# NIHR HTA Programme

# 18 December 2012

The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

Health Technology Assessment Programme
National Institute for Health Research
Evaluation, Trials and Studies Coordinating Centre
University of Southampton, Alpha House
Enterprise Road, Southampton, SO16 7NS

tel: +44(0)23 8059 5586
fax: +44(0)23 8059 5639

email: hta@hta.ac.uk
web: www.hta.ac.uk

# VIDAL

# Vitamin D and Longevity (VIDAL) trial: randomised feasibility study

EudraCT number: 2011-003699-34
LSHTM Reference number: QA343
ISRCTN46328341

## Study Protocol, Version 3, 25.07.2012

SPONSOR: London School of Hygiene & Tropical Medicine
FUNDERS: NIHR Health Technology Assessment programme
TRIAL COORDINATING CENTRE: London School of Hygiene & Tropical Medicine

**Protocol authorised by:**

| | | | |
|---|---|---|---|
| **Name:** | Prof Julian Peto | **Role:** | Chief Investigator (non-clinical) |
| **Signature:** |  | **Date:** | 25th July 2012 |
| **Name:** | Dr Adrian Martineau | **Role:** | Chief Investigator (clinical) |
| **Signature:** |  | **Date:** | 25th July 2012 |
| **Name:** | Patricia Henley | **Role:** | Sponsor representative |
| **Signature:** |  | **Date:** | 25th July 2012 |

# Main Contacts

### Trial Management Group


Chief Investigator:

Professor Julian Peto
Department of Non-Communicable Disease Epidemiology
London School of Hygiene & Tropical Medicine
Keppel Street
London
WC1E 7HT
Tel: 020 7927 2632
E-mail: julian.peto@lshtm.ac.uk

Clinical Chief Investigator:

Dr Adrian Martineau
Senior Lecturer
Barts and the London School of Medicine and Dentistry
58 Turner Street
London
E1 2AB
Tel: 020 7882 2551
E-mail: a.martineau@qmul.ac.uk

Co-investigators:

Professor Irwin Nazareth
Professor of Primary Care and Population Sciences
Department of Primary Care & Population Health
UCL Royal Free Site
Rowland Hill Street
London
NW3 2PF
Tel: 020 7830 2394
E-mail: i.nazareth@pcps.ucl.ac.uk

Mrs Louise Letley
Senior Nurse Manager
c/o Professor Irwin Nazareth
Department of Primary Care & Population Health
UCL Royal Free Site
Rowland Hill Street
London
NW3 2PF
Tel: 020 7670 4850
E-mail: louiseletley@btinternet.com

Professor Peter Sasieni
Professor of Biostatistics & Cancer Epidemiology
Centre for Cancer Prevention
Charterhouse Square
London
EC1M 6BQ
Tel: 020 7882 3544
E-mail: p.sasieni@qmul.ac.uk

Dr Oliver Gillie
Health Research Forum
68 Whitehall Park
London
N19 3TN
Tel: 020 7561 9677
E-mail: olivergillie@blueyonder.co.uk

Dr Petra Wark
Research Fellow
Imperial College London
School of Public Health
Department of Epidemiology and Biostatistics
St Mary's Campus
Norfolk Place
London
W2 1PG
Tel: 020 7594 8477
E-mail: p.wark@imperial.ac.uk

Ms Terri Harding
PCRN Northern and Yorkshire Network Manager
Northern and Yorkshire PCRN
1st Floor
E Wing Wellington House
Falcon Court
Stockton
TS18 3TS
Tel: 01642 615 600
E-mail: Terri.Harding@nyren.co.uk

Dr Alec Miners
Lecturer in Health Economics
Health Services Research Unit
London School of Hygiene & Tropical Medicine
Keppel Street
London
WC1E 7HT
Tel: 020 7927 2069
E-mail: alec.miners@lshtm.ac.uk

Principal Investigators (GPs) from participating study sites:

Dr Alun Cooper
Bridge Medical Centre
Wassand Close
Three Bridges
Crawley
West Sussex
RH10 1LL
West Sussex PCT
Tel: 01293 526025
Fax: 01293 553490
E-mail: alun.cooper@gp-h82047.nhs.uk

Dr SJ Tomlinson
Medwyn Surgery
Medwyn Centre
Reigate Road
Dorking
Surrey
RH4 1SD
Surrey PCT
Tel: 01306 883816
Fax: 01306 742280
E-mail: stewart.tomlinson@medwynoh.co.uk

Dr TJC Fooks
Pulborough Medical Group
Spiro Close
Pulborough
West Sussex
RH20 1FG
West Sussex PCT
Tel: 01798 872815
Fax: 01798 872123

Dr Jo Nash
Southbourne Surgery
337 Main Road
Southbourne
Elmsworth
Hampshire
PO10 8JH
West Sussex PCT
Tel: 01243 388 740
Fax: 0844 884 0136
E-mail: southbourne.surgery@nhs.net

Dr Jennifer Litchfield
Poundhill Medical Group
1 Crawley Lane
Pound Hill
Crawley
West Sussex
RH10 7DX
West Sussex PCT
Tel: 0844 477 1816
Fax: 0844 477 1817

Dr Raj Sharma
Sea Road Surgery
39-41 Sea Road
Bexhill-on-Sea
East Sussex
TN40 1JJ
Hastings and Rother PCT
Tel: 0844 477 8690
Fax: 0844 4778691

Dr C Kelly
Sunny Mead Surgery
15-17 Heathside Road
Woking
GU22 7EY
Surrey PCT
Tel: 01483 772760
Fax: 01483 730354
E-mail: carmelannkelly@btinternet.com

Dr Caroline Haddy
Backwell & Nailsea Medical Group
Backwell Medical Centre
15 West Town Road
Backwell
Bristol
Avon
BS48 3HA
North Somerset PCT
Tel: 01275 465100
Fax: 01275 795609
E-mail: Caroline.Haddy@gp-L81060.nhs.uk

Dr Judy Craig
Dr Kownacki & Partners
Albany House Medical Centre
3 Queen Street
Wellingborough
Northamptonshire
NN8 4RW
Northamptonshire PCT
Tel: 0844 477 8786
Fax: 01933 229236
E-mail: Judy.Craig@gp-k83026.nhs.uk

Professor Irwin Nazareth
Keats Group Practice
1b Downshire Hill
London
Greater London
NW3 1NR
Camden PCT
Tel: 0844 477 3102
Fax: 0844 477 3105
E-mail: i.nazareth@ucl.ac.uk

Dr Andrea Dexter
South Axholme Practice
Haxey Surgery
30 Church Street
Haxey
Doncaster
DN9 2HY
North Lincolnshire PCT

Tel: 01427 757 566
Fax: 01427 874944
E-mail: a.dexter@nhs.net

Dr Ewart Jackson-Voyzey
Axbridge Surgery
Houlgate Way
Axbridge
Somerset
BS26 2BJ
Somerset PCT
Tel: 01934 732464
Fax: 01934 733488
E-mail: Ewart.Jackson-voyzey@axbridgewedmoredoctors.nhs.uk

Dr Nicholas Hargreaves
Burn Brae Medical Group
Hexham Primary Care Centre
Corbridge Road
Hexham
Northumberland
NE46 1QJ
Northumberland PCT
Tel: 01434 603627
Fax: 01434 613033
E-mail: nick.hargreaves@gp-a84024.nhs.uk

Dr Nick Taylor
Dr Moss & Partners
28-30 Kings Rd
Harrogate
North Yorks
HG1 5JP
North Yorkshire & York PCT
Tel: 01423 560261
Fax: 01423 701266
E-mail: nick.taylor@gp-b82013.nhs.uk

