by research staff that are directly involved in managing the project.

### 9.5 Survey Data Items

Information will be obtained on various demographic characteristics, lifestyle factors, medical history, investigations and procedures. Copies of the surveys are in Mailouts 2, 7 and 9.

## 10. Setup of Randomisation Process

The NHMRC CTC will be responsible for maintaining the double blinded status of the study. Investigators, the study team, urologists, mpMPI radiology staff and participants will remain blinded until completion of the data analyses. Strategies to reduce the potential for unblinding will be covered by pre-trial testing of blinding procedures.

The method of randomisation is that of minimisation, through a central IVRS system. Treatment allocation will be balanced using this method based on the strata (identified in the protocol). This will ensure that there is a reasonable balance in treatment allocation over the course of the trial.

The trial coordinator will liaise with statisticians at the NHMRC CTC to setup a hotline that will facilitate the randomisation process. Dialling this hotline will enable the trial coordinator to obtain a kit number and a randomisation-specific identification number, upon entering each participant's details. When further top-up is required the trial coordinator will re-contact this hotline and upon provision of the randomisation-specific identification number, a new kit identification number will be generated that will allow continuation of the same supplementation.

In the event of an emergency, valid medical or safety reason the blind may be broken when knowledge of patient's treatment group is necessary for further patient management.

The code break will be held by the NHMRC CTC and are the responsibility of CIC-(*Prof Val Gebski*). A request will be submitted to the study team that unblinding is required for a trial participant and an assessment to unblind will be made in consultation with the research team and the TMC. A formal request will then be submitted by the PI to the NHMRC CTC.

The study team will document all stages of the unblinding process and disseminate to the IDMC, the Sponsor and Lead HREC.

## 11. Manufacture of Trial Supplements

The vitamin D, in the form of cholecalciferol (50,000IU), and placebo will be supplied as identical tablet/capsules. The first batch was manufactured by API Consumer Brands (New Zealand), according to study requirements, will expire in December 2018. API Consumer Brands (NZ) no longer manufacture this product. As of January 2019, a new batch of supplements will be manufactured by Bio-Tech Pharma (USA), according to study requirements.

All supplements and placebos will be supplied in a blister pack in batches of 10 tablet/capsules/blister, and assigned a kit number (*see Setup of Randomisation*). Details of this kit number (containing vitamin D or placebo) will be provided to the Clinical Trials Centre.

Both products will have identical packaging to include the following:

- name of the sponsor
- pharmaceutical dosage form, route of administration, quantity of dosage units
- the batch and/or code number to identify the contents and packaging operation
- the participant study ID number
- directions for use
- “for clinical trial use only”
- the name of the PI
- a trial reference code allowing identification of the trial site
- the storage conditions (below 25C)
- the period of use (use-by date, expiry date)
- “keep out of reach of children”
- Details advising return of empty packaging and unused products to treatment centre

Destruction of unused or part-used supplementation will only be done after the finalisation of the trial and the compilation of the final report, or when supplements are close to reaching expiration date. This will be documented to record the identification of the batches, actual quantities destroyed and participant numbers involved.

## 12. End of Study Treatment/Withdrawal Procedure

All participants will be mailed a closure letter at the end of study (Mailout 10). They will also be mailed a newsletter on trial findings.

### 12.1 Patient Withdrawal

A participant may be withdrawn by their treating urologist or study team from the trial at any time for the following reasons:

- Adverse Event (AE), Adverse Reaction (AR), Serious Adverse Event (SAE) or Suspected Unexpected Serious Adverse Reaction (SUSAR)
- Unacceptable toxicity
- Undercurrent illness which prevents remaining on AS
- Any alteration in the participant’s condition which justifies the discontinuation of participation in the clinician’s opinion
- Protocol violation requiring discontinuation of participation
- Participant is not compliant with study procedures
- Lost to follow up
- Participant withdrawal of consent

In the case of withdrawal of consent, the participant may contact their treating urologist or call the study team on the FreeCall number to request to be withdrawn. A Withdrawal Form is included in the Recruitment Pack provided during enrolment.

Unless a patient states otherwise, it is assumed that data for that participant will not be excluded from the final analysis.

The treating clinician will explain that withdrawal from the trial does not include withdrawal from follow-up.

Withdrawn participants will not be replaced.

### 13. Audits/Monitoring

A risk assessment has been carried out and an appropriate monitoring plan has been developed. Monitoring will be a combination of central monitoring (e.g. database checks) and the IDMC review. There will be limited on-site monitoring: all participating investigators and groups must agree to direct access to all trial related sites, source data documents and reports for the purpose of monitoring by the sponsor and audit and inspection by domestic and foreign regulatory authorities.

