PROVENT: A randomised, double blind, placebo controlled feasibility study to examine the clinical effectiveness of aspirin and/or Vitamin D3 to prevent disease progression in men on Active Surveillance for prostate cancer

Protocol, Version 4.0, 16th February 2017

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- Tissue storage and pathology review
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- Urine testing for exploratory research and sample storage
  Molecular Epidemiology Laboratory, Centre for Cancer Prevention, Wolfson Institute, Queen Mary University of London, Charterhouse Square, London, EC1M 6BQ

- Tissue for CCP (ii) Score
  Myriad Genetics, Inc., 320 Wakara Way, Salt Lake City, UT 84108, USA

Participating Sites:
Up to seven UK Centres

Investigator Agreements

Chief Investigator:
The clinical study as detailed within this research protocol (Version 4.0, 16th February 2017), and any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

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GLOSSARY OF ABBREVIATIONS

25(OH)D	25-hydroxycholecalciferol or 25-hydroxyvitamin D or calcidiol
AE	Adverse Event
AR	Adverse Reaction
AS	Active Surveillance
Barts CTU	Barts Clinical Trials Unit
CCP (i)	Centre for Cancer Prevention
CCP (ii)	Cell Cycle Progression
CCP MEL	Centre for Cancer Prevention, Molecular Epidemiology Laboratory.
CI	Chief Investigator
COX1 & 2	Cyclo-oxygenase 1 & 2
CRF	Case Report Form
CS	Clinically Significant
DMC	Data Monitoring Committee
DRE	Digital Rectal Examination
eCRF	electronic Case Report Form
FSH	Follicle Stimulating Hormone
FTA	Fast Technology Analysis
G6PD	Glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GI	Gastro Intestinal
GMP	Good Manufacturing Practice
H Pylori	Helicobacter pylori
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IU	International Unit
ISF	Investigator Site File
LH	Luteinising Hormone
MCCL	Maximum Cancer Core Length
MEL	Molecular Epidemiology Laboratory
MHRA	Medicines and Healthcare products Regulatory Agency
MREC	Main Research Ethics Committee
MRI	Magnetic Resonance Imaging
NSAID	Non-Steroidal Anti Inflammatory Drug
PIRADS	Prostate Imaging-Reporting and Data System
PIS	Patient Information Sheet
PSA	Prostate Specific Antigen
PPI	Protein Pump Inhibitors
PSF	Pharmacy Site File
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SNO	Study Number
SNP	Single-nucleotide polymorphisms
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCCL	Total Cancer Core Length
TMG	Trial Management Group
TMF	Trial Master File
TRUS	Trans Rectal Ultrasound

STUDY SYNOPSIS

Title	A randomised, double blind, placebo controlled feasibility study to examine the clinical effectiveness of aspirin and/or Vitamin D3 to prevent disease progression in men on Active Surveillance for prostate cancer
Short Title	PROVENT
Protocol Version Number and Date	Version 4.0 16th February 2017
Methodology	Randomised, double blind, placebo controlled, 3x2 factorial feasibility study
Study Duration	Two years & seven months, (comprising 12 months recruitment, 18 months treatment plus ≥ 30 days for post treatment pharmacovigilance).
Phase of Trial	Feasibility Study (prior to Randomised Phase III trial)
Coordinating Centre	Barts Clinical Trials Unit, Centre for Cancer Prevention, Queen Mary University of London
Trial Sites	Up to seven UK centres
Number of Subjects	102 males
Main Objective	To demonstrate the acceptability and feasibility of recruitment to a randomised chemoprevention study of standard (300mg) or low dose (100mg) aspirin vs. placebo and/or Vitamin D3 vs. placebo in patients enrolled on an Active Surveillance programme for prostate cancer.
Main Outcome Measures	Rate of patient recruitment to a randomised chemoprevention study in men enrolled on an Active Surveillance programme for prostate cancer
Inclusion Criteria	1. Male subjects aged 16 years or over with an estimated life expectancy of more than three years 2. Willing and able to provide written informed consent 3. Corrected serum calcium ≤ 2.65mmol/l 4. No previous treatment for prostate cancer (including surgery, hormone therapy, radiotherapy, cryotherapy) 5. Must have undergone a multi-parametric MRI of the prostate, deemed assessable by the local radiologist, and any lesions seen must have undergone targeted biopsy, (transrectal or transperineal) within 12 months of study registration. 6. Histologically confirmed prostate cancer* following prostate biopsy (including at least 10 cores of prostate tissue) in men opting for Active Surveillance as their primary cancer therapy. *PROVENT Prostate Cancer Criteria. All must be met for Inclusion:

	• Gleason score 6 or 7 (Gleason 3+3 or 3+4) • Clinical and radiological stage <T3 • Serum PSA ≤15.0 ng/ml • Less than 10mm of cancer in a single core
Exclusion Criteria	1. Previously treated prostate cancer (including radiotherapy, hormone therapy, brachytherapy or surgery) 2. Currently enrolled, or has been a participant within the last 30 days, in any other investigational drug or device study. 3. Current daily use of aspirin or NSAIDs; or daily dietary supplements/medication containing more than 400 IU (10 micrograms per day) Vitamin D3; or chronic use (defined as > 6 months continuous daily use) of either aspirin or >400IU Vitamin D3 within two years of study enrolment 4. Current or previous use of 5-α reductase inhibitors such as finasteride or dutasteride 5. Not willing to comply with the procedural requirements of this protocol including repeat prostate biopsies 6. Known allergy/sensitivity to or intolerance of aspirin, other salicylates or NSAIDs e.g. ibuprofen/ naproxen 7. Prior history of gastro-intestinal bleeding or ulceration, severe dyspepsia or inflammatory bowel disease 8. Haemophilia or other bleeding diatheses 9. Prior history of renal stone disease 10. Chronic renal disease (≥stage 4) 11. Known hypercalcaemia (corrected serum calcium >2.65 mmol/l) or untreated hyperparathyroidism 12. Any bowel condition that would make repeat transrectal biopsy hazardous or difficult to perform e.g. recto-urethral fistula, or prior bowel surgery such as abdomino-perineal resection. 13. Any malignancy (other than non-melanoma skin cancer) that has not been in complete remission for five years

	14. Any serious co-existent medical condition that would make repeat prostate biopsy hazardous e.g. anti-coagulation requiring continuous administration 15. Severe Asthma 16. G6PD deficiency 17. Pre-existing macular degeneration 18. All contraindications to aspirin and Vitamin D3, including concomitant therapy with any medication that may interact with aspirin or Vitamin D3 (see section 4.10) 19. Regular consumption of alcohol units greater than the recommended daily limit of 3-4 units per day (men)
Statistical Methodology and Analysis	Sample size calculations have suggested that 800 men are needed for a future definitive randomised chemoprevention study of standard (300mg) or low dose (100mg) aspirin vs. placebo and/or Vitamin D3 vs. placebo in patients enrolled on an Active Surveillance programme for prostate cancer. The feasibility study aims to demonstrate the acceptability and viability of recruitment to this larger study. Data from the feasibility study will be used to determine the number of centres required to enable the larger, 800 patient trial to fully recruit within 4 years. The feasibility study sample size was chosen to examine acceptance rates and the time required to recruit 102 patients. We plan to recruit 102 patients over 12 months. If the true recruitment rate is 33.3% then approaching 300 individuals, and therefore recruiting ≥100, would achieve 89% power to show that the true recruitment rate is above 25% (using a two-sided binomial proportion test with a 0.05 significance level).

1.0 Introduction

1.1 Background

Prostate cancer screening, through the use of Prostate Specific Antigen (PSA), has markedly increased the reported incidence of prostate cancer such that the disease is now the most common cancer to affect men in the Western World[1]. This trend has been accompanied by a stage migration of the disease such that many men diagnosed with prostate cancer today maybe considered to harbour low to intermediate risk or favourable-risk prostate cancer[2, 3].

This trend has led to the recognition that many men diagnosed with low to intermediate risk prostate cancer may have little to gain from traditional radical prostate cancer therapies, such as surgery or radiotherapy, given their risk of dying from their disease is very low[4]. If men with low to intermediate

risk prostate cancer have little to gain in terms of survival following radical therapy, they have much to lose with regard to the morbidity of radical therapy. For example, men undergoing surgery for prostate cancer report rates of urinary incontinence of 20-30% one year after surgery, while 60-70% report erectile dysfunction[5]. Men undergoing radiation therapy again report high rates of impotence, similar to that of surgery, at long term follow up while many men report bowel dysfunction as a result of radiation[6].

Active Surveillance, or expectant management, has emerged as a management strategy to reduce the toxicity of prostate cancer treatment by targeting radical prostate cancer therapy at those men that harbour the more aggressive prostate cancers which are destined to progress over time.[7]. Men choosing to enter an Active Surveillance programme for prostate cancer undergo a combination of repeat serum PSA testing, repeat prostate biopsy and, increasingly, prostate imaging to identify whether the cancer is progressing over time. By use of this approach, a significant proportion of men diagnosed with prostate cancer will avoid the toxicity of radical prostate cancer therapy.

Depending upon the criteria used to define prostate cancer progression; 30-50% of men entered into an Active Surveillance programme are identified as experiencing disease progression and subsequently undergo radical therapy[8, 9]. A high proportion of men are therefore still experiencing the harms associated with prostate cancer therapy. It would therefore be highly advantageous to identify an agent that would be able to reduce the number of men experiencing disease progression while enrolled in an Active Surveillance programme.

The purpose of this study is to test the feasibility of recruiting to the larger randomised trial that would assess the efficacy of both aspirin and/or Vitamin D3 to prevent prostate cancer progression in men entered into an Active Surveillance programme.

Criteria for Active Surveillance

A number of different criteria exist for Active Surveillance[8]. The criteria for surveillance are often based on a combination of factors including serum PSA, PSA density together with histological biopsy findings (including the number of positive prostate cancer cores), the percentage of positive cancer cores to negative cancer cores, and the grade of the cancer on prostate biopsy.

Criteria for cancer progression

Again, criteria for disease progression are numerous. Many have used PSA velocity while on surveillance, although increasing data suggest that PSA dynamics on surveillance do not correlate with adverse findings on repeat prostate biopsy. Such adverse features correspond to more extensive disease on repeat biopsy together with higher grade disease on repeat biopsy. Generally, if a man transitions from what is regarded as lower risk disease to clinically significant disease, many clinicians would recommend he undergoes radical therapy.
The criteria for cancer progression for this study will be based on any of the following:

- the development of a minimum 0.2cc lesion, with a PIRADS score of 4/5, on multi-parametric imaging where no MRI lesion was identified at the screening MRI, or an MRI scan demonstrates that a lesion identified at screening has increased in volume by >33%
- An upgrading of MRI stage of disease to ≥T3.
- A 50% increase in serum PSA at 12 months from baseline.
- Histological disease progression defined as an increase in Gleason scores from:
  - Gleason 3+3 to Gleason score 7 or higher
  - Gleason 3+4 (score 7) to 4+3 (score 7) or
  - Gleason 4+3 to a higher score
- A 50% increase in maximum cancer core length (MCCL)
- Development of metastases

1.2 Aspirin

Aspirin, otherwise known as acetylsalicylic acid, is a common anti-inflammatory drug used for analgesia and as an antipyretic. Aspirin is listed within a class of drugs known as Non-Steroidal Anti-Inflammatory

Drugs (NSAID). These drugs inhibit the enzyme cyclo-oxygenase which is involved in the metabolism of prostaglandins and thromboxanes, which in turn are involved in many physiological pathways including inflammation and platelet function. Aspirin is a reversible inhibitor of cyclo-oxygenase 1 (COX-1) which differentiates aspirin from other NSAID medication such as diclofenac which also inhibits the COX-2 enzyme together with COX-1, both of which are inhibited in an irreversible manner.

Increasingly, data are being made available to suggest that aspirin, in contrast to other NSAIDS, may have anti-carcinogenic properties [10-12]. Data are emerging for a number of cancer types, although this was first demonstrated for colorectal cancer where it has been shown to reduce incidence by up to 25%[10]. Data are now emerging for prostate cancer. For example, Kashiwaqi[13]recently demonstrated that aspirin down-regulated the androgen receptor which drives prostate cancer metabolism, together with down-regulating prostate specific antigen (PSA) levels within prostate cancer cells. Furthermore, Kashiwaqi demonstrated that aspirin up-regulates prostaglandin receptor subtype EP3, which again influences androgen receptor expression and cell proliferation. This is thought to be important in prostate carcinogenesis.

A number of epidemiological studies have also provided data on the benefit of aspirin on prostate cancer incidence and progression. For example, Murtola[14] recently identified, using national prescription database information matched to Finnish national registry databases, that aspirin decreased prostate cancer risk in a dose-dependent fashion. Shebl[15], using data from the Prostate, Lung, Colon and Ovary (PLCO) Cancer Screening Trial, identified an 8% reduction in prostate cancer incidence in those taking more than 75mg of aspirin daily. Zoarsky[16] identified that aspirin lowered the incidence of biochemical failure, a harbinger of prostate cancer metastasis and death, after radical prostate radiation therapy. This finding was replicated by Choe[17].

However, although aspirin has been shown in several overviews to have an impact on prostate cancer, no direct comparisons of low dose (100mg) versus standard dose (300mg) have been undertaken and there is uncertainty as to whether the low dose effect observed on platelets is adequate to explain the reductions seen for cancer[18].

Aspirin is generally a well-tolerated medication; however, it is known to cause gastrointestinal bleeding and therefore should be taken with caution by those that have a previous history of peptic ulcer disease. Patients who test positive for *Helicobacter pylori (H. pylori)*, also known to increase the risk of GI bleeding [19], should be adequately treated for this infection if taking aspirin. In addition, aspirin is known to cause hives and angio-oedema in a small proportion of people and can worsen the symptoms of asthma.

1.3 Vitamin D

Vitamin D is a fat-soluble secosteroid responsible for intestinal absorption of calcium and phosphate. In humans there are two important related compounds, Vitamin D2 (ergocalciferol) and Vitamin D3 (cholecalciferol). The body can also manufacture Vitamin D3 from 7-dehydrocholesterol using sunlight. When ingested, cholecalciferol is converted to 25(OH)D (calcidiol) in the liver and subsequently converted to calcitriol by the kidneys, and by other organs including the prostate gland. This conversion is by hydroxylation. Calcitriol is the biologically active form of Vitamin D and controls calcium and phosphate metabolism.