Dr Fran Adams
MyHealth (formerly Strensall Medical Practice)
Strensall Health Care Centre
Southfields Road
Strensall
York
North Yorkshire
YO32 5UA
North Yorkshire & York PCT
Tel: 01904 490532
Fax: 01904 491927
E-mail: Fran.Adams@gp-B82080.nhs.uk

Dr P S Townsend
Gibson Lane Practice
Gibson Lane
Kippax

Leeds
West Yorkshire
LS25 7JN
Leeds PCT
Tel: 0113 287 0870
Fax: 0113 232 0746
E-mail: phil.townsend@nhs.net

Dr Mark Lee
Chapeloak Surgery
347 Oakwood Lane
Leeds
West Yorkshire
LS8 3HA
Leeds PCT
Tel: 0113 295 3750
Fax: 0113 295 3760
E-mail: rachelandmarkinbots@hotmail.com

Dr Kim P Hearn
Dr Hearn & Partners
Montpelier Health Centre
Bath Buildings
Montpelier
Bristol
BS6 5PT
Bristol PCT
Tel: 0117 942 6811
Fax: 0117 944 4182
E-mail: kim.hearn@gp-l81012.nhs.uk

Dr AS Raghunath
St Andrews Group Practice
Marmaduke Street
Hessle Road
Hull
Yorkshire
HU3 3BH
Hull Teaching PCT
Tel: 01482 336810
Fax: 01482 336826
E-mail: raghu.raghunath@nhs.net

Dr Hilary Pinnock
Estuary View Medical Centre
Boorman Way
Whitstable
Kent
CT5 3SE
Eastern and Coastal Kent PCT
Tel: 01227 284300
Email: hilary.pinnock@ed.ac.uk

| | |
|---|---|
| Statistician: | Ms Clare Gilham |

Department of Non-Communicable Disease Epidemiology
London School of Hygiene & Tropical Medicine
Keppel Street
London
WC1E 7HT
Tel: 020 7927 2068
clare.gilham@lshtm.ac.uk

Trial Manager: Ms Christine Rake
Department of Non-Communicable Disease Epidemiology
London School of Hygiene & Tropical Medicine
Keppel Street
London
WC1E 7HT
Tel: 020 7927 2861
E-mail: christine.rake@lshtm.ac.uk

**Trial Coordinating Centre**

For general queries, supply of trial documentation, and collection of data, please contact:

| | |
|---|---|
| Trial Manager: | Ms Christine Rake |
| Address: | Department of Non-Communicable Disease Epidemiology<br>London School of Hygiene & Tropical Medicine<br>Keppel Street<br>London<br>WC1E 7HT |
| Tel: | 020 7927 2861 |
| E-mail: | christine.rake@lshtm.ac.uk |
| Fax: | 020 7927 2862 |

**Sample storage and assay**

| | |
|---|---|
| Address: | Dr Mike Hill<br>Laboratory Director<br>CTSU Wolfson Laboratories<br>Clinical Trials Service Unit<br>Richard Doll Building<br>Old Road Campus, Roosevelt Drive,<br>Oxford<br>OX3 7LF |
| Tel: | 01865 743743 |

**Trial Pharmacy**

| | |
|---|---|
| Address: | Josephine Falade<br>Pharmacist: Clinical Trials<br>Pathology and Pharmacy Building<br>Royal London Hospital<br>80 Newark St<br>London<br>E1 2ES |
| Tel: | 020 324 60126 |

**Clinical Queries**

Clinical queries should be directed to the Trial Manager who will direct the query to the appropriate person.

**Sponsor**

London School of Hygiene & Tropical Medicine is the research sponsor for this study. For further information regarding the sponsorship conditions, please contact:

Clinical Trials QA Manager
London School of Hygiene & Tropical Medicine (LSHTM)
Keppel Street
London WC1E 7HT
Tel: +44 207 927 2626
Email: Patricia.Henley@LSHTM.AC.UK

**Funder**

NIHR Health Technology Assessment programme

This protocol describes the VIDAL feasibility study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the Trial Coordinating Centre to confirm they have the most recent version.

Problems relating to this trial should be referred, in the first instance, to the Trial Coordinating Centre.

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, protocol and all applicable local regulations.

## Table of Contents

## GLOSSARY OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AR | Adverse Reaction |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| CTA | Clinical Trial Authorisation |
| CTIMP | Clinical Trial of Investigational Medicinal Product |
| DBP | Vitamin D Binding Protein |
| DMC | Data Monitoring Committee |
| DSUR | Development Safety Update Report |
| EC | European Commission |
| EMA | European Medicines Agency |
| EU | European Union |
| EUCTD | European Clinical Trials Directive |
| EudraCT | European Clinical Trials Database |
| EudraVigilance | European database for Pharmacovigilance |
| GAfREC | Governance Arrangements for NHS Research Ethics |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| HES | Hospital Episodes Statistics |
| IB | Investigator Brochure |
| ICF | Informed Consent Form |
| IMP | Investigational Medicinal Product |
| IMPD | Investigational Medicinal Product Dossier |
| ISRCTN | International Standard Randomised Controlled Trial Number |
| IU | International Units (1 µg = 40 IU vitamin D3) |
| JRO | Joint Research and Development Office |
| MA | Marketing Authorisation |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MRC | Medical Research Council |
| MS | Member State |
| Main REC | Main Research Ethics Committee |
| NHS R&D | National Health Service Research & Development |
| PI | Principal Investigator |
| QA | Quality Assurance |

| | |
|---|---|
| QC | Quality Control |
| QP | Qualified Person for release of trial drug |
| RCT | Randomised Control Trial |
| REC | Research Ethics Committee |
| SAR | Serious Adverse Reaction |
| SAE | Serious Adverse Event |
| SDV | Source Document Verification |
| SOP | Standard Operating Procedures |
| SmPC | Summary of Product Characteristics |
| SSA | Site Specific Assessment |
| SSAR | Suspected Serious Adverse Reaction |
| Subject | An individual who takes part in a clinical trial |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| VDR | Vitamin D Receptor |
| 25(OH)D | 25-hydroxyvitamin D |

## Note on units:

Vitamin D3: 1 µg = 40 IU. A dose of 4,000 IU/day is thus 100 µg/day.
25(OH)D (25-hydroxyvitamin D): 1 ng/ml = 2.5 nmol/L. A circulating level of 30 ng/ml is thus equivalent to 75 nmol/L.

## KEYWORDS

Vitamin D, randomised trial, dietary supplement, longevity, survival

## STUDY SUMMARY

**TITLE** Vitamin D and Longevity Trial (VIDAL): randomised feasibility study

**DESIGN** Randomised controlled trial, with cluster randomisation of GP practices to either: (a) unblinded randomisation of open label vitamin D v. no treatment (800 people in 10 practices) or (b) double-blind randomisation of vitamin D v. placebo control (800 people in 10 practices). Within each practice, participants will be individually randomised to either vitamin D or control.

**AIMS**

1. To demonstrate the feasibility of a larger (n=20,000) randomized trial of prolonged vitamin D supplementation in people aged 65 to 84.
2. To provide estimates of cost and establish the study design and procedures required for the main trial for which this is a feasibility study.
3. To compare the effects of blinded versus open study design on trial recruitment and compliance.