### 14. Ethics

This clinical trial will be conducted on humans at sites under the control of private hospitals, therefore it will be conducted according to the “National Statement on Ethical conduct in Human Research” Ethical approval will be sought from the following certified Human Research Ethics Committees:

- Macquarie University Ethics Committee
- Bellberry Limited
- Westmead Research Office, Westmead Hospital
- Obtain site authorisation from Regional Governance Officers following site specific assessment (PD2010\_056: Research – Authorisation to Commence Human Research in NSW Public Health Organisations) at the following sites:
  - Macquarie University Hospital - NSW
  - Westmead Private Hospital - NSW
  - The Sydney Adventist (SAN) Hospital - NSW
  - Royal North Shore Private Hospital - NSW
  - St George Private Hospital - NSW
  - Hurstville Private Hospital – NSW
  - Urology Private Room, Christie Street, St Leonards - NSW
  - Urology Private Room, Bungan Street, Mona Vale - NSW
  - Wesley Urology Clinic - Queensland
  - Australian Urological Association - Victoria
  - Private room, Bairnsdale Regional Health Service, Vic
  - Urology Private Room, Blacktown – NSW
  - Urology Private Room, St Vincent’s - NSW
  - Urology Private Room, SAN Clinic – NSW
  - ProsD Site Private Rooms South Coast Urology\_Chin -NSW
  - Dr Wines added as a Sub-Investigator to Australian Clinical Trials - NSW
  - ProsD Site Private Rooms Macarthur Urology - NSW
  - ProsD Site Brisbane Urology Clinic\_Malone - QLD
  - ProsD Site Private Rooms Nepean Cancer Care Centre (DRs Ko, Ferguson, Arianayagam, Canagasingham - NSW
  - Site Approval Form\_Port MacQuarie - NSW
  - Site Approval Form\_Westmead and MUH\_Dr\_Lau
  - ProsD Site Private Rooms Darlinghurst & Riverina\_Symons
  - Urology Private Room, Glen Waverly - Vic

## 14.1 Protocol Amendments

The protocol, Invitation Letter, Consent Form, Participant Information Sheet and Withdrawal Form and any proposed advertising material will be submitted to the Lead HREC, Regional Governance Officers and host institution(s) for written approval.

The PI will submit and, where necessary, obtain written approval from the above parties for all substantial amendments to the original approved documents.

## 15. Annual Reporting

The PI will be responsible to submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the Lead HREC, host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the Lead HREC, host organisation and Sponsor.

## 16. Safety

### Patient Protection

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\*](#) and any other relevant legislation/guidelines.

## 17. Adverse Event Reporting

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 even that:

- Results in death
- Is life threatening
- Results in hospitalisation
- 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 or not 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.

When an AE/AR/SAE or SUSAR occurs, the following will be documented and recorded in the adverse event log book:

- 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

- Document any action taken in relation to the event
- Record the final outcome

An appropriate AE Report Form will be completed and submitted within 72 hours of receiving notification of the event occurring to the Ethics Secretariat at the Human Research Ethics Committee at WSLHD. Regular updates will be provided until the event has been resolved or a final outcome has been reached.

The Chair of the Independent Data Monitoring Committee will be notified immediately of any events, and also reported to the Lead HREC and Funding Body.

All AE, ARs, SAEs or SUSARs reported will be coordinated to all sites and in annual progress reports to Regional Ethics Officers at site specific ethics committees.

## 18. Serious Breaches

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the PI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the HREC committee.

## 19. Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be established to provide the Trial Management Committee (TMC) 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 and TMC Charter. There will be 6-monthly reviews conducted by the TMC for the purpose of monitoring the conduct of the trial and assessing participant safety.

A Trial Monitoring Plan will also be developed and agreed by the TMC based on the risk assessment which may include onsite monitoring.

The procedures and anticipated frequency of monitoring will be related to participant enrolment, consent, eligibility, allocation of trial groups, adherence to trial intervention, policies to protect participants, reporting of harm and completeness, accuracy and timeliness of data collection.

## 20. Early Termination

This trial is based on previous Australian based randomised controlled trials using similar vitamin D doses that appeared to be safe.<sup>1,2</sup>

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

- incidence of hypercalcaemia and hypercalciuria, 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 average 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 an endocrinologist or a nephrologist respectively, 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.

## 21. Complaints

Complaints from study participants are addressed on a case by case basis. Written records are kept on conversations and actions taken including follow-up investigations.

The Lead HREC will be informed of complaints, as appropriate based on severity. This will occur immediately for major complaints, or via reporting in Annual Reports for minor complaints. Once a complaint has been received and evaluated, the Lead HREC will be informed of the type of remedial action taken. All relevant parties will also be notified to include staff, the treating urologist and the Regional Governance Officer at specific sites.