Some early data are emerging that Vitamin D may influence the incidence of cancer [20-28], although data are not as abundant as for aspirin. Furthermore, a number of studies have demonstrated conflicting results [29, 30]. If Vitamin D does influence the incidence of cancer, the mechanism for action is thought to be due to calcitriol's influence on cellular proliferation, differentiation and apoptosis. The Vitamin D receptor, for example, is known to be highly expressed in epithelial cells known to be at risk of carcinogenesis, such as the breast, skin and prostate. Activation of the receptor is known to stimulate a number of genomic changes in epithelial cells that are known to contribute to maintenance of the differentiated phenotype, resistance to cellular stresses and protection of the genome. For example, Mondul[28], evaluating prostate cancer risk in relation to single-nucleotide polymorphisms (SNP) in four genes shown to predict circulating levels of 25(OH)D, identified that genetic variants related to lower 25(OH)D levels were associated with a decreased risk of aggressive prostate cancer. Through the differentiation pathway it has been suggested that Vitamin D deficiency over time may contribute to the progression of insignificant prostate cancer to clinically significant disease. In this respect, Marshall and

colleagues [31]evaluated Vitamin D supplementation in men with low to intermediate risk prostate cancer, reporting that those receiving Vitamin D had a lower number of positive cancer cores on repeat biopsy at one year.

Oral Vitamin D supplementation may be administered daily or in intermittent bolus doses, however, there is growing support for the use of daily dosing to maintain stable circulating concentrations due to the short circulating half-life of Vitamin D[32]. There is also some recent evidence to suggest that intermittent bolus dosing may be less effective than daily dosing for non-bone outcomes, a phenomenon attributed to potential adverse effects of bolus dosing on Vitamin D catabolism at extra-renal sites of disease[33]. We will therefore administer Vitamin D3 using a daily dose of 4,000 IU (8 drops) in this trial.

In order to verify that the daily dosage of Vitamin D3 supplementation is adequate, serum 25(OH)D concentrations will be measured at baseline and six monthly thereafter. These tests will be carried out centrally, in batches, and the results unavailable to the research sites. They will be viewed only by the Data Monitoring Committee.

Vitamin D3 supplementation is well tolerated with toxicity being very rare. Symptoms of Vitamin D3 toxicity are associated with accompanying hypercalcaemia which can result in anorexia, nausea and vomiting which can progress to renal failure and metastatic calcification in the extreme.

1.4 Rationale for the study

Active Surveillance is a prostate cancer management strategy which is increasingly being employed for men with low to intermediate risk prostate cancer as data emerge regarding the reduced toxicity benefits of this approach. Despite this, 30-50% of men entered into Active Surveillance programmes experience prostate cancer progression during monitoring, the majority experiencing progression within three years of diagnosis [8, 34, 35]. Patients who are considered to have progressed on Active Surveillance undergo radical therapy, and as a result are exposed to the risks of radical therapy toxicity including urinary and bowel dysfunction together with sexual dysfunction. In addition, data are emerging to suggest that a significant proportion of men experience anxiety and discomfort over not receiving any form of cancer therapy, and therefore opt for radical treatment despite having low to intermediate risk prostate cancer which would be ideally managed by Active Surveillance[36, 37].

As such, it would be highly advantageous to identify a minimally toxic therapy that may potentially modify a man's risk of prostate cancer progression while on Active Surveillance. If such a therapy was found to reduce progression, it is likely that more men would choose Active Surveillance as a treatment option rather than opting for radical therapy at the outset. Furthermore, it may prevent men from subsequently requiring radical therapy due to disease progression while on Active Surveillance.

Evidence from clinical studies on therapies that may modify a man's risk of either being diagnosed with prostate cancer or developing clinically significant prostate cancer while on Active Surveillance are largely lacking. This is in part due to the huge cost of performing chemoprevention studies, needing to expose large populations of healthy men to the agent and then subsequently following them up for many years. To date there have been only three studies on prostate cancer chemoprevention in those without a previous diagnosis of prostate cancer, while there is one study in men on Active Surveillance.

The SELECT trial [38, 39]evaluated selenium and vitamin E supplementation in 35,000 men. The study identified that, after 7 years of follow-up, men taking the supplements were nearly 20% more likely to be diagnosed with prostate cancer than those receiving placebo and as a result the study was stopped prematurely. Two other large-scale chemoprevention trials have been performed (Prostate Cancer Prevention Trial[40] and the REDUCE trial[41]), both of which evaluated 5-alpha reductase inhibitors. However, although the number of cancers was reduced in the treatment arms of both studies, a higher incidence of high-grade cancers was noted in both studies and as such, 5 alpha reductase inhibitors have not been widely advocated for prostate cancer prevention.

The REDEEM trial [42]is the only known study to evaluate a chemopreventive agent in men with low to intermediate risk prostate cancer on surveillance. Fleishner and colleagues randomised 302 men to either placebo or dutasteride, a 5-alpha reductase inhibitor. At 3 years, 38% of men had progressed in the dutasteride arm, while 48% of men progressed in the placebo arm, a difference which was statistically

significant. While this would appear to suggest all men entering Active Surveillance should be offered dutasteride, this has not occurred clinically. Reluctance to recommend dutasteride in the surveillance setting appears to stem from worries that a 5 alpha reductase inhibitor may induce high grade cancers as mentioned earlier. In addition, many have questioned the primary end-point of the REDEEM trial that was histological progression of prostate cancer on repeat prostate biopsy and/or therapeutic progression, defined as the clinical decision to proceed to radical therapy.

In the PROVENT study, we aim to test the feasibility of a randomised controlled trial to examine the clinical effectiveness of aspirin and/or Vitamin D3 to prevent disease progression in men on Active Surveillance for low to intermediate risk prostate cancer. These agents were chosen as a number of laboratory studies have suggested that both aspirin and Vitamin D3 may reduce the development of prostate cancer through inhibition of cancer cell proliferation, cancer cell adhesion and angiogenesis, as previously discussed.

If the study identifies that men electing to enter an Active Surveillance programme for the treatment of prostate cancer are willing to participate in a study evaluating aspirin and Vitamin D3, we will proceed to a larger definitive trial where the efficacy of both Vitamin D3 and aspirin to prevent prostate cancer progression will be tested. Sample size calculations have suggested that at least 800 men will need to be enrolled into such a study.

1.5 Risks/Benefits

Up to half of men with low to intermediate risk prostate cancer entered into an Active Surveillance programme experience prostate cancer progression within three to five years of diagnosis. Disease progression often results in the recommendation that the patient undergo radical therapy with its associated toxicity. Furthermore, historic data demonstrate that between 40 - 60% of men with low to intermediate risk prostate cancer in the UK (up to 90% in the USA) have received radical therapy for their disease. Many of these men will have chosen radical therapy due to the possibility of prostate cancer progression on Active Surveillance.

The main objective of this initial randomised feasibility trial is to demonstrate power of recruitment and the potential numbers required for a definitive protocol. The potential will be identified through the disease progression rate (histological or biological). The standard of care for men entering an Active Surveillance programme is careful disease monitoring, including serial serum PSA analysis and repeat prostate biopsies, together with repeat prostate imaging. In the PROVENT feasibility study, low dose (100mg) or standard dose (300mg) aspirin and/or Vitamin D3 compared to placebo will be evaluated in men enrolled into an Active Surveillance programme for prostate cancer. Although both Aspirin and Vitamin D3 have known toxicities, (see section 1.2 and 1.3, both are generally well tolerated. As such, we believe that for men on surveillance, the benefits of taking these agents to prevent prostate cancer progression would outweigh the side effects caused by the medication.

2.0 Trial Objectives and Design

2.1 Primary Objectives and Endpoints

Objective	Endpoints	Assessment Method
To demonstrate the acceptability and feasibility of recruitment to a randomised chemoprevention study of low dose (100mg) or standard dose (300mg) aspirin vs. placebo and/or Vitamin D3 vs. placebo in patients enrolled on an Active Surveillance programme for prostate cancer	Rate of recruitment over a 12 month period. Recruitment rate will be reviewed at 3, 6, 9, and 12 months.	Pre-screening Logs and Eligibility/Randomisation CRFs

2.2 Secondary Objectives and Endpoints

Objectives	Endpoints	Assessment Method
To report response to treatment as determined by serial multi-parametric magnetic resonance imaging (MRI) of the prostate.	The development of a lesion on multi-parametric imaging where no MRI lesion was identified on screening MRI, an MRI scan that demonstrates that a lesion identified on the screening MRI has increased or decreased in volume by greater than 33%, or an upgrading of MRI stage of disease to ≥T3. 50% increase in serum PSA at 12 months from baseline	Results collected on Case Report Forms (CRFs) after MRI scanning
To report biochemical disease progression	Histological disease progression will be defined as an increase in Gleason scores from:	Routine 3-monthly blood samples
To report histological disease progression	Gleason 3+3 to Gleason score 7 or higher Gleason 3+4 (score 7) to 4+3 (score 7) or Gleason 4+3 to a higher score Or a 50% increase in maximum cancer core length (MCCL)	Routine 12-month biopsy
To assess consistency in local reporting and establish the necessity for central review of the pathology reports, in the main trial.		Central review of at least 10% of all prostate biopsy tissue
To report toxicity and/or allergy to both aspirin and Vitamin D3	Aspirin toxicity: Haemorrhagic stroke, anaphylaxis following administration, gastrointestinal bleeding requiring intervention (both medical and surgical) Vitamin D3 toxicity: Hypercalcaemia, Anaphylaxis	Adverse events recorded on the CRF 3-monthly up to month 15th, and then for a further 4mths.
To evaluate an association between androgens and disease progression	Serum androgen levels	Blood sample for serum Vitamin D3 and corrected calcium levels 6 monthly

To evaluate markers of disease progression	Cell Cycle Progression (CCP(ii)) scores See Section 5.7 for details of laboratory assessments	Blood sample every 6 months for serum testosterone, FSH, LH levels Urine sample and testing at Molecular Epidemiology Laboratory, QMUL Prostate biopsy tissue testing by Myriad Genetics

MRI imaging will be reported according to local practice. Lesion volumes will be measured by planimetry on all sequences. Diffusion and/or dynamic contrast enhancement sequences will be included in this assessment [43]. Scans will be reviewed locally by a specialist radiologist, and the baseline and subsequent scan directly and concurrently compared.

Prostate cancer is an androgen sensitive (testosterone responsive) tumour, one treatment of which being complete androgen deprivation. A recent systematic review [44] has suggested that although the level of plasmatic testosterone varies during the day, men with low testosterone levels are more likely to have aggressive prostate cancer. Furthermore, in laboratory studies, FSH has been found to stimulate prostate cell growth in hormone-refractory prostate cancer cell lines while LH expression in prostate cancer tissues has been associated with metastatic disease and a poor prognosis [45]. As such we feel it would be highly advantageous to determine in the PROVENT study if plasmatic levels of either FSH, LH or testosterone correlated with firstly prostate cancer progression and secondly, responsiveness to either Vitamin D3 or aspirin in terms of prevention of prostate cancer progression

Biochemical disease progression concerns changes in serum PSA over the study period. For the purpose of the PROVENT study, biochemical disease progression will be defined as a 50% increase in serum PSA at 12 months from baseline. The definition of biochemical failure or alternatively PSA failure in men on Active Surveillance is very poorly defined.

Unless there is clinical evidence that the disease has progressed during the trial, patients included in PROVENT will leave the study after 18 months plus ≥ 30 days for post treatment pharmacovigilance. Alternatively, patients may be offered entry into the definitive randomised chemoprevention study if available at that time.

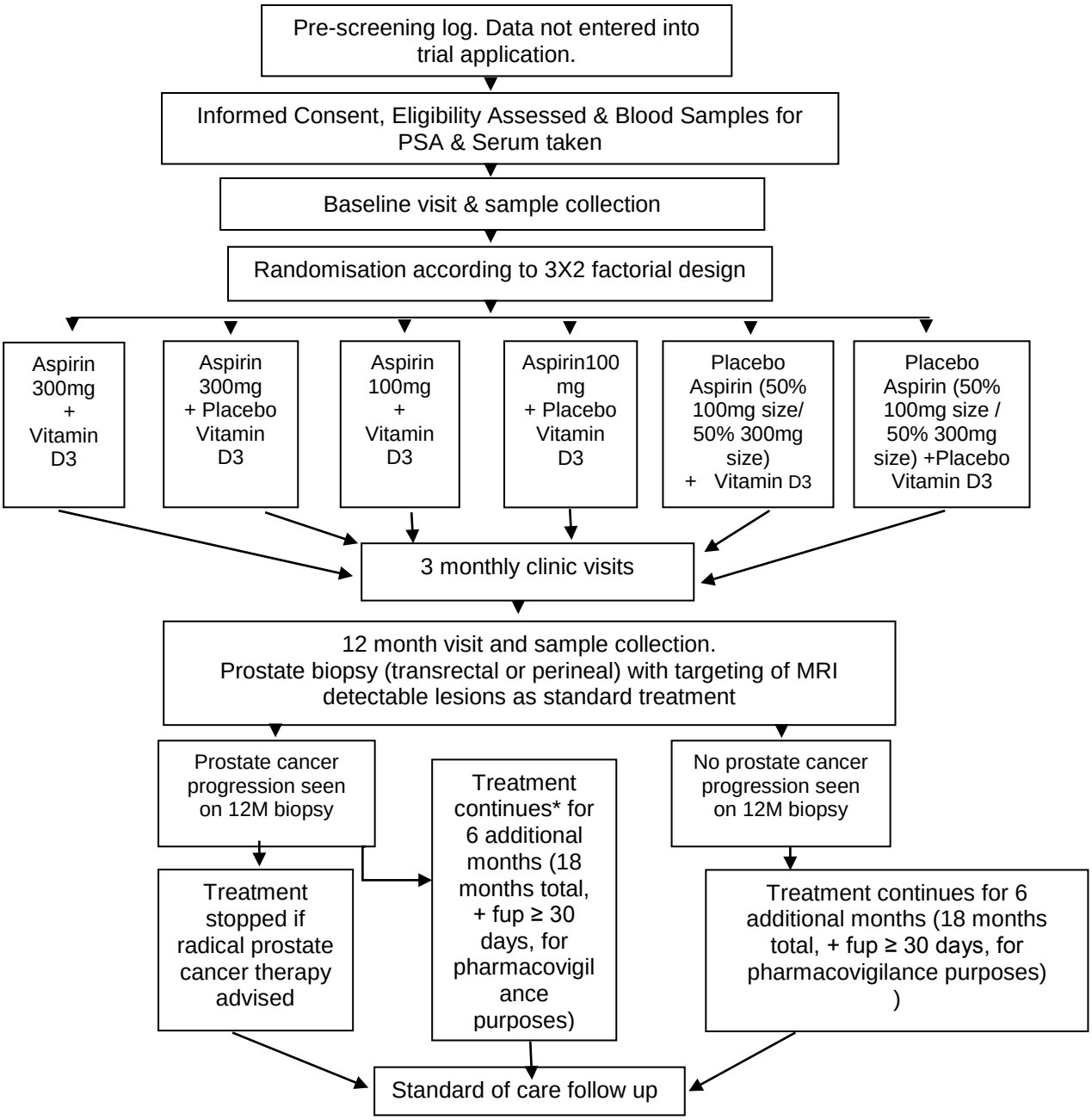
2.3 Trial design

A randomised, double blind, placebo controlled, 3x2 factorial feasibility study comparing low dose (100mg) or standard dose (300mg) aspirin vs. placebo and/or Vitamin D3(4000 IU) vs. placebo in men electing to enter a surveillance programme for prostate cancer.