**OUTCOME MEASURES** The main outcomes of the feasibility study are:

(i) Recruitment rates
(ii) Treatment compliance
(iii) Contamination rates (self-administration of >400 IU vitamin D per day or equivalent among controls)
(iv) Attrition rates over 24 months (failure to attend GP practice for final assessment)
(v) Costs of placebo control versus open control study designs
(vi) Incidence of adverse events (severe and minor events)
(vii) Assessment of infections, prescriptions and frequency of GP visits
(viii) Assessment of blood 25-hydroxyvitamin D (25(OH)D) concentrations at recruitment and at two years in relation to potential determinants of vitamin D status including self-reported treatment compliance
(ix) Assessment of change in systolic and diastolic blood pressure
(x) Cause-specific mortality and cancer incidence and hospital admissions ascertained by flagging or tracing in national record systems, and reasons for any hospital admissions

**POPULATION** 1600 members of the general population registered with a General Practitioner's (GP) practice and aged ≥ 65 years and ≤ 84 years at enrolment.

**PRINCIPAL ELIGIBILITY CRITERIA**

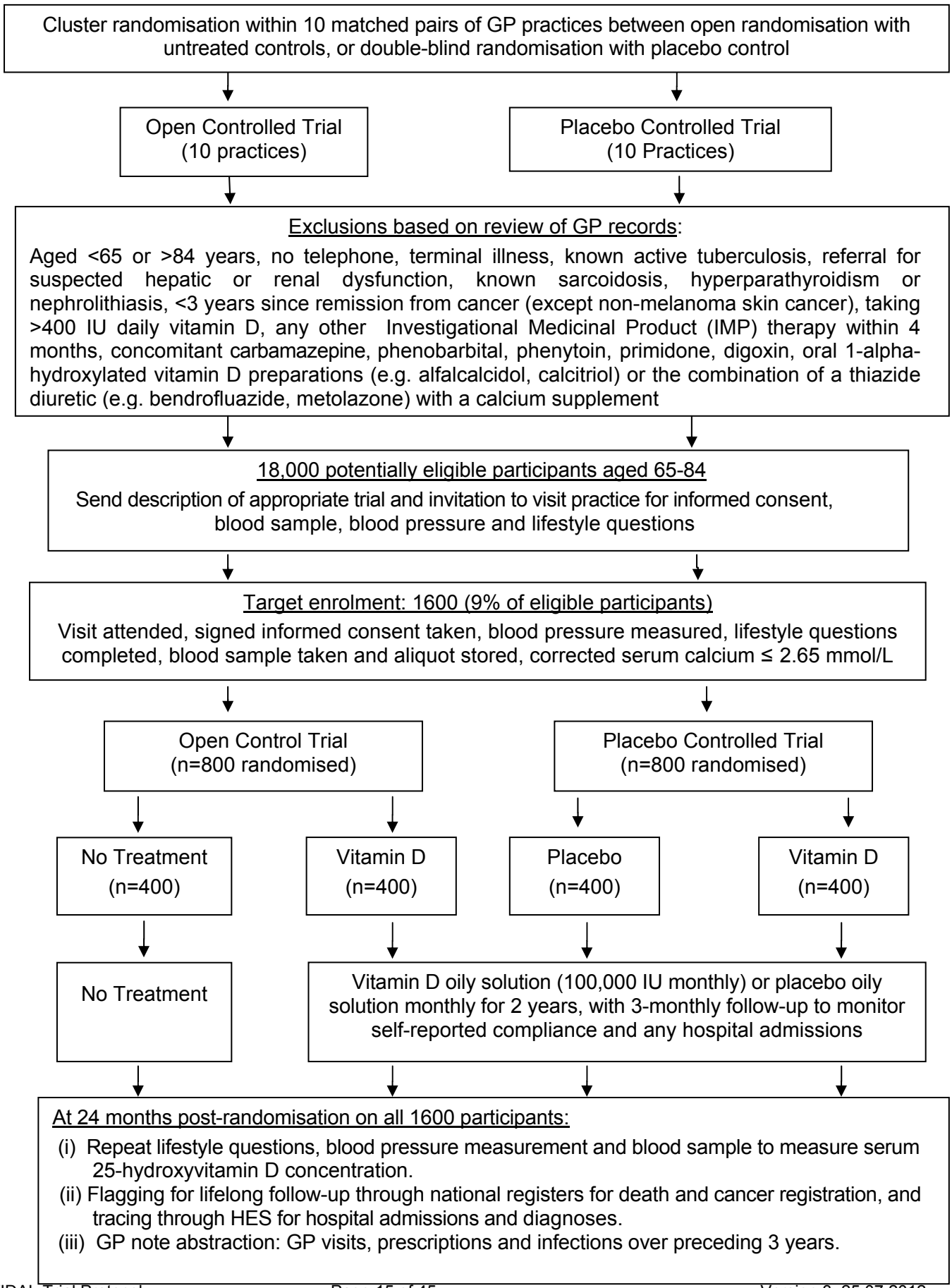
- Age ≥ 65 years and ≤ 84 years at enrolment.
- Contactable by telephone and able to attend enrolment at the GP surgery, and able to give informed consent.
- Baseline corrected serum calcium ≤ 2.65 mmol/L

**TREATMENT**

(i) Participants in double-blind practices will be randomised to receive either 100,000 IU monthly (average 3300 IU/day) of oral vitamin D3 (presented as 5 ml Vigantol® Oil) or double-blind placebo control (5 ml Miglyol® 812 Oil) monthly for 2 years : 800 participants
(ii) Participants in unblinded practices will be randomised to receive either 100,000 IU monthly (average 3300 IU/day) of oral vitamin D3 (5 ml Vigantol® Oil) monthly for 2 years or open control (no treatment): 800 participants

**DURATION** Recruitment 1 year, treatment duration 2 years, study duration 3 years

# STUDY FLOWCHART



# 1. INTRODUCTION

## 1.1 BACKGROUND

A consensus is emerging that circulating 25-hydroxyvitamin D (25(OH)D concentration - the measure of vitamin D status) should be at least 75 nmol/l (30 ng/ml) for optimal health and increased life expectancy (Bouillon et al., 2005, Bischoff-Ferrari et al., 2006). Eighty percent of men and 87% of women aged over 65 years living independently in the UK have levels of 25(OH)D below 75 nmol/l (Hirani and Primatesta, 2005). Several epidemiological studies, notably the EPIC study of 1248 cases of colorectal cancer drawn from a population of more than half a million, report a correlation between low circulating 25(OH)D and the risk of developing various cancers (Giovannucci, 2005, Jenab et al., 2010, Lim et al., 2006). Low levels also correlate with reduced survival after cancer diagnosis, and cancer survival is improved among patients diagnosed in summer and autumn (when vitamin D status is highest) compared to those diagnosed in the winter (Lim et al., 2006). Giovannucci and colleagues suggested that the correlation between predicted 25(OH)D levels based on several risk factors (skin colour, obesity, latitude and physical activity) and total cancer incidence and mortality in their large cohort could be partly due to a direct effect of vitamin D (Giovannucci et al., 2006). A meta-analysis of studies of serum levels of 25(OH)D concluded that a daily intake of at least 1000 IU/day of vitamin D would substantially reduce colorectal cancer incidence (Gorham et al., 2007). Positive associations have however been reported between vitamin D status and risk of prostate cancer (Ahn et al., 2008) and pancreatic cancer (Stolzenberg-Solomon et al., 2010) highlighting the need for large randomised trials. Evidence on vitamin D and heart disease includes a nested case-control study in which men with 25(OH)D levels <37 nmol/l had a relative risk of myocardial infarction of 2.42 (95% CI= 1.53-3.84) relative to men with sufficient levels (>75 nmol/l) (Giovannucci et al., 2008). A systematic review suggested that optimal serum 25(OH)D for all endpoints should exceed 75 nmol/l (Bischoff-Ferrari et al., 2006) and that this can be achieved with doses of 1,800 to 4,000 IUs vitamin D per day without increasing health risks(Bischoff-Ferrari et al., 2010). Other effects of low circulating 25(OH)D may include compromised immunity (Cannell et al., 2006, Holick, 2007); we have previously demonstrated that the active metabolite of vitamin D induces antimicrobial activity in vitro (Martineau et al., 2007) and have performed a randomized controlled trial showing that vitamin D supplementation enhances immunity to mycobacteria (Martineau et al., 2007). These pleotropic effects are supported by experimental studies. The active metabolite of vitamin D, 1,25-dihydroxyvitamin D, suppresses proliferation and induces differentiation of cancer cells in vitro, and its receptor and the enzyme that synthesises it are both expressed in many cell types (Giovannucci, 2005).