## 22. Confidentiality, Storage and Archiving of Study Data

All information collected and storage of study data fully conforms 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.
- At recruitment identifying information will be collected on the paper Consent Form
- Electronic and paper Medical records will be assessed to review PSA and biopsy results. These will be temporarily noted on paper data collection forms then the information will be entered into the secure study database.
- All biopsy and mMPRI results will be recorded and stored and adhere to confidentiality policies as practised by the laboratory
- Study participants details and medical information will be held on the database at the Cancer Council NSW and the Clinical Trials Centre

Early 2017, all data on the study database will be stored at the AZURE Data Centre, 400 Harris Street, Ultimo, Sydney, NSW, 2007. Only authorized staff will have access to the data.

To enable the Cancer Council NSW to protect the privacy of individuals participating in research studies and the integrity of our datasets, we note the following:

1. Cancer Council NSW exclusively leases several servers within the secure AZURE data centres, and will have sole access rights to the datasets stored on the relevant servers. No disclosure of data to third parties will take place
2. The data centres are geo-redundant, offering Cancer Council NSW the ability to back up data across two separate locations, enabling more effective disaster recovery
3. The arrangement will not involve any offshore transfer of data, as both the primary and backup servers are located within Australia
4. The data centres have a number of security features, including 24-hour video surveillance, fire protection, raised flooring and permanent onsite security personnel
5. The AZURE platform is currently accredited to international standards (ISO 27001) for Information technology – security techniques - Information security management

In particular:

- We do not consider that any additional obligations are triggered with respect to APP 1 (Privacy Policy), APP 3 (Collection), APP 5 (Notification) or APP 6 (Use and Disclosure), as under the proposed arrangement, no disclosure of personal information will occur.
- As the personal information will remain within Australia at all times (and under the effective control of Cancer Council NSW), APP 8 (Cross border Data Flows) is not triggered.
- We consider that the redundancy, disaster recovery and security features outlined above will significantly enhance our ability to ensure the quality (APP 10) and security (APP 11) of personal information.

Confidentiality will be maintained at all times. All information will be de-identified with all potential identifying information removed from health information.

Data will be entered into a password protected database. Once entered into the database, all identifying information for the study participant will be removed and each participant will be allocated a unique ID number.

Study computer files will be stored in password protected folders on password protected servers in the Cancer Council NSW.

Any identifying paperwork will be stored in locked filing cabinets at the Cancer Council NSW.

The study results will be de-identified and presented in the form of aggregate statistical data, individual participants will not be identifiable either directly or indirectly from any published material.

Data will remain the property of the Cancer Council NSW and Macquarie University regardless of personnel changes.

All information will be owned by the research team and reports or publications to peer reviewed journals will be owned by their authors who will primarily be members of the research team.

Data will be archived for 10 years after the completion of the study as specified by NHMRC.

## 23. Indemnity

Arrangements for insurance to cover the potential legal liability for harm to study participants from the management, design or conduct of the trial will be provided. Insurance will provide indemnity for all researchers, study staff and external providers from and against all actions, claims, demands, costs or expenses (to include legal costs) made or prosecuted in any manner based upon or attributable to injury of any person or loss of or damage to property which may arise from conducting the ProsD trial.

## 24. Trial Registration

This trial will be registered on the Australia and New Zealand Clinical Trial Registry <http://www.anzctr.org.au> established at the NHMRC Clinical Trials Centre, University of Sydney.

## 25. References

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## Mailouts 1 to 10 - Illustrated in Figure 3

### Mailout 1 (invitation):

- Letter of invitation
- Participant information and consent form (PICF)

### Mailout 2 (baseline data collection):

- Letter and instructions for completing survey and blood draw
- Baseline survey
- Pathology request form for blood (Form 1)
- *Ineligible letter will be sent to notify those ineligible.*

### Mailout 3 (soon after randomisation):

- Letter with instructions on initial loading dose and blood draw/urine sample
- Two blister packs (24 tablet/capsules)
- Pathology request form for blood and urine tests- kidney function and calcium toxicity (Form 2)

### Mailout 4 (PSA monitoring at 3 months):

- Letter requesting blood draw for clinical monitoring of PSA with additional request to monitor kidney function and calcium toxicity
- Pathology request form for blood (Form 3)

### Mailout 5 (PSA monitoring at 6 months and ProsD at 6 months):

- Letter requesting blood draw for clinical monitoring of PSA with additional request to monitor kidney function and calcium toxicity, and also blood draw for ProsD trial
- Pathology request form for blood (Form 4 for PSA and Form 5 for ProsD)

### Mailout 6 (PSA monitoring at 9 months):

- Letter requesting blood draw for clinical monitoring of PSA with additional request to monitor kidney function and calcium toxicity
- Pathology request form for blood (Form 6)