The aim is to proceed to a definitive trial if the PROVENT Data Monitoring Committee identify, after a 9 month initiation period, that study recruitment is adequate i.e. average of 6 patients recruited per

month, and that data monitoring of 50% of the feasibility group shows minimal adverse effects in any of the arms of the trial. This will also depend on funding being secured for the main trial.

2.4 Trial Scheme Diagram



* If deemed appropriate by treating physician

3.0 Subject Selection

3.1 Number of Subjects and Subject Selection

This feasibility study aims to randomise 102 men within a period of twelve months. The study population is male patients over 16 years of age, who have been diagnosed with prostate cancer, have an estimated life expectancy of more than three years, and who have opted for Active Surveillance as their preferred prostate cancer therapy.

Participants must fulfil the inclusion and exclusion criteria. All patients who meet the eligibility criteria and are randomised will be included in the intention to treat (ITT) analysis.

17 men will be randomised into each of the six study arms in a 3 x 2 factorial design with a 1:1:1:1:1:1 ratio. In order to maintain treatment blinding, placebo aspirin will be size matched with the active treatment, and given as either a small (100mg) size or standard (300mg) size.

3.2 Inclusion Criteria

1. Male subjects aged 16 years or over with an estimated life expectancy of more than 3 years

2. Willing and able to provide written informed consent

3. Serum calcium (corrected) ≤2.65mmol/l

4. No previous treatment for prostate cancer (including surgery, hormone therapy, radiotherapy, cryotherapy)

5. All subjects must have undergone Magnetic Resonance Imaging (MRI) of the prostate with targeted biopsy of any identified lesions in addition to standard systematic biopsy.

6. Histologically confirmed prostate cancer following prostate biopsy including at least 10 cores of prostate tissue, in men opting for Active Surveillance as their primary cancer therapy.

   Biopsies should be at least a 10-core systematic ultrasound guided prostate biopsy. For the majority of men the route of biopsy is likely to be transrectal, although the perineal route is not a contraindication to study participation. Targeted biopsies may be performed via the transrectal or perineal route. Men are eligible for the PROVENT study providing concordance exists between the location of MRI detected lesion and the location of positive biopsy core. If no concordance exists, a further prostate biopsy with lesion targeting will be required prior to randomisation, and histological analysis must fulfil study definition as a low to intermediate risk prostate cancer.
   Targeted biopsies of MRI lesions must be sent in a separate pot/s from systematic biopsies and be clearly labelled. A minimum of two targeted biopsies per MRI detected lesion is required.
   At 12 months, all men will be required to undergo repeat prostate biopsy. Again, the route of biopsy, transrectal or perineal, is not mandated. Patients must have systematic and targeted biopsies at the 12-month point using the same methods as described at study entry.

   All patients included in the study should be enrolled in an Active Surveillance management programme for prostate cancer. Patients may be included if they have Gleason 6 or 7, (Gleason 3+3 or 3+4), organ confined disease, with a PSA of 15.0 ng/ml or less, and have a clinical and radiological stage of less than T3. The largest cancer core length should be less than 10mm.

   Patients must have undergone a multi-parametric MRI deemed assessable by the study radiologist, and any lesions seen must have undergone targeted biopsy (transrectal or transperineal) within 12 months of study registration.

3.3 Exclusion criteria

1. Previously treated prostate cancer (including radiotherapy, hormone therapy, brachytherapy or surgery).

2. Currently enrolled, or has been a participant within the last 30 days, in any other investigational drug or device study.

3. Current, daily use of aspirin or NSAIDs, or daily dietary supplements/medication containing more than 400 IU (10 micrograms per day) of Vitamin D3; or chronic use (defined as >6 months continuous daily use) of either aspirin or replacement Vitamin D3 within two years of study enrolment (Paracetamol will be recommended where aspirin or NSAID might normally be used for pain or fever)

4. Current or previous use of 5-α reductase inhibitors such as finasteride or dutasteride

5. Not willing to comply with the procedural requirements of this protocol including repeat prostate biopsies

6. Known allergy/sensitivity to, or intolerance of, acetylsalicylic acid, other salicylates or NSAIDs e.g. ibuprofen/naproxen

7. Previous history of gastro-intestinal bleeding or peptic ulceration, severe dyspepsia or inflammatory bowel disease

8. Haemophilia or other bleeding diatheses

9. Prior history of renal stone disease

10. Chronic kidney disease (≥stage 4)

11. Known hypercalcaemia (serum calcium >2.65 mmol/l) or untreated/uncontrolled hyperparathyroidism

12. Any bowel condition that would make repeat transrectal biopsy hazardous or difficult to perform e.g. recto-urethral fistula, or prior bowel surgery such as abdomino-perineal resection.

13. Any malignancy (other than non-melanoma skin cancer) that has not been in complete remission for five years

14. Any serious co-existent medical condition that would make repeat prostate biopsy hazardous e.g. anti-coagulation requiring continuous administration.

15. Severe Asthma

16. G6PD deficiency

17. Pre-existing macular degeneration

18. All contraindications to aspirin and Vitamin D3, including concomitant therapy with any medication that may interact with aspirin or Vitamin D3 as listed in section 4.10

19. Regular consumption of alcohol units greater than the recommended daily limit of 3-4 units per day (men)

3.4 Criteria for treatment discontinuation and early withdrawal

Treatment discontinuation

One year following study entry, patients will undergo disease reclassification to identify cancers that have progressed over the 12-month period. Disease reclassification will include repeat MRI of the prostate, together with repeat systematic and targeted prostate biopsy. Any patient whose cancer has progressed as defined in section 1.1, may continue on the study, providing they;

- are still deemed suitable for continued surveillance by their treating clinician
- do not undergo radical therapy &
- are authorised to do so by the Principal Investigator at that centre.

The reason for continuing on Active surveillance should be documented on the eCRF.

Patients undergoing radical therapy will discontinue study medication and an End of Study eCRF will be completed. No more study follow-up appointments will take place. The decision to proceed with radical therapy will be at the clinician's and patient's discretion. Unless explicitly requested in writing, by the

participant, data collected up to the 'End of Study' date will remain part of the trial. This will usually include the 12mth samples & eCRFs, as in most cases, these will have already been collected by the time the results of the disease reclassification are available.

Where a radical prostatectomy is carried out, every effort will be made to obtain pathological data and/or tissue, providing it can be acquired before the participant attends their PROVENT End of Study appointment. It is estimated that up to 30% of men will be identified to have disease progression upon disease reclassification.

Where progression is found and/or the decision is made to undergo radical therapy after 12 months but before 18 months, the participant will be required to leave the trial. An End of Study form must be completed, ≥ 30 days after the participant took their last dose of IMP, for post treatment pharmacovigilance. Samples that would normally have been obtained at the 18 month follow-up appointment, will be collected wherever possible.

Early withdrawal

Patients may withdraw from the trial at any time at their own request or they may be withdrawn at any time at the discretion of the investigator if it is considered to be in the best interest of the patient. Patients can withdraw without giving a reason, but if a reason is given this should be documented in the eCRF and medical notes. It is possible for a patient to withdraw from treatment but continue to be followed up via eCRF, in clinic or by telephone. A 'Withdrawal from Treatment' eCRF will be completed. If patients do not wish to continue in this way, an 'End of Study' eCRF will be completed and they will not have any further visits.

The main analyses will be by intention to treat, therefore, data and samples collected up to the time of withdrawal of consent will be included in the study analyses, as stated in the consent form. Such data or samples will be included in the analysis, unless explicitly forbidden, again, in writing by the participant.

Patients may be withdrawn from trial medication, and/or the study in the event of:

- Unacceptable toxicity/intolerable side effects
- Inter-current illness
- Patient withdrawing consent
- Patient unable to comply with the study schedule
- Interruption of study drug intake for greater than 60 days
- Patient chooses to come off Active Surveillance and undergo active therapy
- Rise in serum calcium above upper limit of normal or 2.65mmol/l
- Identification of higher risk disease unsuitable for surveillance following 'For Cause' repeat prostate biopsy precipitated by an increasing PSA
- Development of new dyspeptic symptoms, or any sign of gastro-intestinal bleeding (haematemesis, melaena, decreased haemoglobin)
- Any episode of haemorrhage or development of a bleeding disorder
- Development of a condition not compatible with the study, or the addition of a new incompatible medication e.g. NSAID, or other product as in section 4.10
- Disease progression

Data concerning toxicity will be collected using the diary cards issued to all participants, which will allow symptoms to be classified as mild, moderate or severe. Data will also be collected on the Case Report Forms regarding gastro-intestinal bleeding and hypercalcaemia. Blood calcium levels will be monitored six monthly and any emergency hospital admissions reported, in which hypercalcaemia is identified, will be documented and followed up by the research team.

Patients who interrupt study drug intake for a cumulative total of greater than 60 days, in a 3 month period between follow-up appointments, will be considered as non-compliant and will be discontinued from the study. An 'End of Study, eCRF will be completed, and no further follow-up appointments conducted. These patients will be included in the intention to treat and safety analyses. They will be included in the efficacy assessment only if they have received at least three 90 day cycles of treatment.

Patients will be considered to be lost to follow-up if there has been as no contact for ≥6 months from the last scheduled clinic visit. These patients will be included in the intention to treat and safety analyses. They will be included in the efficacy assessment only if they have received at least three 90 day cycles of treatment.

4.0 Investigational Medicinal Product

Further information can be found in the PROVENT IMP/Pharmacy Manual & IMP Management Plan.

4.1 IMP details

Aspirin, Vitamin D3 and placebos are considered IMPs in this trial.

Vitamin D3 active product

Trade name:	Vigantol® Oil
Composition:	0.5mg Vitamin D3/ml in Miglyol®812 vehicle oil (40 drops/1ml = 20,000 IU/0.5mg cholecalciferol)
Presentation:	Glass bottle with dropper containing 10mls Vigantol® Oil
Dosage regimen:	8 drops or 4,000 IU (0.1mg) per day over 18 months
Route of administration:	Oral

Vitamin D_3 placebo

Trade name:	Miglyol®812 Oil
Composition:	A pharmacopoeia-listed mixture of palm oil and coconut oil containing medium chain triglycerides that is used as the excipient for Vitamin D3 in Vigantol® Oil; it is thus identical to Vigantol® Oil in every respect (except for the absence of Vitamin D3)
Presentation:	Glass bottle with dropper containing 10mls Miglyol® 812 Oil
Dosage regimen:	8 drops placebo oil per day over 18 months
Route of administration:	Oral

Aspirin standard dose active product

Composition:	acetylsalicylic acid
Presentation:	HDPE plastic bottles containing white enteric coated tablets
Dosage regimen:	1 x 300mg tablet daily over 18 months
Route of administration:	Oral

Aspirin low dose active product

Composition:	acetylsalicylic acid
Presentation:	HDPE plastic bottles containing white enteric coated tablets
Dosage regimen:	1 x 100mg tablet daily over 18 months
Route of administration:	Oral

Aspirin Placebo in two sizes

Composition	No active ingredient
Presentation:	HDPE plastic bottles containing white enteric coated tablets matched to either 300mg or 100mg size
Dosage regimen:	1 x tablet daily over 18 months
Route of administration:	Oral

NB: No IMPD is provided for the Aspirin placebo even though it differs in composition from the active IMP because, as noted in CT-1, this placebo has been submitted to the Regulatory Authority in the UK,

and the manufacturer concerned has provided a Letter of Authorisation for access to the sIMPD for this placebo.
In the case of

4.2 Formulation of IMP

Vitamin D_3	Oily solution containing 0.5mg Vitamin D_3 per ml in Miglyol®812 vehicle oil
Vitamin D_3 placebo	Miglyol®812 oil identical to Vigantol® Oil without the addition of VitaminD_3
Aspirin standard dose	White enteric coated tablets containing 300mg aspirin
Aspirin low dose	White enteric coated tablets containing 100mg aspirin
Aspirin placebo	White enteric coated tablets identical in appearance but not composition to aspirin 100mg and aspirin 300mg. In addition they are without the active ingredient

4.3 IMP supply

The Vitamin D_3 and matched placebo, and aspirin and matched placebos will be manufactured and supplied according to principles of GMP, and supplied specifically for the PROVENT study. Each pack will carry a unique medication code.

Manufacturer/supplier of Vitamin D3 and matched Vitamin D3 placebo:	Merck Serono GmbH Alsfelder Str. 17 D-64289 Darmstadt Germany
Merck Sorono will obtain vehicle oil for Vitamin D3 and placebo from:	Caesar & Loretz GmbH Herderstrasse 31 Hilden, D-40721 Germany
Manufacturer/supplier of aspirin and matched aspirin placebos:	Bayer HealthCare Pharmaceuticals Bayer Pharma AG Müllerstrasse 178 Gebäude S101 13353 Berlin, Germany

4.4 Prescription of IMP

The Trial Delegation Log will specify the names of all study staff authorised to prescribe the IMP for this study. Study specific prescription and dispensing forms that have been pre-agreed with the pharmacy will be used.

Pharmacies will be provided with a copy of the current Delegation Log to ensure that they are aware of the assigned prescribing healthcare professionals for the study at that site.

4.5 Preparation and Administration of IMP

Six months' supply of IMP will be issued at randomisation, and then subsequently every six months during a follow-up visit. Each six months' supply will consist of:

5 bottles each containing either 10ml Vigantol® Oil (oily solution of Vitamin D3, concentration 0.5mg/ml) or 10ml Miglyol®812 Oil (placebo)
PLUS
4 HDPE plastic bottles, each containing 52 gastro resistant tablets of either 300mg aspirin or 100mg aspirin or placebo aspirin.

The quantity of IMP dispensed on each occasion will be sufficient to allow for two late running or missed appointments. The study medication will be taken for 18 months, unless prostate cancer progression is found at the 12 month, 'for cause' biopsy appointments, in which case medication will be discontinued.