A meta-analysis of published randomized trials on the effect of vitamin D on overall mortality (Autier and Gandini, 2007) showed a marginally significant reduction in overall mortality of 7% (95% CI 1%-14%: p<0.05). 82% of treated patients received vitamin D*3* (cholecalciferol), the remainder vitamin D*2* (ergocalciferol), either orally or by injection. Average daily doses ranged from 300 IU to 2,000 IU, the frequency of treatment ranged from daily to 4-monthly, and follow-up ranged from 6 months to 7 years. The meta-analysis included a British study of 2686 people aged 65-85 years randomised to 100,000 IU oral vitamin D*3* or placebo every four months over five years (Trivedi et al., 2003). The authors' main recommendation was for large population-based randomised trials of prolonged vitamin D3 treatment at adequate dose, with total mortality as the primary endpoint.

The International Agency for Research on Cancer (IARC) Working Group on vitamin D and cancer, of which Prof Peto was a member, reviewed the epidemiological evidence on vitamin D and cancer and concluded that the evidence was strong for colorectal cancer

but inconclusive for other individual cancers (IARC Working Group on Vitamin D, 2008) Their report concluded: “The only way to further address the cause-effect issue is to organise new randomized trials to evaluate the impact of vitamin D on all-cause mortality and on the incidence and mortality from common conditions including cancer. These trials should make sure that key parameters of vitamin D status (e.g., serum 25-hydroxyvitamin D levels before and in trial) can be assessed.”

## 1.2 RATIONALE FOR CURRENT STUDY

The proposed regimen (100,000 IU monthly, equivalent to 3300 IU per day) is less than the current tolerable upper intake limit of 4000 IU/day for vitamin D in North America, defined as “the highest daily level of chronic nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population” (Institute of Medicine, 2011). Indeed a risk assessment based on a review of clinical trial data concluded that a daily dose of at least 10,000 IU/day is safe (Hathcock et al., 2007), and the Institute of Medicine report accepts that this intake represents the NOAEL (no observable adverse effect level), which was adjusted for uncertainty to establish an upper limit of 4000 IU per day (Institute of Medicine, 2011).

The epidemiological evidence that various other vitamins prevent cancer has been disproved in randomized trials (Greenwald et al., 2007). Associations between inadequate vitamin D status and increased risk of cancer reported in the observational studies described above could also be at least partly due to confounding, and no adequately powered trial has tested vitamin D in doses that are high enough to achieve serum 25(OH)D concentration > 75 nmol/l. Although the majority of observational studies report associations between vitamin D deficiency and susceptibility to a range of pathologies, some studies are null, and a few report the opposite association; the existing evidence is thus not sufficient as a basis for a universal policy of high-dose vitamin D supplementation. Several investigators have recommended that randomized trials are needed to assess whether increases in circulating 25(OH)D can effectively decrease risk of disease, for example, colorectal cancer (Jenab et al., 2010) and heart disease (Giovannucci, 2009). The importance of trials of oral supplements of vitamin D is emphasized by the finding that in practice it is difficult for most people resident in the UK to obtain optimal vitamin D from sunlight or diet (Rhodes et al., 2010).

The main trial for which this is the feasibility study will be a randomized trial with 20,000 subjects aged 65-84 years treated for 5 years and followed for a further 5 years. A trial of that size will be needed to detect the 7% reduction that vitamin D supplementation might plausibly achieve in total mortality in healthy adults aged over 65 (Autier and Gandini, 2007). If self-administered vitamin D supplementation were shown to confer substantial health benefits it would be routinely recommended and widely adopted. This would also provide a rationale for a national policy of vitamin D supplementation for the general population, a review of the relative risks and benefits of sun exposure, and a revision of existing policy on vitamin D fortification of foods. If we show no benefit or unforeseen disadvantages this will also be a valuable contribution to knowledge.

An important public health priority is therefore to demonstrate the feasibility of a large randomized trial of prolonged vitamin D supplementation in older people, and to show that this will increase serum 25(OH)D to >=75 nmol/l in the majority of subjects. As well as demonstrating an expected increase in circulating 25-hydroxyvitamin D levels, the feasibility study will provide estimates of cost and establish the study design and procedures required for the main trial. An important feature of the feasibility study will be the comparison of a placebo control group with an open control group with no treatment. Randomized double-blind placebo-controlled trials are considered the gold standard, particularly where the endpoint is subjective, but an open control design may be

acceptable where the main endpoint is overall mortality. The primary purpose of this feasibility study is to ascertain recruitment levels, but the study will also include a cluster randomized comparison of the effects of placebo versus open control trial design on the reliability of self-reported infections and other adverse effects as well as on recruitment, participant acceptability and treatment compliance. The study will thus provide much needed evidence on an important methodological (and economic) issue in the design of pragmatic trials in preventive medicine.

# 2. STUDY OBJECTIVES

## 2.1 PRIMARY STUDY OBJECTIVES

The primary aim of the feasibility study is to establish the procedures required to conduct the main trial. We shall determine the recruitment rate and the compliance rate (the proportion adhering to allocated treatment over 2 years) in practices with placebo control, and in practices with open control. We shall also determine contamination rates in those allocated to placebo and those allocated to open control (ie self-administration of >400 IU vitamin D per day or equivalent). IMP adherence and use of additional vitamin D supplements will be studied both by self-report and from blood levels of 25(OH) vitamin D at entry and at 2 years.

## 2.2 SECONDARY STUDY OBJECTIVES

(i) To compare costs of blinded and open label study designs, and hence to determine whether the extra costs of placebo control would be justified in the main trial.
(ii) To provide unbiased data on the incidence of adverse events (vitamin D v. placebo control).
(iii) To provide unbiased data on infections, prescriptions and frequency of GP visits (vitamin D v. placebo control), and to estimate the bias in these measures in participants allocated to vitamin D in an open control design.
(iv) To analyse circulating 25(OH)D at recruitment and at 2-year follow-up in relation to allocated treatments and other potential determinants of vitamin D status, particularly self-reported sun exposure.
(v) To analyse the change in systolic and diastolic blood pressure from recruitment to 2 years between vitamin D and control groups.
(vi) To establish the feasibility of flagging for lifelong follow-up through national registers for death and cancer registration, and tracing through the Hospital Episodes Statistics database (HES) for hospital admissions and diagnoses.

# 3. STUDY DESIGN

This is a two year randomised controlled feasibility trial on 1600 people aged 65-84 comprising two study designs:

(i) Blinded study: Participants in double-blind practices will be randomised to receive either 100,000 IU monthly (average 3300 IU/day) of oral vitamin D3 (presented as 5 ml Vigantol® Oil) or double-blind placebo control (5 ml Miglyol® 812 Oil) monthly for 2 years: 800 participants
(ii) Open label study: Participants in unblinded practices will be randomised to receive either 100,000 IU monthly (average 3300 IU/day) of oral vitamin D3 (5 ml Vigantol® Oil) monthly for 2 years or control (no treatment): 800 participants

Twenty GP practices will be cluster randomised to either blinded or open label study design. We will identify 10 pairs of GP practices matched on region and socioeconomic

profile (deprivation score based on practice postcode) and randomly select one practice within each matched pair in which participants will be individually randomised between vitamin D and placebo, while participants in the other practice will be individually randomised between open-label vitamin D and open control.