### Mailout 7 (PSA monitoring, and ProsD at 12 months):

- Letter to request completion of survey, blood draw and MRI scan at 12 months.
- Re-supply of one blister pack (12 tablet/capsules)
- Follow-up survey at 12 months
- Pathology request form for blood (Form 7-PSA and Form 8-ProsD)
- MRI request form

### Mailout 8 (PSA monitoring at 18 months):

- Letter requesting blood draw for clinical monitoring of PSA with additional request to monitor kidney function and calcium toxicity
- Pathology request form for blood (Form 9)

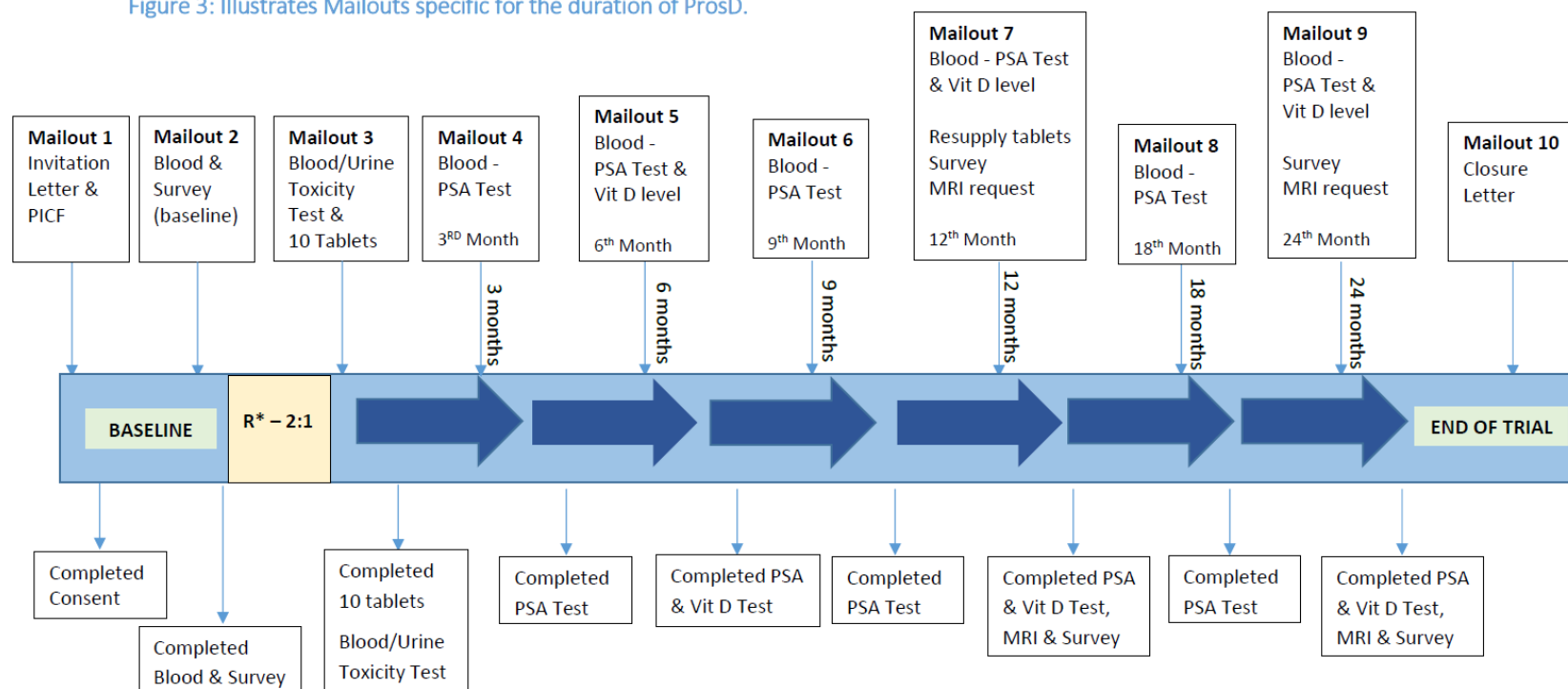
### Mailout 9 (PSA monitoring, and ProsD at 24 months):

- Letter to request completion of survey, blood draw and MRI scan
- Follow-up survey at 24 months
- Pathology request form for blood (Form 10-PSA and Form 11-ProsD)
- MRI request form

### Mailout 10:

- Closure letter

Figure 3: Illustrates Mailouts specific for the duration of ProsD.



\*Randomisation 2:1 by NHMRC Clinical Trial Centre

Note: PSA tests in Mail Out 4, 5, 6, 7, 8 and 9 will be determined from date of biopsy  
Vit D level tests in Mail Out 5, 7, and 9 will be determined from the Toxicity Call date