Aspirin
The once daily dose of aspirin or placebo aspirin will be given orally, and should be swallowed whole with water. It should be taken with food at the same time each day. A missed dose of study drug may be taken later, providing there are at least 6 hours before the next scheduled dose. Patients will be given a diary card as an aide memoire, and if a dose is missed completely, it should be recorded as 'not taken' in the patient diary.

Compliance will be assessed six monthly. Patients will be requested to bring their remaining study medication to their six, twelve and 18 month visits for reconciliation by the pharmacy. The number of tablets taken will be calculated by subtracting the number of tablets returned from the number of tablets dispensed, and the diary card will provide supporting information if necessary.

Participants will be advised that aspirin or placebo aspirin tablets should be stopped 7 days prior to any surgical procedure wherever possible (see section 4.11)

Vitamin D3
The daily dose of Vitamin D3 or placebo will also be taken orally. It will be presented as 8 drops of oily solution that can be swallowed from a teaspoon or soaked into bread to aid palatability. A missed dose of Vitamin D3/placebo may be taken later the same day, or with the next dose, however, if a dose is missed completely, it should be recorded as 'not taken' in the patient diary.

Patients who vomit after taking the study medication will be advised not to take any further study medication that day, but to document the event on their diary card. Subsequently, if they continue to vomit after taking their medication they should stop the medication and contact their local centre. Patients who are unable to tolerate the medication will be withdrawn from the study.

Compliance will be assessed six monthly. Patients will be requested to bring their remaining study medication to their six, twelve and 18 month visits for reconciliation. Unused medication will be assessed by estimating the amount of oil left in the bottle i.e. full, three quarters, half etc., and the diary card will provide supporting information if necessary.

Should any participant be hospitalised as part of a Serious Adverse Event (SAE), every effort will be made to obtain the discharge summary from the hospital concerned, and any missed doses documented.

4.6 Packaging, Labelling and Distribution of IMP

A dedicated pharmaceutical supplier and distributor will be responsible for the packing, labelling and supply of all IMPs for this study:

Nova Laboratories Ltd
Martin House

Gloucester Crescent
Wigston
Leicester
LE18 4YL

Tel: 0116 223 0100
Fax: 0116 223 0101

Participating pharmacy departments will be responsible for dispensing the IMP and storing adequate supplies.

The study is double blind and placebo controlled, therefore neither the participant nor the investigator will be aware of the randomised IMPs. Both active and placebo IMP will have identical packaging, labelling and appearance; however, the aspirin **dose** will not be blinded due to different tablet size for 100mg and 300mg.

The bottles/containers will be labelled 'Vitamin D3 oil/placebo oil' and either 'aspirin 300mg/placebo aspirin' or 'aspirin 100mg/placebo aspirin' respectively. Bottles will be fitted with child-resistant caps and the label will state that the drug is for clinical trial use only and should be kept out of reach of children. The packaging for the active agent and placebo will be identical.

Each bottle containing Vitamin D3/placebo Vitamin D3 will hold sufficient oil for at least 6 weeks with an allowance for wastage caused by adherence of oil to the glass. The containers for the aspirin/placebo aspirin will contain sufficient tablets for six months' supply plus an additional four weeks to allow continuity of treatment should the patient's appointments be delayed. Prescriptions for a pack containing Vitamin D3/placebo and aspirin/placebo will be issued six monthly, and will show a unique code number that corresponds exactly to a numbered pack in the pharmacy.

A pre-printed, detachable label affixed to the outer carton containing the six month supply of IMP will be detached by the pharmacy member when it is dispensed. This label will then be attached to the patients' Drug Dispensing Log located in the Pharmacy Site File. Patients will be supplied with sufficient medication to last until the next visit. In the event of loss or damage to their IMP, patients will be asked to contact a member of their local research team who will arrange for them to be replaced.

IMPs will be packaged and labelled with a unique pack code according to Good Manufacturing Practice (GMP) principles, and in accordance with Annex 13 (Manufacture of Investigational Medicinal Products).

4.7 Accountability/Receipt/Storage and Handling of IMP

The Investigator, or a delegated individual (e.g. pharmacist), must ensure that the study drug is stored and dispensed in accordance with hospital standard operating procedures and applicable regulatory requirements. The medication provided for this study is for use only as directed in the protocol.

Drug dispensing and accountability logs will be provided to the sites in a Pharmacy Site File and a system will be established to ensure that:

- Deliveries of investigational products from Bayer Healthcare and Merck Serono GmbH are received by a responsible person at the distributing pharmaceutical lab e.g. pharmacist or suitable pharmacy designee, and are handled and stored correctly

- Distribution of investigational products to participating centres is managed by a responsible person e.g. pharmacist or suitable pharmacy designee

- Deliveries of investigational products from the distributor are received by a responsible person e.g. pharmacist or suitable pharmacy designee, and are correctly handled and securely stored.

- Investigational products are dispensed in accordance with the protocol, local dispensing policies, and normal excursion management practices. Ideally, investigational products will be dispensed

directly to study participants. However, if the local dispensing policy permits the LCO to collect the study IMP from pharmacy on behalf of the participant, all procedures documented in the latest version of the PROVENT IMP/Pharmacy Manual, must be adhered to, e.g. a review of the chain of custody stages, use of a 'Chain of Custody' Log

- Participants return any unused investigational product and empty containers to the Research Team for return to pharmacy

- A Dispensing Log is accurately maintained. This will include the initials and study number of the participant to whom the investigational product was dispensed, the pack number from the outer carton, the date of dispensing and the date any unused investigational product is returned to the pharmacy. Any discrepancies must be accounted for on the Dispensing Log. This record is in addition to any drug accountability information recorded in the CRF.

- On completion of each patient's treatment, the Dispensing Log will be returned to the coordinating centre or collected at a monitoring visit, and a copy retained in the PROVENT pharmacy file.

The patients will return unused tablets and bottles of oil every six months, and these will be returned to the pharmacy for reconciliation and disposal or destruction locally as agreed. Details of the remaining quantities of drugs will be collected by a member of the research team at regular intervals so that these may be recorded on the CRF. A Drug Destruction Form will be completed by the pharmacist or suitable designee and filed in the PROVENT pharmacy site file.

Certificates of delivery or return, and destruction, must be signed by a pharmacist or suitable pharmacy designee and copies retained in the Pharmacy Site File.

4.8 Dispensing of IMP

Participating pharmacies will dispense a six months' supply of IMP to the participant on receipt of the study specific prescription form. The patient's details and pack code will be recorded on the PROVENT Dispensing Log and the detachable label from the container attached to the Log. The medication dispensed will contain the correct amount of IMP required to complete 6 months of treatment, plus an additional 4 weeks to allow for two delayed appointments of up to two weeks.

Participants will be asked to record the date of any missed dose on the diary card provided to them every 3 months. Should a participant damage or mislay his medication, he should contact the local co-ordinator or a member of the research team, who will liaise with the PROVENT Coordinating Centre and arrange for replacements to be delivered to the pharmacy. Once the patient has collected the medication, the details should be documented on the PROVENT Dispensing Log.

Local dispensing guidelines will be followed, and each staff member who dispenses the IMP will sign the PROVENT Dispensing Log to document appropriate IMP tracking. Trial initiation and set-up will be carried out by the central co-ordinating team, and members of the trial team at participating pharmacies should ensure that they have had study specific training and their involvement documented on the PROVENT trial delegation log.

4.9 IMP Stability

The Vitamin D3 and matched placebo should be stored below 25°C and protected from light. It should not be used after the expiry date stated on the packaging.

The aspirin and matched placebo should be stored below 25°C in a dry environment. Excursions outside this normal range may be tolerated for short periods. It should not be used after the expiry date stated on the packaging

IMPs should be stored in the numbered packs in which they are supplied, and the individual components not separated. Pharmacies will be responsible for dispensing in line with their local dispensing procedures and normal excursion management practices. If the IMP does experience an excursion outside the ranges stipulated by the manufacturer, guidance will be sought from that manufacturer.

4.10 Prior and Concomitant Therapies

Concomitant medicines will be recorded at baseline and at all subsequent visits. The case report forms will document details of all current prescription or self-medication, and any used in the previous six months.

Participants should not currently be taking any concomitant aspirin, aspirin containing products or NSAIDs, or have taken these regularly (daily for 6 months or more) within two years of randomisation. Vitamin D3 supplements containing greater than 400IU (10micrograms) per day, or replacement Vitamin D3 medication prescribed by a physician, should not have been taken regularly (daily for 6 months or more) within two years of randomisation.

Individuals should not be taking any other investigational agents/drugs, nor any of the following medication:

Potential Aspirin Interactions:

Enhanced effects ranging up to an increased risk of side effects:

- Anticoagulants / Thrombolytics: Acetylsalicylic acid can increase the risk of bleeding when taken before thrombolytic treatment. Attention should therefore be paid for signs of external or internal bleeding (e.g. bruising) in patients who are scheduled to undergo thrombolytic treatment.
- Antiplatelet drugs, e.g. ticlopidine, clopidogrel: the bleeding time can be prolonged.
- Other non-steroidal anti-inflammatory drugs and anti-rheumatics in general: risk for gastrointestinal bleedings and ulcers are increased.
- Systemic glucocorticoids (with the exception of hydrocortisone as replacement therapy for Addison's disease): increased risk for gastrointestinal side effects.
- Alcohol: elevated risk of gastrointestinal ulcers and bleeding with excessive intake.
- Digoxin: elevated plasma level
- Antidiabetics: the blood glucose level can be reduced.
- Methotrexate: decrease in elimination and displacement from protein binding sites by salicylates.
- Valproic acid: displacement from protein binding sites by salicylates.
- Selective-Serotonin-Re-uptake Inhibitors (SSRIs): elevated risk of gastrointestinal bleeding due to synergistic effects.

Weakening of effects:

- Aldosterone antagonists (spironolactone and canrenoate);
- Loop diuretics (e.g. furosemide);
- Antihypertensives (especially ACE inhibitors);
- Uricosuric agents (e.g. probenecid, sulphinpyrazone).

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to clinical SPC/low dose aspirin situation imply that no firm conclusion can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Accordingly, patients should not take aspirin in conjunction with any of the above-mentioned substances unless expressly instructed to do so by a doctor.

Potential Vitamin D3 drug interactions:

- Phenytoin or barbiturates: Plasma concentrations of 25-OH D may be decreased and metabolism to inactive metabolites may be increased.
- Thiazide diuretics can lead to hypercalcaemia due to reduced calcium excretion via the kidneys. Therefore, plasma and urinary calcium levels should be monitored during long-term treatment.
- Glucocorticoids: Simultaneous administration can impair the effect of Vitamin D3.
- Digitalis (cardiac glycosides): Oral administration of Vitamin D3 may increase the efficacy and the toxicity of digitalis due to increased calcium levels (risk of cardiac arrhythmias). The ECG as well as plasma and urinary calcium levels and possibly also digoxin and digitoxin plasma levels should be monitored in such patients.
- Vitamin D3 metabolites or analogues (e.g. calcitriol): It is recommended to combine with Vigantol Oil only in exceptional cases and with monitoring of serum calcium levels.
- Rifampicin and isoniazid: May increase the metabolism of Vitamin D3 and reduce its effectiveness.
- Dovonex cream (calcipotriene) – may increase serum calcium levels

The following drugs should be used with caution due to the potential decrease in efficacy that may occur with high doses of vitamin D3

- Calcium channel blockers (verapamil, diltiazem, nifedipine, nicardipine): Vitamin D3 in large doses may decrease the efficacy of these drugs
- Statins (atorvastatin and lovastatin): efficacy may be reduced with Vitamin D3.

Patients must be instructed not to take any medications, including all over the counter products such as vitamins, minerals, and other dietary supplements, without first consulting with the investigator.

The concurrent administration of other anticancer therapy, including cytotoxic, hormonal or immunotherapy are prohibited during the study treatment phase.

4.11 Dose modification/reduction/delay

Administration of the Vitamin D3/placebo may be delayed if a participant experiences symptoms of hypercalcaemia.

Dyspepsia has been shown to be a risk factor for NSAID GI bleeding [46]. Therefore, should new dyspeptic symptoms arise, or a gastrointestinal bleed occur (melaena, haematemesis, decreased haemoglobin) during the course of the study, then treatment with aspirin/aspirin placebo should cease immediately and permanently, and the patient will withdraw from the study.

Helicobacter pylori (*H. pylori*) has also been shown to be a causative factor in GI bleeding, and all participants will undergo a detection test for this at randomisation as a precaution. Patients will be allowed to start their study medication, including aspirin/placebo aspirin, prior to obtaining the result of this test, as patients are not normally tested for this infection before commencing aspirin therapy and the maximum aspirin dose in this study is very low. If the test result is positive, the patient will be required to take a course of proton pump inhibitors (PPIs) and antibiotics if they wish to continue on the study, to reduce any additional risk of gastric bleeding. In all cases, the GP will be informed of the result of the test, and if positive, the patient will also be sent a copy of the GP letter and asked to see his GP to complete a course of treatment. They will not need to stop the study medication, but may not continue on the study without completing the H Pylori treatment. Once treated, there is no requirement to retest for this infection (as per NICE guidelines).

As a precautionary measure, the aspirin/placebo tablets should be stopped 7 days prior to prostate biopsy, or any other planned surgery [47, 48]. These may be restarted if there are no signs of significant bleeding 48 hours after the procedure, or at the discretion of the treating clinician. Patients will be reminded about this in the clinic, and information is also included in the PIS and Diary Cards.
There is no need to stop the Vitamin D3/placebo IMP prior to surgery.

Patients who require analgesia or antipyretic treatment during the course of the trial will be advised to use paracetamol rather than aspirin, ibuprofen or other NSAIDs. Any additional use of aspirin or NSAID

should be avoided, and where unavoidable, should be recorded on the patient diary card provided, and the Concomitant Medications eCRF

Administration of IMP will be discontinued in the following circumstances:

- Development of hypercalcaemia confirmed by blood sample
- Development of new dyspepsia symptoms or gastro-intestinal bleeding
- Development of a condition which requires treatment with a prohibited concomitant therapy
- Development of a condition which, in the judgement of the investigator, adversely affects the participant's safety, compliance or ability to complete evaluations
- If the investigator concludes that this course of action is in the participant's best interests

Should a patient become concerned that a symptom is potentially related to a study medication, it would be preferable to consider a dose interruption e.g. an alternate daily dose, or offer a 'treatment holiday', rather than stop treatment completely. Dose interruptions can be up to 30 days in the case of suspected toxicity. Longer 'treatment holidays' must be discussed with the PROVENT CCO. However, patients who interrupt study drug intake for a cumulative total of greater than 60 days, in a 3 month period between follow-up appointments, will be considered as non-compliant and will be discontinued from the study. An 'End of Study, eCRF will be completed

'Treatment holidays' can also be used in other special circumstances, at the discretion of the PI, but any dose interruptions of greater than two weeks, for reasons other than toxicity must be discussed with the PROVENT CCO. All variations in dose regime/daily dose, must be documented on the relevant eCRF, & in the patient diary.