## 3.1 STUDY OUTCOME MEASURES

### 3.1.1 Primary outcomes of the feasibility study

The primary aim of the feasibility study is to establish the procedures required to conduct the main trial: our target is to randomise 1,600 participants aged 65-84 through 20 GP practices.

Primary outcome measures:
1. The overall recruitment rate (the proportion of invited participants who are randomised) and comparison of recruitment rate in blinded versus open control studies.
2. The overall level of compliance with study medication and comparison of blinded medication versus open label vitamin D compliance (to evaluate whether participants taking open label vitamin D are more or less compliant than those who are unaware of IMP status). A randomized participant is defined as compliant:
(i) If allocated to vitamin D: they report taking at least 19 (79%) of the 24 monthly doses of allocated IMP, and attend the 2-year follow-up visit.
(ii) If allocated to no vitamin D (whether placebo or open control): they report taking a total of <300,000 IU of vitamin D supplements over the 2 years of the study, and attend the 2-year follow-up visit. (The current UK RDA of 400 IU/day is 292,000 IU over 2 years).

These will be combined as a single outcome measure, which is the number of people we must invite to get one person complying with allocated treatment, to demonstrate that the main trial is feasible. It equals the number invited divided by the number randomised and compliant.

### 3.1.2 Secondary outcomes of the feasibility study

(i) The overall level of attrition (failure to attend the final 2-year visit), and a comparison of attrition between open label and blinded practices.
(ii) Costs of blinded versus open label study designs.
(iii) Comparison of incidence of serious adverse events between vitamin D and control in blinded practices.
(iv) Comparison between vitamin D and control of numbers of infections, GP prescriptions and GP visits (a) in blinded practices, and (b) in open-label practices. This will provide an estimate of the bias in these measures in participants allocated to vitamin D in an open control design.
(v) Blood 25(OH)D concentration at recruitment and at 2 years in relation to allocated treatment and other potential determinants of vitamin D status (self-reported sun exposure, diet and use of vitamin D supplements).
(vi) Comparison of change in systolic and diastolic blood pressure from recruitment to 2 years between vitamin D and control groups.
(vii) Cause-specific mortality and cancer incidence will be ascertained by flagging in the National Health Service Information Centre (NHS IC).
(viii) Hospital records will be collected by NHS number linkage with the Hospital Episode Statistics (HES) database.

### 3.1.2 Additional trial assessments

**Before randomisation:**

1) The practice nurse will record details of foreign holidays, sunbathing, sunbed use and use of vitamin supplements on the online Case Report Form (CRF) at the GP practice with all participants before randomisation.
2) A blood sample will also be taken, and corrected serum calcium will be assayed before randomisation to establish eligibility. Aliquots (plasma and buffy coat) will be stored in liquid nitrogen for 25(OH)D assay at the end of the study, and (subject to additional funding and optional additional consent) for further analyses including genetic studies.

**At two years:**

1) All 1600 participants will attend the GP practice 2 years after randomization. A further blood sample for 25(OH)D assay and responses to the same questions asked at recruitment will be obtained to quantify differences in vitamin D status and factors that may affect it between the intervention and control groups in blinded versus open label studies.
2) Summaries of GP records for all participants will also be extracted for GP visits, prescriptions and infections for one year pre-randomisation and 2 years post-randomisation.

### 3.2 ADDITIONAL UNFUNDED STUDIES

The participant information sheet will explain that there are many possible effects of vitamin D and that we hope to obtain further funding and ethical approval for more extensive analyses of blood samples (including genetic studies). Optional additional informed consent will therefore include permission (subject to further ethical approval) for long-term storage and unspecified analyses, including genetic studies, of the blood samples taken at entry and 2 years.

### 3.3 RISKS AND BENEFITS

There are many suggested benefits of vitamin D supplementation for human health (Holick, 2007). Those reported in meta-analyses include prevention of fractures (Bischoff-Ferrari et al., 2005) and falls (Bischoff-Ferrari et al., 2004) and reduction in all-cause mortality (Autier and Gandini, 2007).

Vitamin D supplementation is generally very safe; the principal risk relates to the very rare phenomenon of vitamin D hypersensitivity (Vieth, 1999). This manifests as hypercalcaemia, and may arise in individuals with hyperparathyroidism or granulomatous disease (Sharma, 2000). We seek to minimize the risk of harm arising from administration of vitamin D to study participants by the following measures:

1. Baseline exclusion of participants at increased risk of vitamin D hypersensitivity (i.e. those with baseline hypercalcaemia); those known to have active tuberculosis, sarcoidosis, hyperparathyroidism, past or present nephrolithiasis, vitamin D intolerance, referral for suspected hepatic or renal dysfunction, any malignancy other than non-melanoma skin cancer not in remission for ≥ 3 years; and those taking oral 1-alpha-hydroxylated vitamin D preparations (e.g. alfalcalcidol, calcitriol) or the combination of a thiazide diuretic (e.g. bendrofluazide, metolazone) with a calcium supplement; or a dietary supplement containing or equivalent to more than 400 IU (10 micrograms) per day vitamin D.

2. Ensuring that all participants are aware of symptoms of hypercalcaemia, and advising them to contact their GP if they develop these symptoms, so that their GP can arrange for a blood test for hypercalcaemia (and report hypercalcaemia as a suspected adverse reaction to the Trial Coordinating Centre).

3. Three-monthly monitoring of participants for study medication compliance (and reasons for non-compliance) and hospital admissions (excluding outpatient visits and A&E attendances which do not result in admission).

4. Instituting therapy for hypercalcaemia for any study participant developing this complication: usually hypercalcaemia is effectively managed by simple rehydration, but effective pharmacological interventions are also available if hypercalcaemia does not resolve with rehydration alone (Bushinsky and Monk, 1998).

# 4. PARTICIPANT ENTRY

## 4.1 PRE-RANDOMISATION OR PRE-REGISTRATION EVALUATIONS

Participants will undergo a blood test at the screening visit to detect possible hypercalcaemia before randomisation. Individuals with a baseline corrected serum calcium level > 2.65 mmol/L will be excluded from the trial (see section 5.1.3).

## 4.2 INCLUSION CRITERIA

- Age ≥ 65 years and ≤ 84 years at enrolment
- Contactable by telephone, able to receive recorded deliveries by post, and able to attend enrolment at the GP surgery
- GP notes for the previous year are available

## 4.3 EXCLUSION CRITERIA

- Known active tuberculosis, sarcoidosis, hyperparathyroidism, past or present nephrolithiasis, vitamin D intolerance, referral for suspected hepatic or renal dysfunction, terminal illness, any malignancy other than non-melanoma skin cancer not in remission for ≥ 3 years
- Planning to move from the GP practice or to emigrate within 5 years
- Any other condition that in the PI's or CI's judgement might compromise participant safety or compliance, interfere with evaluation or preclude completion of the study.
- Baseline corrected serum calcium > 2.65 mmol/L
- Taking dietary supplement or other medication containing more than 400 IU (10 micrograms) per day vitamin D
- Concomitant therapy with any of the following: carbamazepine, phenobarbital, phenytoin, primidone, digoxin, oral 1-alpha-hydroxylated vitamin D preparations (e.g. alfalcalcidol, calcitriol) or the combination of a thiazide diuretic (e.g. bendrofluazide, metolazone) with a calcium supplement
- Treatment with any other investigational medical product or device up to 4 months before first dose of IMP

## 4.4 WITHDRAWAL CRITERIA

Treatment may be interrupted or discontinued permanently by participant choice or at the GP's discretion. This will be monitored, but participants will remain under follow-up. The main analyses will be by intention to treat, so the only participants withdrawn from the trial will be those who specifically withdraw consent for further passive follow-up through national record systems (NHS Information Centre) and GP records. No further follow-up will be arranged for withdrawn participants after this point. Data collected up to the time of

withdrawal will be included in study analyses unless participants specifically withdraw permission to do so.

# 5. ENROLMENT AND RANDOMISATION PROCEDURE

## 5.1 RANDOMISATION OR REGISTRATION PRACTICALITIES

### 5.1.1 Trial application and database

Online CRF (VIDAL App): This web based application will be held on a secure server at The Cancer Prevention Trials Unit at Queen Mary University of London (see section 12). Each practice will only have access to its own participants' full records, whereas the Trial Coordinating Centre will have access to data collected after consent for the purposes of contacting participants, sending study medication, monitoring sites, flagging etc. For monitoring purposes the Trial Coordinating Centre will also have access to the anonymous record of the initial telephone call by the practice nurse (see below). This anonymous record will contain only the local study identifier and yes/no responses to eligibility items.

Allocation of practices to open label or double-blind randomisation
Before the study begins, practices will be randomised within matched pairs (see 5.1.5) to the blinded study or open control study.

Pre-consent Spreadsheet: Study recruitment will take place through 20 GP practices. In the first instance, each GP practice will generate a locally stored spreadsheet listing all registered patients aged 65-84 (including NHS number, name, sex, date of birth, address and telephone number) for the purpose of screening and inviting potentially eligible patients to participate in the trial.

The practice nurse will screen the GP notes of each participant in the spreadsheet to exclude ineligible participants, including those judged to lack the mental capacity to give informed consent. Eligibility of respondents will be confirmed by the local PI (GP) before sending out study invitations by post. Respondents will then be telephoned by the practice nurse to confirm eligibility. Before this call, the practice nurse will access the online VIDAL app to create a new anonymous record for the respondent, entering only the components of a unique local identifier for each participant (from the spreadsheet), then entering eligibility items during the call. The unique local identifier will be automatically derived by the VIDAL app once the practice nurse has entered the participant's first and last initial, and the two-digit day of their date of birth. These items will be added to a 2-letter practice code and a 4-digit line number to create a local unique identifier for each participant. Potentially eligible participants will then be offered a screening visit appointment where informed consent will be obtained from those agreeing to participate in the trial. The unique participant identifier and dates of pre-consent correspondence and telephone calls will be recorded on the spreadsheet, which will be held on the practice computer and not otherwise accessible.

After reviewing participant eligibility and obtaining informed consent at the screening visit, the practice nurse will access the VIDAL app to enter the participant's personal details (including NHS number, name, sex, date of birth, address and telephone number), record baseline systolic and diastolic blood pressure, height, weight and waist circumference, administer the online CRF questions and take the baseline blood samples. The practice nurse may delegate some responsibilities to appropriately trained, named practice staff (eg height, weight and waist circumference measurement, administration of lifestyle questions or taking blood). The practice may also initially administer a paper copy of the

baseline visit questions if required in consultation with the Trial Coordination Centre. Apart from paper copies of the baseline visit data, signed informed consent and any postal responses from participants, including postal replies to 3-monthly follow-ups, the VIDAL app will constitute the source data (an electronic CRF). Upon completion of the screening visit, a copy of the signed informed consent form will be sent to the Trial Coordination Centre.

After verifying participant eligibility (by checking the copy of the informed consent form and the online blood calcium result) the Trial Coordinating Centre will telephone the participant to confirm that they are still willing to be randomised. The current date, a unique trial number and the allocated medication pack number will then be added to the VIDAL app automatically, and the pharmacy will be instructed to send that medication pack to the participant. The VIDAL app will contain details of all subsequent participant contacts, including: sending and receipt of first (at randomisation) and second (at 1 year) treatment packs, monthly automated telephone, e-mail or text message reminders to take medication, 3-monthly follow ups (dates due, sent and acknowledgement received), 2-year blood sample, adverse event reports, address changes, and any other notes by practice staff. Apart from postal and e-mail communications from participants and from the GP practice to the Trial Coordinating Centre, the VIDAL app will thus constitute the primary data source on follow-up after randomisation. All items will be accessible by the Trial Coordinating Centre and the relevant practice.

If at the initial visit a participant is found to be ineligible or does not consent to participate in the trial, the date of the visit and reason for non-participation (but no identifying or other data) will be added to their anonymous record on the VIDAL app.

### 5.1.2 Invitation of potential study participants to attend screening visit

The staff at each practice will identify potentially eligible participants aged 65-84 from GP practice records based on the eligibility criteria listed in section 4 (approximately 900 per practice). Each GP practice will then contact potentially eligible participants by letter (on site specific headed paper) with an accompanying participant information sheet describing the study in detail. Mailings to these potential participants will contain reply slips and pre−paid, return addressed envelopes for participants to indicate whether, having read the letter and participant information sheet, they are interested in attending the GP surgery for an enrolment visit. Eligibility of respondents will be confirmed by the local PI (GP). Respondents will then be telephoned by the practice staff to confirm eligibility and arrange a screening visit at their GP surgery, at least 24 hours after the phone call, where signed informed consent will be obtained from those agreeing to participate in the trial. It is expected that at least 9% (80 per practice) will participate.

Respondents who do not speak English fluently can bring a relative or friend to interpret when they attend the GP practice for consent and enrolment. This will be explained when the practice nurse telephones to arrange the enrolment visit if the potential participant appears not to understand English adequately. They will also be asked if they wish to be sent the patient information sheet and consent form translated into their language before attending the practice for informed consent and enrolment. Advocacy services for translation and interpreting will be used when required.

### 5.1.3 Enrolment / Screening visit

Informed consent: At the screening visit, the practice nurse will review the inclusion and exclusion criteria with the potential participant to verify eligibility. The nurse will then obtain written informed consent to participate in the trial, after explaining the aims,

methods, anticipated benefits and potential hazards of the study. Written informed consent will include vitamin D assays on blood samples taken during the study, and access to all written and electronic medical records and databases. Participants will also be consented to be flagged for lifelong automatic follow-up for mortality and cancer registration through the NHS Information Centre and NHS Central Register, and for hospital admissions through HES. Consent will also include permission (i) to access GP records to abstract information about infections, prescriptions and the frequency of GP visits made in the year leading up to randomisation and 2 years post randomisation; and (ii) to store their personal data centrally at the Trial Coordinating Centre for the purposes of sending trial medication and trial follow-up. Additional optional informed consent will be obtained for long-term storage of blood samples and unspecified tests (including unspecified genetic analyses) for future research, subject to further ethical approval. During the consent process, the practice nurse will explain that participants are completely free to refuse to enter the study or to withdraw at any time during the study for any reason.

Lifestyle questions, blood pressure and BMI: The online CRF will record details on quality of life, foreign holidays, sunbathing, sunbed use, ethnic origin and use of vitamin supplements, with responses from potentially eligible consented participants being recorded by the practice nurse (or trained delegate) during the enrolment visit. Participants will also have their systolic and diastolic blood pressure, height, weight and waist circumference measured and recorded. Any paper copies of the baseline visit data must be entered onto the online VIDAL app immediately afterwards to allow automated eligibility checks to be performed without delay.