Full treatment may be restarted after an appropriate interval, (no longer than 60 days), if symptoms have resolved, or a decision may then be made about withdrawal, if symptoms persist. Any variation in dose regime should always be documented on the relevant Case Report Form and in the patient diary.

Participants who discontinue the study drugs for any reason will not be considered to have left the study, and will be followed up for primary and secondary outcome measures. These patients will be included in the intention to treat and safety analyses.

4.12 Return/Recall or Destruction of IMP

At the termination of the study, or at the request of the sponsor, any unused study drug remaining must be destroyed according to local standard procedures, and should be documented and accounted for in the pharmacy Accountability/Destruction Logs. A copy of the Drug Destruction Form should be filed in the PROVENT pharmacy file.

Unused products that have passed their expiry date or have insufficient shelf life must be entered onto the Drug Accountability/Destruction Log. A copy of all destruction logs must be signed by pharmacy staff and returned to the sponsor to confirm destruction.

Participants will be asked to return unused medication to the research clinic staff who will then return the pack to pharmacy. The pharmacist will document the quantities on the Dispensing Log, and these details will be collected by a member of the research team at regular intervals for recording on the CRF. The pharmacy will record the pack numbers and quantity of tablets/oil on the Accountability/Destruction Log, and the IMPs may then be destroyed according to local practice.

5.0 Study procedures

All procedures are summarised in the Schedule of Assessments table in section 5.5

5.1 Informed Consent Procedures

Potentially eligible patients who have been recently diagnosed with prostate cancer will be identified by the clinical team in the outpatient clinic, having undergone MRI scanning and systematic and/or targeted prostate biopsy. In addition, patients already managed by Active Surveillance may be eligible for PROVENT providing they have undergone disease reclassification (prostate biopsy plus MRI imaging) within the previous 12 months. These patients will be identified in the follow up clinic by the clinical staff.

The clinical care team at each site will be responsible for informing the patient of his diagnosis and discussing the available treatment options, including (if appropriate) Active Surveillance. Patients for whom Active Surveillance is a treatment option will be assessed by a clinician for study eligibility and, if suitable, will be given a Patient Information Sheet (PIS) explaining the PROVENT study. This will be documented in the patient's notes.

The Investigator will discuss the study with the patient, and, if interested, the Investigator or a trained member of the research team will explain the study in more detail. The patient's details will be added to the locally held Pre-screening Log, using only his initials and day (dd, 1 to 31) of birth as identifiers. . The patient will then be given a further appointment to return and discuss their preferred treatment with the Investigator as per normal practice, giving at least 24 hours to consider his treatment options and read the PIS.

The Principal Investigator is responsible for ensuring that participants are fully aware and understand all the requirements expected of them. If the Investigator has concerns about a patient's understanding of the trial and PIS, and/or of their ability to adhere to the protocol requirements, the patient will not be entered into the trial.

At the follow up appointment, the clinician/Investigator will discuss the patient's choice of treatment, and, if his preferred option is Active Surveillance, his interest in the trial will be established. Should he wish to take part in the research written informed consent will be obtained before proceeding further and he will receive a pre-randomisation ID,

The Investigator, or a Research Nurse trained in taking informed consent (as documented in the Site Delegation Log), is responsible for obtaining written informed consent from each subject prior to participation in any study specific procedures. This follows a full explanation of the aims, methods, anticipated benefits and potential hazards of the study. Participants will be reassured that they are free to refuse all involvement in the study, or may withdraw their consent at any time, and for any reason with no effect on their standard of care.

The informed consent consultation should take place in a confidential appropriate environment. Neither the PI, nor any other trial staff should coerce or unduly influence a patient's decision to participate or continue to participate in the trial. All questions about the study should be answered to the satisfaction of the patient. This should occur prior to consent being obtained and the consent form signed.

For the consent to be valid, each box on the consent form should be initialled, and the consent form must be signed and dated by both the person taking consent and the person giving consent at the same occasion. Each person should clearly print their name by their signature and date only their own signature. Where consent is taken by someone other than the Investigator, the Investigator must be readily available to ensure medical oversight, and must countersign the consent form prior to the patient receiving their first dose of IMP.

Once all parties have signed and dated the consent form, the original must be filed in the Investigator file. In addition, a copy of the form must be given to the participant, and a further copy must be filed in the patient's notes. A record of the discussion should be made by the Investigator in the medical notes.

Both the PIS and CF should be printed on local trust headed paper for the trial site where the patient is consented, and should show the date and version number. The contact details of the person/s to contact for further information about the study must also be given.

Should new safety information become available which may result in significant changes in the risk/benefit analysis, the PIS and Consent Form will be reviewed and updated accordingly. All participants actively involved in the trial will be informed of the updated information and given a copy of the revised

PIS and the correspondingly revised consent form to sign, in order to confirm their wish to continue in the study.

5.2 Screening Procedures

Recruitment will take place primarily in specialist prostate clinics at participating centres, and the locally held Pre-screening Log will be completed for each potentially eligible patient who will be given a copy of the Patient Information Sheet. The log will be completed with only the patient's initials and day (dd) of birth. If a patient is found to be ineligible, or does not wish to participate, the date of the visit and reason for non-participation will be added to the Pre-screening Log and the personal identifiers will be removed. The site is responsible for forwarding completed copies of their pre-screening logs, without personal identifiers, to the CCO at regular intervals.

Sites will be provided with a template study invitation letter, and poster advertising the trial, to assist with the recruitment process. In addition there is a trial website. The site address, www.provent.org.uk is provided to participants in the Patient Information Sheet and on the diary & wallet cards they will receive.

Once a patient has agreed to participate, and written informed consent has been obtained, the Investigator or a suitably trained member of the research team will be responsible for further screening of each subject prior to participation in the study. The pre-randomisation Eligibility Assessment CRF will establish whether the potential participant fulfils the eligibility criteria for the study.

Participants are required to have a corrected serum calcium level of 2.65mmol/l or less confirmed prior to commencing study medication. An existing serum result will be acceptable if taken within 2 months prior to the Eligibility Assessment date; alternatively, a further sample will be taken for this once consent has been obtained.

As an additional precaution, eligible patients will also be screened for *Helicobacter pylori*. This test will require the patient to bring a stool specimen to their randomisation appointment. A collection pot will be provided for this at the screening visit, and instructions given on how to collect the sample. The test should not be carried out within 4 weeks of antibiotic or 2 weeks of PPI use, as these may lead to false negative results. Patients will be given an alternative treatment if currently taking PPIs.

Patients whose H Pylori test is positive will be informed of the result and will require treatment for 7 days with an appropriate antibiotic and PPI therapy if they wish to continue in the study (see section 5.4).

Once all parties have signed the consent form, & screening has confirmed the patient's eligibility, the patient may be randomised and the outcome added to the locally held Pre-screening Log. At this stage the participant's status on the application will be updated from 'registered', to 'randomised'.

5.3 Randomisation Procedures

The principal method of randomisation will be by means of a bespoke web-based application, developed by Barts CTU, which will be accessible to all relevant research staff. Staff will be trained in the use of this application. The application eCRF will reaffirm patient eligibility and require confirmation that the consent form has been satisfactorily signed and countersigned.

Eligible participants will be randomised in a 6-arm 1:1:1:1:1:1 design to receive one of the following:

1. Aspirin 300mg + Vitamin D3
2. Aspirin 300mg + Vitamin D3 placebo
3. Aspirin 100mg + Vitamin D3
4. Aspirin 100mg + Vitamin D3 placebo
5. Aspirin placebo + Vitamin D3

6. Aspirin placebo + Vitamin D3 placebo

Randomised blocks will be used to maintain balance amongst these 6 arms. In addition, the aspirin placebo groups will be block randomised to either small or large aspirin placebo tablets.

The allocated unique study number will correspond to a particular arm of the trial. When a patient is randomised, a pack number associated with that patient's study number will be automatically generated by the PROVENT app. The pre-labelled packs containing the medication for that study number will already be in the pharmacy at that centre, labelled with a unique pack identification number.

In the event that the web application is unavailable, randomisations will be able to be made by an email or a FAX backup system.

Once the patient has been successfully randomised, this will be documented within the PROVENT application, and on the locally held PROVENT Pre-screening Log.

5.4 Visit Schedule

Initial screening in routine clinic
Patients will normally attend a routine clinic to learn their diagnosis and treatment options. Those men identified as suitable candidates for Active Surveillance, and who appear to fulfil the inclusion criteria for the study, will be informed about the PROVENT study as an option within Active Surveillance. The clinic doctor will explain the study to the patient and a Patient Information Sheet will be given to him to take home for consideration. A follow up appointment will be arranged for him to return to confirm his treatment preference, and his initials and day (dd) of birth will be recorded on the locally held Pre-screening Log.

Consent Visit
If, at the follow up appointment, the patient expresses a wish to take part in the study, the Investigator or Research Nurse will explain the aims, methods, anticipated benefits and potential hazards of the trial, ensure they have been fully understood and allow the patient the opportunity to ask questions. If the patient is still willing to take part, he will be given a pre-randomisation registration ID. This will be generated within the PROVENT application using the patient's initials and day, (DD), of birth. The consent form will be completed and signed as previously described, & the Eligibility Assessment eCRF will be completed using the pre- randomisation ID for reference.

Serum Calcium Testing
An existing serum calcium result will be acceptable if taken within 2 months prior to the Eligibility Assessment date. Alternatively, once consent has been obtained, a blood sample will be taken to confirm serum calcium is within the acceptable range for participation in the study. The result will be obtained prior to the randomisation visit and, if above the accepted range, the patient and his GP will be informed of the result and the randomisation visit cancelled.

PSA Testing
An existing PSA result will be acceptable if taken within 3 months prior to the Eligibility Assessment date. Alternatively, once consent has been obtained, a blood sample will be taken to confirm the PSA level is within the acceptable range for participation in the study. The result will be obtained prior to the randomisation visit and, if above the accepted range, the patient and his GP will be informed of the result and the randomisation visit cancelled.

Finally, an appointment will be made for the randomisation visit, and a stool specimen requested for the Helicobacter Pylori (H Pylori) test.

Helicobacter pylori testing
H pylori is a risk factor for gastric ulceration and bleeding, therefore all participants will undergo testing to rule out infection at randomisation as an additional precaution. As stated in Section 5.2 the test should not be carried out within four weeks of antibiotic treatment, or within two weeks of taking PPI's. For patients taking regular Proton Pump Inhibitors (PPIs), these must be discontinued, and an alternative treatment, such as an H2 antagonist, prescribed for the two weeks preceding the test date. Patients will be required to bring the stool specimen to their randomisation appointment. GPs will be informed of the

result and, where positive, patients will be required to visit their GP and undergo a combination of antibiotic and PPI treatment if they wish to continue in the study (See section 4.11). Participants may continue to take their study medication whilst taking the H Pylori treatment.

Randomisation Visit

Where necessary the result(s) of the serum calcium, and/or PSA tests will be assessed by a member of the PROVENT team prior to this visit to confirm eligibility. If the patient's serum calcium level is 2.65mmol/l or less, the patient may join the study. A PSA result of 15.0 ng/ml or less is required before a patient can be recruited into the trial.

If eligibility is confirmed, patients will be randomised via the online PROVENT app, and a unique study number allocated. Relevant eCRFs (Appendix 1) will be completed by the Investigator or a member of the research team, with paper based backup CRFs available in case of system failure or for additional convenience. Where paper CRFs are used, they should be kept in the investigator site file and will be reviewed as part of source data verification during site monitoring. Patients will be identified only by initials and trial number.

A digital rectal examination (DRE) will be carried out by the Investigator, clinician or a Nurse Specialist followed by the collection of a 20-35ml, first catch urine specimen for exploratory research. A 2.5ml sample will be transferred into each of the provided collection tubes as per the collection kit instructions and labelled with the unique sample identifier. These will need to be frozen locally in an ultra-low temperature freezer, (-60 to -90°C) within one hour of collection. The date and time the samples were frozen must be recorded in a separate log and sent to CCO when requested.

Residual urine will be transferred into each of the provided collection tubes and frozen locally in an ultra-low temperature freezer (-60 to -90°C) until ready to be batch shipped for translational research. These translational research samples will be analysed at a later date, & may also be made available to the scientific community outside of QMUL, for ethically approved research. Where this occurs, the samples will always remain pseudo-anonymised, i.e. identified by a unique identifier.

Blood samples will be taken as directed in the Laboratory Manual for baseline serum androgens and Vitamin D3 levels, and an additional sample taken for translational research. Any routine samples not previously collected may also be taken at this time.

The stool specimen will also be collected at this visit and sent to the local laboratory to be tested for H Pylori infection.

Finally, a PROVENT prescription, and wallet cards will be issued, and an appointment arranged for three months' time in the regular Active Surveillance clinic. A **six months'** supply of study medication may then be collected from the hospital pharmacy by the patient.

Biopsy samples taken at different stages and where tumour has been confirmed, will be requested by the local site staff from the relevant pathology laboratory, and where available, sent to the Orchid Research Tissue Bank for current & future storage. Anonymised pathology report forms will also be requested for central review.

Ideally, two formalin fixed paraffin embedded (FFPE) biopsy samples with cancer confirmed should be sent. However, if this is not feasible, one biopsy block with tumour confirmation with the corresponding Heamatoxylin & Eosin stained slides, is acceptable. The samples will be used for CCP(ii) score analysis, pathology review and translational research. For the CCP(ii) score analysis, the samples will be sectioned and sent to Myriad Laboratories. The remaining biopsy material will be tissue microarrayed (please refer to the Orchid Tissue Bank SOPs; LAB005 & LAB023)

Follow-up Visits

Once randomised, participants will attend routine Active Surveillance appointments every three months (+/- 7 days wherever possible), and with the exception of the 'End of Study' visit, follow up PROVENT appointments will take place at the same time. Hence only one additional visit is required.

The literature suggests that once Aspirin's anti-platelet effect wears off, (7 to 10 days after stopping the drug), prothrombotic effects may manifest acutely within 30 days, particularly in those who either have risk factors for, or a history of cardiovascular disease. [49-52]. Therefore, the End of Study Visit will take place at 18 months plus ≥ to 30 days, to accommodate a pharmacovigilance period, when AEs & SAEs may still be reported.