Blood samples: Participants will also be asked to give 12.5 ml of blood (9 ml lithium heparin vacutainer and 3.5 ml SST vacutainer). The 3.5 ml aliquot of blood will be sent by the practice to their local laboratory for corrected serum calcium assay to establish trial eligibility prior to randomisation. The 9 ml aliquot of blood will be sent to the Clinical Trials Service Unit in Oxford for separation of buffy coat, assay of circulating 25(OH)D level (assay performed at the end of the study), and long term storage of buffy coat and plasma (as 3 aliquots) in liquid nitrogen. Subsequent genetic and other analyses, if funded, may include common variants of the vitamin D receptor and vitamin D binding protein genes, alterations such as DNA methylation and telomere length, and more extensive blood chemistry, including serum creatinine at entry and 2 years to assess the effect of vitamin D on renal function.

### 5.1.4 Assessment of Eligibility by Trial Coordinating Centre

The signed informed consent will be retained by the GP practice, and a copy will be sent by the practice to the Trial Coordinating Centre. The Trial Coordinating Centre (and automated VIDAL app) will confirm participant eligibility by (i) checking that the signed informed consent is satisfactorily completed, (ii) checking that the corrected serum calcium result has been entered on the website and is no higher than 2.65 mmol/L and, (iii) checking that the online lifestyle questions have been satisfactorily completed for each participant. Participants will then be telephoned by the Trial Coordinating Centre to confirm their eligibility and check that they are still willing to participate in the trial. The participant will then be randomised. Participants found to be ineligible because of hypercalcaemia (i.e. with a baseline corrected serum calcium > 2.65 mmol/L) will be advised during the phone call that the GP practice will be in contact to discuss whether any treatment is indicated.

### 5.1.5 Randomisation Procedures

**Cluster randomisation of GP practices:**

Before the study starts the 20 participating GP practices will be matched in pairs on region and social mix (deprivation index of the Ward of the GP practice based on the GP practice postcode). They will then be randomised, one to the blinded study and one to the open control study, within each pair by the VIDAL app.

**Individual randomisation of eligible participants within the practices:**

The VIDAL app will generate a random sequence of allocations for each practice balanced in blocks of 6 or 8 so that the next participant's allocation cannot be predicted but succeeding allocations maintain a 1:1 ratio of vitamin D or control within each practice.

The Royal London Hospital pharmacy will hold the medication packs, labelled with a pack code according to Good Manufacturing Practice (GMP) principles. Packs for open control practices will all contain open label vitamin D. Packs for blinded practices will identify the contents as "vitamin $D_3$ oil / placebo oil". The allocated treatment can be determined from the pack code from a master list supplied by the manufacturer. This will be entered onto the online CRF (VIDAL app), but access will be restricted to independent trialists at The Cancer Prevention Trials Unit at Queen Mary University of London who will hold copies for the purpose of unblinding.

After checking eligibility and telephoning the participant to confirm consent (see 5.1.4 above) the Trial Coordinating Centre will instruct the VIDAL app to randomise and to issue the next available pack code for the randomly allocated treatment, unless it is open control (i.e. no treatment). Participants allocated to open control will receive a letter from the Trial Coordinating Centre explaining that they will be re-contacted at 2 years for a follow-up visit and further blood sample. For all other participants (open-label vitamin D, blinded vitamin D, placebo control) the VIDAL app will produce a covering letter addressed to the participant and a prepaid return slip carrying the participant's name, study ID and allocated pack code for the first year of treatment. The VIDAL app will also send an electronic prescription to the clinical CI or a delegated clinician, who will print and sign the prescription and either take it directly to the pharmacy, or return it to the Trial Coordinating Centre. If the latter, the Trial Coordinating Centre will forward signed prescriptions to the pharmacy in batches. A member of the Trial Coordinating Centre staff will attend the pharmacy approximately weekly to send by recorded delivery the covering letter, prepaid return slip and allocated medication pack to the participants. Participants will be asked to confirm receipt and pack code and record the date when their first dose of study oil was taken by posting the return slip in the reply-paid envelope to the Trial Coordinating Centre. Participants will also be asked to record the date each dose of study oil is taken (from month 1 to 12) on the front of the treatment pack. The participant will be telephoned two weeks later by the Trial Coordinating Centre if confirmation of delivery has not been received.

A year later the VIDAL app will issue the next available pack code for the allocated treatment, and the second year's medication will be sent by the same procedure.

Participants will be asked to retain both treatment packs (for year 1 and year 2) and bring them along to the final (2-year) visit to the GP practice for the purpose of returning unused doses of study oil and confirming the date each dose of oil was taken (as recorded by each participant on the outside of the treatment packs).

## 5.2 UNBLINDING

A list of all randomised participants specifying name, sex, date of birth, practice, allocated treatment and corresponding pack code(s), will be accessible from the online CRF (VIDAL app) by independent trialists at The Cancer Prevention Trials Unit at Queen Mary University of London, to enable them to break the code if clinically necessary, but will not be accessible by any VIDAL Trial personnel. Specified staff at The Cancer Prevention Trials Unit at Queen Mary University of London will also be given a copy of the file provided by Nova Laboratories specifying the pack codes and contents (whether vitamin D or placebo) of all treatment packs. As this is a study of a micro-nutrient at a dose below the tolerable upper intake limit, 24-hour unblinding is not necessary.

A GP or the sponsor may request an emergency code break in the following circumstances:

a) In case of a suspected serious adverse reaction (SAR or SUSAR) where knowledge of participant allocation may influence clinical management of a study participant.

b) In any other circumstance in which the GP or clinical CI considers that an emergency code-break is indicated.

# 6. TREATMENTS

## 6.1 TREATMENT ARMS

### 6.1.1 Definition of each IMP

IMP will be manufactured, supplied, labelled (description and pack code) and packaged by Nova Laboratories Ltd. according to principles of GMP. The packs and each bottle will be labelled as "vitamin $D_3$ oil / placebo oil" for the blinded practices and as "vitamin $D_3$ oil" for open control practices. An additional label on the treatment pack will have 12 spaces for the participant to record the date when each monthly dose was taken.

**Active drug**

| | |
|---|---|
| Trade name: | Vigantol® Oil |
| Composition: | 0.5 mg vitamin $D_3$ /ml in Miglyol® 812 vehicle oil |
| ATC code: | A1 1 CC05 (cholecalciferol) |
| Pharmaceutical form: | Oily solution |
| Dosage regimen: | 24 x 5 ml (= 24 x 2.5 mg) over two years |
| Route of administration: | Oral |
| Manufacturer | Merck Serono GmbH<br>Alsfelder Str. 17<br>D-64289 Darmstadt<br>Germany |

**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 $D_3$ in Vigantol® Oil; it is thus identical to Vigantol® Oil in every respect (except for the absence of vitamin $D_3$ ). |
| ATC code: | Not applicable |
| Pharmaceutical form: | Oily solution |
| Dosage regimen: | 24 x 5 ml over two years |
| Route of administration: | Oral |

| | |
|---|---|
| Manufacturer | Caesar & Loretz GmbH<br>Herderstrasse 31<br>Hilden, D-40721<br>Germany |

### 6.1.2 Product sourcing, manufacture and supply

**Authorisation number:** MIA(IMP) 13581

**Authorisation holder:** Nova Laboratories Ltd., Martin House, Gloucester Crescent, Wigston, Leicestershire, LE18 4YL. A named pharmacist in the Royal London Hospital pharmacy will be the recipient.

### 6.1.3 Treatment supply and dose

Blinded (placebo control) practices: Nova Laboratories Ltd. will prepare packs each containing 12 monthly doses of medication labelled as "vitamin $D_3$ oil / placebo oil" and carrying a unique pack code. One will be issued at randomisation, and one year later participants will be sent a second pack containing the same medication. Each pack will contain either 12 bottles each containing 5 ml Vigantol® Oil (oily solution of vitamin $D_3$, concentration 0.5 mg/ml) or 12 bottles, each containing 5 ml Miglyol® 812 oil (placebo). Nova Laboratories Ltd will be responsible for generating a random sequence of pack codes balanced in blocks of 10 to order the labelling of the packs so that succeeding pack codes maintain a 1:1 ratio of vitamin D or placebo. (This is for the convenience of the pharmacy, where packs will be ordered by pack code. Participants will be independently randomised by the VIDAL app – see section 5.1.5 above.) The next unallocated blinded pack code for a participant's allocated treatment will be issued by the VIDAL app, both for the first year of treatment when a participant is randomised, and a year later for the second year.