Where a participant fails to stop treatment at the 18mth time point, or does not attend their 'End of Study' appointment, the LCO is responsible for checking their AE status via a telephone call at least 30 days after the date the participant has stated they stopped their IMP dose.

Follow-up CRFs will be completed at each visit (Appendix 1), and any required blood samples taken as scheduled. A further post-DRE urine sample will be collected at the 12 and 18 month visits.

Participants will be asked to return their unused medication six monthly at the 6, 12, & 18 month timepoints for compliance evaluation. Diaries will be checked at each visit, and a new diary card will be issued every three months. In addition, a PROVENT prescription will be issued six monthly, enabling a further supply of study medication to be dispensed by the pharmacy.

Prior to the 12-month appointment, arrangements will be made for a repeat MRI scan and prostate biopsy as per routine care. As previously stated in Section 4.11, patients will be advised to stop the study tablets for a week prior to their biopsy appointment, and for two days after the procedure has taken place.

Patients will continue on the study for 18 months unless their prostate cancer is found to have progressed when reclassified following prostate biopsy. Any patient whose cancer has progressed but is still deemed suitable for continued surveillance by their treating clinician may continue on the study if authorised by the Principal Investigator at that centre. Participants with cancer progression, undergoing radical therapy, must come off the trial, and an 'End of Study' eCRF must be completed. Data collected up to that point will remain part of the trial. Where a radical prostatectomy is carried out, every effort will be made to obtain pathological data and/or tissue, providing it can be acquired before the participant attends their PROVENT End of Study appointment. It is estimated that up to 30% of men will be identified to have disease progression upon disease reclassification'
. A patient whose cancer is found to have progressed before or after the 12-month biopsy will be managed as for rising serum PSA (see below).

For patients who continue on the study for the full 18 months, plus ≥30 days duration, following their Final Visit they will either revert to routine 3 monthly Active Surveillance appointments, or be offered the opportunity to enter the main PROVENT study if available at that time. In this event, it will be necessary for further consent to be obtained from the patient.

Management of rising serum PSA during the study period
Patients may experience a rising serum PSA during the 18-month study period. It is at the clinician's discretion to either recommend a 'for cause' repeat prostate biopsy, or alternatively, recommend radical therapy. However, it is recommended that an off-protocol 'for cause' prostate biopsy only be performed if the patient's PSA doubling time is less than 12 months. In addition, it is recommended but not mandated that all patients undergo repeat biopsy for a rising serum PSA rather than undergo immediate radical therapy.

Prostate biopsy
Participants will be required to stop the trial tablets for 7 days prior to prostate biopsy. If there is no sign of significant bleeding in the urine or from the rectum 48 hours after the biopsy, the tablets may be restarted. There is no requirement to stop the Vitamin D3/placebo Vitamin D3.

Repeat biopsies may occur from week 48 to week 56 depending on clinic waiting times; therefore study medication may be taken for up to four weeks more, or less, than 12 months in the weeks leading up to the routine biopsy.

Patients will undergo biopsy with prophylactic antibiotic administration as per normal procedures. This may be either a TRUS biopsy or a template biopsy and performed under local anaesthesia or general

anaesthesia using a 12 Hz ultrasound probe. The procedure will comprise a standard systematic biopsy together with targeted biopsies taken from any MRI detected abnormalities.

Biopsy cores should be sent to local laboratories separately from each region of the prostate, with no more than two cores per pot, and labelled according to the region of the prostate sampled. In patients with MRI detected prostate lesions, at least one targeted biopsy core should be directed to each lesion and placed in a separately labelled pot. Tissue taken will be processed locally as per the PROVENT Laboratory Manual.

If clinically necessary, repeat biopsy can be brought forward, or not performed, at the discretion of the Investigator. Alternatively, a patient may decide to leave the trial and undergo radical prostate cancer therapy during the 18-month study period; however the case should be presented at a multidisciplinary team meeting before an alternative management strategy is commenced. Patients who undergo radical treatment will stop trial medication at this point and not be followed up. Patients remaining on Active Surveillance but not undergoing a repeat biopsy will remain in the study for analysis as PSA dynamics over the study period will still be available.

Abnormal laboratory test results

A laboratory abnormality in one of the study specific tests, such as serum corrected calcium or H Pylori, may require the subject to undergo treatment. A value flagged, for example, as 'clinically significant' must be entered on the Adverse Event CRF. In addition, the test may need to be repeated at the Investigator's discretion. The Investigator may use his/her own judgment as to whether the abnormal finding is sufficient reason to immediately withdraw the patient from the study.

Any laboratory value that meets the definition of Serious Adverse Event must be reported as an SAE (refer to 7.1.3). In addition, the patient should be reassessed for continuation in the study and any indicated and appropriate therapies should be initiated.

5.5: Schedule of Assessment (in diagrammatic form)

Barts and The London School of Medicine and Dentistry

Assessment/Action	Pre-study	Screening & Consent	Randomisation Visit	3 month visit	6 month visit	9 month visit	12 month visit	15 month visit	18month visit	Pre 18 month withdrawal	End of Study[d]
Pre-Screening log completed	X										
Patient Information Sheet issued	X										
Eligibility Assessment CRF completed		X									
Informed Consent Form Signed		X									
Randomisation			X								
Medical history		X									
Height & weight			X				X			X[c]	
Research urine samples for:											
Exploratory Research			X				X		X		
Translational research			X				X		X		
Digital Rectal Exam (SP)			X[a]	X[a]			X[a]	X[a]	X[a]	X[a]	
MRI Scan	X[b]						X[b]			X (if scanned)	
Prostate biopsy for: Translational research tissue and CCP (ii) analysis	X[b]						X[b]			X (if biopsied)	

Assessment/Action	Pre-study	Screening & Consent	Randomisation Visit	3 month visit	6 month visit	9 month visit	12 month visit	15 month visit	18month visit	Pre 18 month withdrawal	End of Study[d]
Helicobacter pylori test			X								
Blood samples for:											
PSA	X [b]	X [b]		X[a]			X[a]	X[a]	X[a]	X[a]	
Serum calcium	X [b]	X [b]			X		X		X	X[c]	
Testosterone			X		X		X		X	X[c]	
LH			X		X		X		X	X[c]	
FSH			X		X		X		X	X[c]	
Serum Vitamin D3			X		X		X		X	X	
Translational research			X		X				X	X	
Adverse Event(s)				X	X	X	X	X	X[d]	X	X
Prescription issued			X		X		X				
Patient Diary Issued			X	X	X	X	X	X			
Patient diary checked for compliance				X	X	X	X	X	X	X	

Key:

a - Standard practice
b -Prior to appointment, or at screening if the test result is not within a valid time frame; 2 months prior to the date of the Eligibility Assessment for the serum calcium result & 3 months prior to the date of the Eligibility Assessment for the PSA result.
c – Where withdrawal is prior to 12month follow-up
d – Where a participant fails to stop treatment at the 18mth time point, or attend their 'End of Study' appointment, the LCO is responsible for checking their AE status via a telephone call at least 30 days after the date the participant states they have stopped their IMP dose.

5.6 Follow up procedures

In the event of non-progression of cancer following the 12-month prostate biopsy, treatment with study medication will continue for the remaining six months of the trial, pending transfer to the main trial if the option is available.
Alternatively, if progression **is** seen at biopsy, as described in section 1.1, patients may exit the study. Tissue will be sought from patients undergoing radical prostatectomy providing it can be acquired before the participant attends their PROVENT End of Study appointment. This will be stored in the Orchid Research Tissue Bank.

5.7 Laboratory Assessments

In addition to the routine blood samples taken as standard practice in an Active Surveillance programme, a range of tests specific to the PROVENT study will also be collected. These will include six monthly serum Vitamin D3, androgen and calcium levels. Samples will also be taken at baseline and 18 months for translational research. These samples will be stored for future analysis to identify molecular and genetic markers of aggressive prostate cancer, as per the Laboratory Manual. Results of routine blood tests, including three monthly PSA, will be evaluated during the study.

Infection with *Helicobacter Pylori* (*H. Pylori*) will be assessed using a standard stool test at baseline only and tested locally in the laboratories at participating centres.
Urine samples will be collected at baseline and 12 months for exploratory research (see Section 2.2), and at baseline, 12 and 18 months for translational research as per the Laboratory Manual. Testing will take place in the Molecular Epidemiology Laboratory, Centre for Cancer Prevention, Queen Mary University of London.

Residual urine will be frozen locally at each site until shipped and finally stored within an ultra-low temperature freezer (-60 to -90°C), at the Molecular Epidemiology Laboratory, Queen Mary University of London, for future analysis to identify molecular and genetic markers of aggressive prostate cancer. They may also be made available to the scientific community outside of QMUL, for ethically approved research. Where this occurs, the samples will always remain pseudo-anonymised, i.e. identified by a unique identifier.

Paraffin embedded tissue will be collected from diagnostic biopsy samples taken prior to joining the study, and from samples collected at biopsy or surgery during/after the study, and stored by Queen Mary University of London until shipped for Cell Cycle Progression (CCP (ii)) score analysis by Myriad Laboratories, Salt Lake City, USA.

A minimum 10% sample of all prostate biopsy tissue received will undergo a central pathology review by the collaborating study pathologist at Centre for Molecular Oncology, Barts Cancer Institute, Queen Mary University of London to ensure consistency of reporting. Anonymised copies of all pathology report forms will be obtained for central review.

All prostate tissue samples will be sent to the Barts CTU who will arrange onward transfer to the appropriate laboratories. Tissue samples will be stored for future research in the Orchid Research Tissue Bank (ORTB), Barts Cancer Institute, Queen Mary University of London, as stated in the consent form, pending further ethical applications.

5.8 Radiology Assessments

Patients will undergo Magnetic Resonance Imaging (MRI) prior to entry and at 12 months as part of their routine treatment on Active Surveillance.

Progression of prostate cancer will be defined as the development of a lesion on multi-parametric imaging where no MRI lesion was identified on the screening MRI, or alternatively, an MRI scan that demonstrates that a lesion identified on screening MRI has increased in volume over the study period by greater than 33%.

Patients will undergo multi-parametric MRI imaging of the prostate. The scan will be performed & reported using each site's routine practice and locally defined parameters. The details of the procedure & the results will be recorded on a 'MRI Procedure & Results' eCRF. In addition, a pseudo-anonymised copy of the report will be uploaded to the PROVENT application.

5.9 End of Study Definition

The end of trial is defined as Last Patient Last Visit (LPLV), including at least 30 days for Pharmacovigilance reporting.

5.10 Procedures for Unblinding

A 24-hour unblinding service is not proposed for the PROVENT study, as it is felt that this is not required given the two particular medications being trialled.

Patients admitted as an emergency with bleeding or haemorrhage would be treated in the same way irrespective of any medication they might have taken, as the primary concern is to stop the bleeding. Salicylate levels would be taken to establish the presence of aspirin which would negate the need for unblinding.

In the event of an overdose of study medication (aspirin/ placebo and/or Vitamin D3/placebo) the patient should be referred immediately to an emergency care facility. In the majority of cases, treatment for suspected aspirin or Vitamin D3 overdose is the treatment of symptoms arising from the overdose.

If aspirin is taken in overdose, it is easily and quickly detected by measuring the patient's plasma salicylate level (salicylate is the active metabolite of aspirin). Plasma salicylate levels are routinely performed in all patients presenting to the emergency services with suspected aspirin overdose. The plasma salicylate level is readily available at very short notice in all district general hospitals throughout England and Wales. As such, any PROVENT trial patient presenting with an acute overdose of study medication would have their blood drawn for a plasma salicylate level which would identify immediately whether or not aspirin had been taken. While awaiting the test result, patients would be managed as if they had taken an overdose of aspirin. As for any patient presenting to the emergency services with a suspected overdose of aspirin, they would receive immediate assessment followed, in most cases, by gastric decontamination with activated charcoal - a medication that has no deleterious effects. Subsequent treatment would be governed by plasma salicylate levels in a similar manner to any patient with aspirin overdose.

In the case of Vitamin D3 overdose, no immediate effect will occur and, as such, a 24-hour unblinding service is not required. The potential complication is hypercalcaemia, however, chronic overdose of Vitamin D3 would be identified by serum calcium testing which is a requirement within the PROVENT study, at which point unblinding would be performed. If a patient presented to the emergency services with a suspected overdose of Vitamin D, be that an acute or chronic overdose, a serum calcium test would quickly identify that this was the case, allowing standard emergency care to be initiated, and rehydration considered in order to reduce the level of calcium in the blood.

Unblinding for any purpose other than a medical emergency will not generally be allowed, but individual cases should be discussed with the Chief Investigator if it is believed to be necessary for the medical care of the participant.

If an investigator considers it necessary to unblind a patient, requests for unblinding should be sent to the trial coordinating office using the Codebreak Request form. The CI or delegated individual e.g. the trial coordinator will consider the request and, if appropriate, the designated persons will unblind the patient according to the procedure described in the study unblinding document. All efforts should be made to limit unblinding of subjects in order to protect the integrity of the study.

Should a patient request that their treatment is unblinded, the subject must be withdrawn from the study and the details documented in the medical notes and End of Study CRF.

In the event of a treatment code being unblinded, the reason for this decision and the details of those involved in the decision should be documented in the participant's medical notes and, in the event of a Serious Adverse Event, on the SAE form. Unblinding details will be confidential and only those personnel that must be informed for

medical management of the patient will be informed. Wherever possible, the patient himself should remain blinded. Members of the trial co-ordinating team should also remain blinded.

Aspirin overdose can cause hyperthermia, tachypnoea, respiratory alkalosis, metabolic acidosis, hypokalaemia, hypoglycaemia, hallucinations, confusion, seizures, cerebral oedema and coma, therefore if these conditions present they should be managed in a standard fashion in an emergency care unit.

Vitamin D3 overdose can cause nausea, vomiting, diarrhoea, constipation, loss of appetite, headache, tiredness, muscle and joint pain/weakness, thirst, polyuria and dehydration, and hypercalcaemia

5.11 Subject Withdrawal

Patients may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator if it is considered to be in the best interest of the patient. Patients can withdraw without giving a reason, but if a reason is given this should be documented on the relevant eCRF and medical notes.
(See section 3.4 for withdrawal criteria)

5.12 Data Collection and Follow Up for Withdrawn Subjects

Data collected up to the time of withdrawal of consent will be included in the study analyses, as stated in the consent form, unless participants specifically withdraw permission to do so in writing. With the exception of such patients, withdrawn subjects will remain under three monthly follow-up in clinic for the duration of the trial, as the main analyses will be by intention to treat.

6.0 Laboratories

6.1 Laboratories & Testing

Biochemistry Laboratories at participating centres
Routine blood testing for PSA will be carried out in local hospital laboratories as per standard procedure. Serum calcium and androgen levels will also be tested at these laboratories.

Clinical Biochemistry Laboratory, Royal London Hospital
This nominated hospital laboratory will batch test the serum vitamin D samples. The results of these tests will not be released to the research team, but only in an anonymised fashion to the Data Monitoring Committee.

Histopathology Laboratories at participating centres
Prostate biopsy samples will be examined at local accredited hospital laboratories, as per usual practice. Guidelines for standardised examination will be provided by Professor Dan Berney, Professor of Genito-urinary pathology, St Bartholomew's Hospital

Molecular Epidemiology Laboratory, Centre for Cancer Prevention
This research laboratory, under the direction of Professor Attila Lorincz, will carry out exploratory research tests on urine samples collected at baseline and 12months. This laboratory will also store frozen blood and urine samples collected at baseline and 18 months for future exploratory & translational research to identify molecular and genetic markers of aggressive prostate cancer,

Myriad RBM
CCP (ii) score analysis. Formalin-fixed paraffin embedded tissue samples from baseline and 12 months sent in prepared batches to the Myriad laboratories. In addition, the laboratories will receive 15ml baseline, 12 month and End of Study, residual urine samples, for translational research, from each participant. No additional samples are being requested from the patients to facilitate the provision of this.

6.2 Sample collection/labelling/logging

Samples for local testing will be taken as per normal local practice.
Samples taken in addition to normal practice will be de-identified and labelled with a unique identifier and logged in the Case Report Form as detailed in the PROVENT Laboratory Manual.

6.3 Sample Receipt/Chain of Custody/Accountability

Handling of the samples in the laboratories will be as per the PROVENT Laboratory SOPs. Upon arrival at the laboratory staff will ensure that the physical integrity of these samples has not been compromised in transit and that all samples are accounted as per the labeling. The samples should be logged on receipt in an accountability log as documented in the laboratory SOP.

6.4 Sample Analysis Procedures

Standard tests carried out routinely in the local laboratories include blood testing for PSA, serum androgen levels and corrected calcium. In addition, a standard faecal Helicobacter pylori test will be carried out locally.

The non- standard tests are for research purposes only and are not diagnostic. These include serum Vitamin D3 levels, urine samples for exploratory and translational research, prostate tissue samples for CCP (ii) Score analysis and translational research, and blood samples for translational research.

6.5 Sample Storage Procedures

Samples that will not be tested immediately will be stored as detailed in the PROVENT Laboratory SOP.

6.6 Data Recording/Reporting

For locally performed testing, data will be recorded in the patient record as per standard practice. The local PI or delegate will transcribe relevant results into the eCRF which will hold the data.

All other research testing will be recorded by individual laboratories and transferred to the PROVENT Co-ordinator as detailed within individual agreements.

See also Section 9.0 for data confidentiality

7.0 Pharmacovigilance

7.1 General Definitions

7.1.1 Adverse Event (AE)

(See Appendix 2 for Safety Reporting Flowchart)
An AE is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of an Investigational Medicinal Product (IMP), whether or not considered related to the IMP.

7.1.2 Adverse Reaction (AR)

An AR is any untoward and unintended response in a subject to an Investigational Medicinal Product (IMP), which is related to any dose administered to that subject. All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

7.1.3 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An SAE fulfils at least one of the following criteria:

- Is fatal – results in death
- Is life-threatening

- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Since there is no risk arising from the transfer of any PROVENT IMP products via seminal fluid, it has been deemed unnecessary to collect & record pregnancies where the father is a PROVENT study participant.

Serious Adverse Reaction (SAR)
An SAR is an adverse reaction that is classed as serious and which **is consistent with** the information about the medicinal product as set out in the Summary of Product Characteristics (SmPC) for Aspirin or Vitamin D3.

7.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

The definition of a SUSAR is any serious adverse event related to an IMP that is both suspected to be related to the IMP and unexpected. In this case the event is not outlined in the SmPC for Aspirin or Vitamin D3.

7.2 Investigator's Assessment

7.2.1 Seriousness

The Principal Investigator responsible for the care of the patient, or, in his absence, an authorised doctor within the research team, as specified on the site delegation log, is responsible for assessing whether the event is serious according to the definitions given in section 7.1.

7.2.2 Causality

The Principal Investigator must assess the causality of all serious adverse events/reactions in relation to the trial treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.

7.2.3 Expectedness

The Principal Investigator must assess the expectedness of all SAEs according to the definition given and by referring to the summary of product characteristics (SmPC). If a SAR is unexpected, then it is defined as a SUSAR.

7.2.4 Severity

The Principal Investigator must assess the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on patient/event outcome criteria.

Mild: Some discomfort noted but without disruption of daily life
Moderate: Discomfort enough to affect/reduce normal activity
Severe: Complete inability to perform daily activities and lead a normal life

7.3 Notification and reporting of Adverse Events or Reactions

If the AE is not defined as serious, the participant is followed up by the research team. The AE is documented in the participants' medical notes (where appropriate) and the CRF. (See Appendix 2 for Flowchart for Safety Reporting)

7.4 Notification and Reporting of Serious Adverse Events and SUSARs

7.4.1 Serious Adverse Events (SAEs)

SAEs must be reported to Barts CTU, acting on behalf of the sponsor, within 24 hours of the PI or research team becoming aware of the event (this delegation is documented in the 'Conditions of Sponsorship Agreement'). They should also be recorded in the subjects' notes and the relevant eCRF.
The Barts CTU will forward the SAE to the sponsor within 1 working day of receipt. Day zero for reporting to the MHRA is the day that the Barts CTU is notified of a medically assessed SUSAR.
The initial report must be made by completing a SAE eCRF accessible via the PROVENT web application. In addition the SAE eCRF must be signed electronically within the web application by the PI or delegate. If for any reason the web application cannot be accessed, a paper SAE CRF should be completed and faxed to the following number;

Reporting SAEs to Barts CTU/Sponsor

Web app: https://www.cptu-edc.org
Fax: 020 7882 3886

Nominated co-investigators will be authorised to sign the SAE forms in the absence of the CI at the coordinating site, or nominated Sub-investigators in the absence of the PI at the participating sites. The report should be as complete as possible, including details of the current illness and the serious AE, the reason why the event was considered serious, date of onset and stop date (if applicable), diagnostic procedures and treatment of the event, relevant medical history and concomitant medication and action taken with the IMP (if applicable).

The Barts CTU will identify any missing information for each reported SAE. Requests for follow up will be sent for further processing to the investigator. Follow up information will be required at regular intervals from the investigators until all queries are resolved or no further information can be reasonably expected. Following this, the PROVENT CI (or delegate) will review all SAEs. The CI (or delegate) will confirm expectedness and relatedness. He/She has the right to upgrade if judged to be necessary, but only once discussed and agreed with the PI. A record of this discussion should be made in the participant's medical notes, and within the notes section of the relevant eCRF.

The original and any subsequent follow up of Serious Adverse Event CRFs will be recorded in the PROVENT web application. The local sites should keep all signed copies of SAE reports within their IF.

Whilst the IMPs in this study are expected to be well tolerated, the contents of Section 4.8 'Undesirable Effects' in the SmPCs for aspirin & Vitamin D will act as the RSI for the trial. The SmPC with current regulatory approval for the trial will be used to assess SAE reports to identify SUSARs.

Expected Non-Reportable SAEs
In the event of planned hospitalisations, this will be noted in the patient's notes and CRFs but will not be reported as a SAE. Similarly, progression of prostate cancer will not be reported as a SAE as this is an expected outcome for patients in this study but it will be recorded within the application. . Should the patient be withdrawn from the study for disease progression, an End of Study CRF will be completed.

7.4.2 Suspected Unexpected Serious Adverse Reactions (SUSARs)

For SUSARs, the PI or co-investigator(s) will need to complete additional SUSAR related questions within the SAE eCRF.
These questions constitute the SUSAR eCRF, which must be signed electronically within the web application by the PI or delegate within 24 hours of becoming aware of the event. If for any reason the web application cannot be accessed, a paper SUSAR CRF should be completed and faxed to the number above in section 7.4.1.

The Barts CTU will inform the CI (or delegate), and sponsor immediately so that they can review the information jointly and report to the MHRA within the allocated timelines.
The sponsor has a legal obligation to report SUSARs to the MHRA within 7 days (for fatal or life threatening SUSARs), or 15 days for all other SUSARs. Barts CTU will notify the REC of any SUSARs within the same timeframes. Barts CTU will also inform the IMP supplier within the timescale agreed.

All participating sites will be informed of SUSARs that occur during the trial by the Barts CTU, as and when they occur. If warranted, an investigator alert may be issued, to inform all investigators involved in any study using the same drugs that this serious adverse event has been reported.

The original and any subsequent follow up of SUSAR eCRFs must be electronically signed by the PI or delegate, within the PROVENT web based application, and the form/s must be emailed to the sponsor. A copy of the form(s), together with the email confirmation of receipt, from the Sponsor, must be kept within the TMF. The local sites should keep all SUSAR CRFs within their IF.

7.5 Urgent Safety Measures

The CI may take urgent safety measures (USM) to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety, in accordance with Regulation 30 of the Medicines for Human Use (Clinical Trials) Regulations 2004. The measures should be taken immediately. In this instance, the authorisation of the Licensing Authority Approval prior to implementing these safety measures is not required. However, The CI will make every effort to discuss the USM with the Sponsor and if possible the MHRA via telephone prior to implementation.

It is the responsibility of the CI to inform both the MHRA and REC immediately and in writing within 3 days, in the form of a substantial amendment. A copy of the correspondence with regards to this matter will be sent to the sponsor and the IMP supplier.

7.6 Annual Safety Reporting

The Development Safety Update Report (DSUR) will be sent to the REC, MHRA and IMP suppliers by the CI or delegate, following the sponsor's review, using the DSUR form. The date of the anniversary is the date on the 'notice of acceptance letter' from the MHRA. The CI will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the trial.

The CI will send the Annual Progress Report to the main REC, following review by the sponsor, using the HRA template (the anniversary date is the date on the 'favourable opinion' letter issued by the REC).

7.7 Procedures for Reporting Blinded SUSARs

The responsibility for Pharmacovigilance management and reporting is allocated to the CI by the sponsor. Under these circumstances, a dedicated individual(s), with no involvement in data management of the study will be responsible for the un-blinding event. The un-blinding of single cases by the PI/CI in the course of this study will only be performed if necessary for the safety of the trial subject, or if the participant expresses an explicit wish to know the treatment he is or was receiving. See section 5.10.

Any occurrences will be assessed for seriousness, expectedness and causal relationship as if it was the tested IMP that caused the reaction. If the case appears to be a SUSAR it will be un-blinded to the Sponsor and, if the administered product is the tested IMP, the case will be reported by the sponsor as a SUSAR to the MHRA, the Main Research Ethics Committee and the IMP provider by Barts CTU within the timelines outlined in section 7.4.2. The blind will be maintained for the study team, excluding staff involved in data analysis & interpretation,

7.8 Overview of the Safety Reporting Process/Pharmacovigilance Responsibilities

The CI has the overall pharmacovigilance responsibility. The CI has a duty to ensure that Pharmacovigilance monitoring and reporting is conducted in accordance with the sponsor's requirements.

8.0 Statistical Considerations

8.1 Primary Endpoint Efficacy Analysis

The primary endpoint of the study is the rate of patient recruitment. This will be captured by reporting the proportion of eligible patients that join the trial over the 12-month trial recruitment period.

After a recruitment period of 9 months, the Data Monitoring Committee will identify whether study recruitment has been adequate, i.e. an average recruitment rate of 6 patients per month, and if monitoring of 50% of the feasibility group shows minimal adverse effects in any arm of the trial, this information will be used to justify the main trial.

8.2 Secondary Endpoint Efficacy Analysis

The secondary endpoints include response to treatment as determined by serial multi-parametric magnetic resonance imaging (MRI) of the prostate, biochemical disease progression, histological disease progression together with the evaluation of markers of disease progression.

- Disease progression on MRI will be defined as the development of a MRI detected lesion of 0.2 cc or greater and scoring 4/5 on PIRADS criteria, where no MRI lesion was identified on screening MRI, a 33% increase in the volume of previously identified lesions or an upgrading of MRI stage of disease to ≥3.

. The outcome will be described as a proportion of the study cohort.

Biochemical disease progression will be defined as a 50% increase in serum PSA at 12 months from baseline. Again this will be described as a proportion of the study cohort.

Histological disease progression will be defined as an increase in Gleason score following repeat prostate biopsy from:

Gleason 6 to Gleason score 7 or higher
Gleason 3+4 (score 7) to 4 + 3 (score 7) or
Gleason 4+3 (score 7) to a higher score

Or a 50% increase in maximum cancer core length (MCCL)

8.3 Safety Endpoints

The Data Monitoring Committee will routinely meet six monthly, either face to face or by teleconference call. Their role will be to monitor trial recruitment and drop-out rate over time and to review toxicity data for the study.

No safety issues are anticipated, but in the event of identification of potential safety issues, the DMC will be asked to assess the information available and report back to the TMG and TSC.

8.4 Sample Size

Sample size calculations have suggested that 800 men are needed for a future definitive randomised chemoprevention study of standard (300mg) or low dose (100mg) aspirin vs. placebo and/or Vitamin D3 vs. placebo in patients enrolled on an Active Surveillance programme for prostate cancer.

The current feasibility study aims to demonstrate the acceptability and viability of recruitment to this larger study. Data from the feasibility study will be used to determine the number of centres required to enable the larger, 800 patient trial to fully recruit within 4 years. The principal trial site (BartsHealth) serves a patient population of 2 million, and manages approximately 750 men with newly diagnosed prostate cancer each year, of which around 25% receive Active Surveillance for their disease. We plan to recruit 102 patients over 12 months. If the true recruitment rate is 33.3% then approaching 300 individuals, and therefore recruiting 100, would achieve 89% power to show that the true recruitment rate is above 25% (using a two-sided binomial proportion test with a 0.05 significance level).

8.5 Statistical Analysis

The feasibility study sample size was chosen to examine acceptance rates and the time required to recruit 100 patients. With these numbers, this can be estimated with a standard deviation of about 10% of their true value.

Adherence to allocated therapy will also be assessed, and again, the proportion adhering to their treatment can be assessed within about 10% of the observed value.
The primary endpoint, patient recruitment, will be presented in descriptive format with patient numbers recruited to the trial over time.

For the secondary endpoints we will use a stratified Wilcoxon test to compare median values of the different assays in the active arm vs. placebo for each drug being used, with stratification for the other treatment allocation.

A mixed linear model will be applied on log (1+PSA) to test for dose-by-time interactions and multivariate techniques should help to understand similarities and differences between groups by visualization.

9.0 Data Handling & Record Keeping

9.1 Confidentiality

The Investigator has a responsibility to ensure that patient anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, the Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

The Investigator, and the study team, must be aware of the Data Protection Act 1998 and therefore must adhere to these parameters to ensure that the patient's identity is protected at every stage of their participation within the study. To ensure this is done accordingly, only the patient's initials (first letter of their first name and first letter of their last name) and day (dd) of birth will be used as a means of maintaining anonymity as far as possible without compromising the ability to safely identify the correct individual. This information will be kept on a locally held Pre-screening log, which will be updated accordingly once they have decided whether or not to join the study. If he decides to participate, the patient will be given a pre-randomisation registration ID. This will be generated within the PROVENT application using the patient's initials and day, (DD), of birth. The consent form will be completed and signed as previously described, & the Eligibility Assessment eCRF will be completed using the pre- randomisation ID for reference.
Once the patient has completed Screening and is enrolled in the study, he will be allocated a randomisation or study number by the PI, or a member of the research team, as determined by the computer generated randomisation system.

Should patient information need to be sent to a third party (including correspondence/communication to central laboratories and the sponsor), the PI and the study team should adhere to data protection requirements and should only use the unique study number when corresponding. Any information that is to be collected by these third parties will utilise this anonymised randomisation code for any relevant documents as well as maintaining databases.

The Chief Investigator will be the custodian of the data collected, and no patient identifiable details will be transferred outside the UK. Participants' addresses and personal details will be collected and stored by the trial office, for the purpose of sending study related information.

This information will be stored on a secure database held at the Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, Charterhouse Square, and access will only be available to designated and authorised members of the trial team. The participants may revoke their authorisation for the use of their personal information at any time. Only anonymised data will be used in future publications relating to this study, as detailed in the PIS and Consent Form.

All information generated in the trial will be kept strictly confidential. The researchers conducting the trial abide by the Data Protection Act 1998, and the rights the patient has under this act.

Once consented to participate in the trial, and with their agreement, the patient's GP will be informed of their involvement. Parts of the patient's medical records and the data collected for the trial will be looked at by authorised staff from the individual hospital Trusts where the trial is based, and Queen Mary University of London, who are the sponsor of this trial .These data may also be looked at by representatives of regulatory authorities to ensure that the trial is being carried out correctly, and by representatives from Bayer Healthcare and Merck Serono for the purposes of audit, as stated on the consent form.

All of the above bodies have a duty of confidentiality to the patient as a research participant and no information that could reveal their identity will be disclosed outside the research site.

Computerised records will be stored on a secure password protected encrypted server located on the QMCR network (part of the Queen Mary University of London wider network), and accessible only by authorised staff. All other relevant data will be stored in locked cabinets at the Centre for Cancer Prevention, Wolfson Institute, Queen Mary University of London and accessible only to authorised personnel in relation to this study.

9.2 Study Documents

All relevant trial related documents listed below will be filed in the Investigator Files (IF) and Pharmacy Site Files (PSF). The Centre for Cancer Prevention will inform the CI and staff of any regulatory updates and forward any relevant documentation.

- Signed protocol and any subsequent amendments
- Current Summary of Product Characteristics
- Current/Superseded Patient Information Sheets (as applicable)
- Current/Superseded Consent Forms (as applicable)
- Indemnity documentation from sponsor
- Conditions of Sponsorship from sponsor
- Conditional/Final R&D Approval
- Signed site agreements
- Ethics/MHRA submissions/approvals/correspondence
- CVs of PI and site staff
- UK regulations (GCP) course certificate of each trial team member
- Laboratory accreditation letter (where available), certification and normal ranges for all laboratories used in the study
- Sample IMP labels
- Sample IMP dispensing/accountability logs
- Delegation log
- Staff training log
- Site signature log
- Pre-screening log
- Monitoring visit log
- Correspondence relating to the trial
- Communication Plan between the CI/PI and members of the study team
- SAE reporting plan for the study

9.3 Case Report Forms

Data will be recorded directly to a database using online Electronic Case Report Forms (eCRFs). The eCRFs will be managed by a secure web application, accessible via HTTPS/SSL. Users will be issued with a username and password and will be required to login for web application access; their activity will be tracked using unique user identities and their access to data controlled by defined access roles. Patient Identifiable Data will be encrypted in the database and kept separately from the clinical data. Direct access to the database will be restricted to named users only.

A paper backup system will be established in case of technical failure or for local convenience. Where paper CRFs are used, they should be kept in the investigator file and they will be reviewed as part of source data verification during site monitoring. Patients will be identified only by initials, trial number and day (dd) of birth.

The eCRFs will be completed by the Investigator or suitably trained research staff, as designated in the site delegation log, as accurately and completely as possible throughout the study. If, after screening, a patient is found to be ineligible for the study, the date of the visit and reason for non-participation will be added to their anonymous record on the PROVENT app.

Unless paper CRFs have been used, the PROVENT app will constitute the primary data source for the study, and will be fully accessible by the Trial Coordination Centre. Where data has been collected directly from the

participant, e.g. weight, well-being questions, and entered directly into the trial application, this will be considered to be source data. Sites may also design their own care plans/worksheets depending on their preference, but this must be discussed & pre-agreed with the PROVENT CCO at site initiation visits. Where used, such worksheets must be filed with the participant's hospital notes.
(See appendix 1for CRF summary of data capture)

9.4 Record Retention and Archiving

During the course of the research all records are the responsibility of the Chief Investigator, and must be kept in secure conditions. When the trial is complete, it is a requirement of the Research Governance Framework and Queen Mary University of London Policy that the records are kept for a further 20 years. For trials sponsored by Barts Health or QMUL, the approved repository for long-term storage of local records is the Trust Modern Records Centre. Site files from other sites must be archived at the local repository for that external site for a minimum of five years or as per local practice, and cannot be stored at the Modern Records Centre in London.

9.5 Compliance

The Chief Investigator will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including, but not limited to, the Research Governance Framework and the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended in 2006 and 2008, Trust and Research Office policies and procedures and any subsequent amendments.
In addition, sponsor auditors, Competent Authority inspectors and representatives conducting audit on behalf of Bayer Healthcare and Merck Serono will be allowed access to CRFs, source documents and other trial files to evaluate the trial. Audit reports will be kept confidential.

9.6 Clinical Governance Issues

9.6.1 Ethical Considerations

The Investigator will submit this protocol, any subsequent amendments, and any accompanying material provided to the patient, to an Independent Research Ethics Committee. Written approval from the Committee will be obtained and subsequently submitted to the JRMO to obtain Final R&D approval.

There are no specific ethical issues surrounding this trial, other than there may not be any particular benefit to the participants. Also, in this feasibility study, the optimum treatment time for the products may not be reached, as this is an issue that will be addressed in the full study. However, patients will only be required to attend one further visit outside the normal attendance for active surveillance, and additional tests will be minimal.

9.7 Quality Control and Quality Assurance

9.7.1 Summary Monitoring Plan

Based on the MHRA Guidelines for Type B trials, the Barts CTU Monitoring and Risk Assessment SOP, and the Sponsor's risk assessment, this study was given a risk grading of 'Moderate'.

A combination of On-Site Monitoring (including SDV) and Central Monitoring will be carried out on this trial.

The frequency of the monitoring is detailed in the Monitoring Plan and may change (increase or decrease) depending on the findings from central monitoring or previous monitoring visits. Any changes in monitoring will be agreed with the CI and the Bart's CTU, and approved by the Sponsor.

Please see Monitoring Plan for further details of all monitoring procedures. A summary of all monitoring activity for this study will be provided to the Sponsor on a 3-monthly basis.

9.7.2 Audit and Inspection

Auditing: Definition 'A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements.

This study may be audited by representatives from the coordinating centre, sponsor and IMP suppliers, Bayer Healthcare and Merck Serono. The investigator and institution will be informed of the audit outcome. Investigators are obliged to cooperate in any audit allowing the auditor direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor to discuss any findings or issues. Audit may occur at any time during or after completion of the study.

Inspections may be carried out by the Competent Authority at any time and the Investigator will notify the sponsor immediately if there are any such plans for an inspection.

A study may be identified for audit by any method listed below:

- Via the risk assessment process
- An individual investigator or department may request an audit
- A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations
- Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects

Projects may be randomly selected for inspection by an external organisation e. MHRA

9.8 Serious Breaches in GCP or the Trial Protocol

The sponsor of the Clinical Trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial; or
- The protocol relating to the trial, as amended from time to time in accordance with regulations 22-25, within 7 days of becoming aware of that breach

For the purposes of this regulation a 'serious breach' is a breach which is likely to effect to a significant degree:

- The safety, or physical, or mental integrity of the subjects of the trial
- The scientific value of the trial

The Chief Investigator is responsible for reporting any serious breaches to the sponsor (JRMO) within one working day. The sponsor will notify and report to the MHRA within 7 working days of becoming aware of the serious breach.

9.9 Non-Conformance

A non-conformance is a failure to comply with a quality system. This could be guidelines (Department of Health Research Governance Framework for Health and Social Care 2005 (2nd Edition)), regulations (the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, or Guidelines for Good Clinical Practice), local policies and/or Standard Operating Procedures (SOPs). A non-conformance could be identified through a variety of means, such as complaints, monitoring, internal or external audits

The PROVENT Co-ordinating centre will maintain a log of the non-conformances to ascertain if there are any trends developing which appear to have escalated. The sponsor will assess the non-conformances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependent on severity. If the actions are not dealt with accordingly, the Barts CTU will agree an appropriate action, including an on-site audit.

10.0 Trial Committees

An independent **Data Monitoring Committee** (DMC) will review the trial data and advise the sponsor (directly or indirectly) on the future management of the trial. It will comprise two independent clinicians and an independent statistician. The committee will be chaired by an experienced clinician.
The DMC will review quality and compliance data, as well as safety and efficacy. They will be privy to interim comparisons by arm and see data in a format that will not be shared beyond its independent members. They will be the only group who sees the confidential, unblinded data for the trial as it progresses.
The DMC will meet once before the trial starts and at appropriate intervals as determined by the committee, but at least six monthly.
The committee will review data using the Statistical Analysis Plan and reports produced by the Trial Statistician at the Centre for Cancer Prevention. They will advise the Trial Steering Committee, and may recommend early closure of the trial or discontinuation of any research arm as deemed necessary. Given that this is not a high risk trial and that there will not be any early stopping rule, premature termination of the study will be at the discretion of the DMC and TSC.

A **Trial Steering Committee** (TSC) will be set up to provide overall supervision for the trial on behalf of the Trial Sponsor and Trial Funder, and to ensure that the trial is conducted to the rigorous standards set out in the Medical Research Council's (MRC) Guidelines for Good Clinical Practice. The TSC will concentrate on progress of the trial, adherence to the protocol, patient welfare and consider new information of relevance to the research question. The TSC will act on the advice of the Data Monitoring and Safety Committee to provide advice, through its chair, to the Chief Investigator, Trial Sponsor, the Trial Funder, the Host Institution and the Contractor on all appropriate aspects of the trial. Membership of the TSC will include an independent Chair, at least two other independent members and a patient representative. Representatives of the Trial Sponsor and the Trial Funder will also be invited to all TSC meetings. The final decision regarding whether or not the trial may continue is the responsibility of the TSC.

A **Trial Management Group** (TMG) will be formed to oversee the progress of the trial and act on the advice of the Trial Steering Committee. It will include amongst its members the lead investigators (clinical and non-clinical), trial co-ordinators, and staff from the Centre for Cancer Prevention. The TMG will be responsible for the day-to-day running and management of the trial.

11.0 Publication Policy

This is an investigator-led study sponsored by the C.I.'s substantive employer, Queen Mary University of London. The data collected will not be used to licence/register any pharmaceuticals. Authorship of the final manuscript(s), interim publications, or abstracts will be decided according to active participation in the statistical design, Trial Management Group, accrual of eligible patients and statistical analysis. The final decision about authorship will be made by the Trial Management Group.
Contributing centres, participating investigators and Barts CTU will be acknowledged in the final manuscript. The DMC and the independent Trial Steering Committee will be acknowledged on the main publications. Representative for the sponsor may be added, as appropriate, as co-authors. No participant may present data from the study results unless approved by the Trial Management Group and the sponsor. Any information used for publication in peer reviewed journals will be anonymised and presented at aggregate, and not individual, level. Barts & the London Charity, and CR-UK will be informed of the results. In addition, they will be disseminated to the participants via the PROVENT website.

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13.0 Appendices

Appendix 1.eCRF/CRF Data Collection Summary

eCRF/CRF Data Collection Summary										
	Eligibility Assessment & Consent	**Baseline/ Randomisation**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**18month visit**	**Pre 18month withdrawal**	**End of Study**
Visit Dates	x	x	x	x	x	x	x	x	x	X
Inclusion/Exclusion Criteria fulfilled/checked	x	x								
Informed Consent	x									
Date of Serum Calcium test	x									
Result of Serum Calcium test	x	x								
MRI		x				x			x (if req)	
Prostate Biopsy		x				x			x (if req)	
H Pylori Results		x								
Demographics (including Date of Birth and ethnicity)		x								
Height and Weight		x				x			x (if <12M)	
Medical and Family History		x								
Concurrent Medical Conditions		x	x	x	x	x	x	x	x	
Current/past Medication(s)		x	x	x	x	x	x	x	x	
Adverse Event(s)			x	x	x	x	x	x	x	X
DRE		x	x	x	x	x	x	x	x	
Urine sample for exploratory /translational research		x				x		x	x (if <12M)	
Corrected serum calcium	X	x*		x		x		x	x	
PSA	x	x*	x	x	x	x	x	x	x	
Serum Vitamin D		x		x		x		x	x	
Testosterone/LH/FSH		x		x		x		x	x	
Translational research Blood sample		x						x	x	

Prescription Issued		x		x		x				
Diary card issued		x	x	x	x	x	x			
IMP reconciliation				x		x		x	x	

* If an existing test result is not within the valid time frame; 2 months prior to the date of the Eligibility Assessment for the serum calcium result & 3 months prior to the date of the Eligibility Assessment for the PSA result.

Appendix 2.Flowchart for Safety Reporting