Open control practices: Nova Laboratories Ltd. will prepare packs each containing 12 monthly doses for participants allocated to vitamin D, labelled as "vitamin $D_3$ oil" and carrying a unique pack code. One will be issued at randomisation, and one year later participants allocated to vitamin D will be sent a second pack. Each pack will contain 12 bottles each containing 5 ml Vigantol® Oil (oily solution of vitamin $D_3$, concentration 0.5 mg/ml). The next unallocated open label pack code will be issued by the VIDAL app, both for the first year of treatment when a participant is randomised to open label vitamin D, and a year later for the second year.

2,000 treatment packs for blinded practices and 1,000 for open control practices will be supplied, providing 25% spare capacity to allow for exceeding the recruitment target and for replacing lost packs.

### 6.1.4 Treatment procedure

IMP will be presented as 5 ml oily solution that can be swallowed. It may be mixed with fruit juice or soaked into bread to aid palatability.

## 6.2 DOSE MODIFICATIONS FOR TOXICITY

### 6.2.1 Dose modification / reduction / delay

Administration of IMP may be delayed if a participant experiences symptoms of hypercalcaemia, pending investigation (see section 8). Doses of IMP may be administered up to two weeks before or after the scheduled date of administration.

Administration of IMP will be discontinued in the following circumstances:

1. If a participant develops hypercalcaemia confirmed on two blood samples as in section 8
2. If a participant develops a condition which requires treatment with a prohibited concomitant therapy (see section 4.3)
3. If a participant develops a condition which, in the judgement of an investigator, adversely affects that participant's safety, compliance or ability to complete evaluations
4. If an investigator concludes that this course of action is in the participant's best interests.

Participants who discontinue the study drug for any reason should not be considered to have withdrawn from the study, and will be invited to attend the practice for the final assessment and blood sample at 24 months.

### 6.2.2 Toxicity profiles

The toxicity profile of vitamin $D_3$ is reviewed in the summary of product characteristics (SmPC). This will be reviewed annually and updated if relevant new data come to light.

## 6.3 PREMEDICATION

Not applicable.

## 6.4 INTERACTION WITH OTHER DRUGS

Individuals taking carbamazepine, phenobarbital, phenytoin, primidone, digoxin, or the combination of a thiazide diuretic (e.g. bendrofluazide, metolazone) with a calcium supplement will not be eligible to participate in the study.

## 6.5 DISPENSING AND ACCOUNTABILITY

### 6.5.1 Prescription of IMP

Trial delegation logs will specify the names of physicians authorised to prescribe IMP for this study.

### 6.5.2 Preparation and Administration of IMP

IMP will be prepared by Nova Laboratories Ltd, and shipped to the Royal London Hospital pharmacy. Storage procedures are outlined in the SmPC. The Trial Coordinating Centre will liaise with the Royal London Hospital Pharmacy to send by recorded delivery a covering letter, prepaid reply slip and a twelve month (12 bottle) supply of IMP to the participant, recording the participant details and pack code. Participants will be asked to confirm receipt, confirm the pack code and record the date the first dose of study medication was taken to the Trial Coordinating Centre by returning the prepaid response. Participants will also be asked to record the date each dose of study oil is taken (from month 1 to 12) on the front of the treatment pack. The participant will be telephoned two weeks later by the Trial Coordinating Centre if confirmation of delivery has not been received.

The same procedures will be followed when the second year's medication is sent. When a participant mislays their medication the procedure is similar, except (1) the letter to the participant will state that it is a replacement, and (2) the treatment pack will only contain the bottle(s) of IMP required to complete the current year's treatment.

### 6.5.3 Labelling of IMP

IMP for open control GP practices will all contain open label Vigantol oil (vitamin D). In the double-blind placebo-controlled GP practices, with neither participant nor investigator being aware of a participant's allocation, active and placebo IMP will have identical packaging, labelling and appearance. The 12 bottles in each treatment pack will be labelled month 1, month 2 etc, and participants will record the date on which each monthly dose was taken on a label on the front of the treatment pack.

# 7. SAFETY REPORTING

## 7.1 DEFINITIONS

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

**Adverse Reaction (AR):** all untoward and unintended responses to an IMP related to any dose administered. *All AEs judged as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means that there is evidence to suggest a possible, probable or definite causal relationship (see section 7.2 below).*

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

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

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

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

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

## 7.2 ASSESSING CAUSALITY

The assignment of causality should be made by the local Principal Investigator responsible for the care of the participant (the GP) using the definitions in the table below. Serious adverse events and reactions (whether expected or not) will subsequently be reviewed by the Sponsor / Clinical Chief Investigator.

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

## 7.3 RECORDING AND REPORTING PROCEDURES

**Recording** refers to the detection and recording of adverse events; **reporting** refers to the statutory notification by the sponsor to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Main Research Ethics Committee (MREC).

### 7.3.1 Recording ARs, SARs, SUSARs and other SAEs

All serious adverse events and all adverse reactions will be detected by three procedures:

1. The GP or practice nurse records a serious adverse event or an adverse reaction via the online CRF (VIDAL app) as a result of routine clinical contact with the participant.
2. Hospital admissions, cancer diagnoses and deaths will be identified automatically through the Hospital Episodes Statistics (HES) system and the NHS Information Centre.
3. Hospital admissions for at least one night will also be independently ascertained from all participants except those allocated to open control through their 3-monthly follow-up replies.

In view of the low-risk nature of vitamin D supplementation, only serious adverse events (whether or not causally related, i.e. SAE, SAR or SUSAR) and suspected non-serious adverse reactions (potentially causally related non-serious event, ie AR) will be recorded

by the GP or practice nurse in the safety section of the online CRF (VIDAL app). The criterion for recording an adverse reaction is that there is a reasonable possibility (ie evidence to suggest) that the IMP caused it. Non-serious adverse events deemed unlikely to have a causal relation to the IMP used in this study should not be recorded on the online CRF. Pre-planned hospitalisations (i.e. planned prior to randomisation) and elective treatments of a pre-existing condition do not need to be reported.

Depending on the nature of the reaction or event, the recording and reporting procedures below should be followed. Any questions concerning the reporting of SAEs and ARs should be directed to the Trial Coordinating Centre in the first instance. A flowchart is given in appendix 2 to aid with safety reporting.

### 7.3.2 Non-serious Adverse Reactions (ARs)

Non-serious adverse reactions (i.e. potentially causally-related adverse events), whether expected or not, should be recorded by the GP practice in the adverse reaction section of the online CRF (VIDAL app). The GP can use the table in section 7.2 above to aid in assessing whether an adverse event should be classed as an adverse reaction: events classed as definitely, probably or possibly related to the IMP should be classed as adverse reactions. The Trial Coordinating Centre will receive automatic notification of all new entries through the online CRF. Non-serious adverse reactions do not require any further reporting.

### 7.3.3 Serious Adverse Reactions (SARs and SUSARs) and other Serious Adverse Events (SAEs)

All Serious Adverse Events (SAEs), including Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs), should be recorded in the SAE section of the online CRF (VIDAL app) within 24 hours of the GP practice becoming aware of the event. The Trial Coordinating Centre will inform the Clinical CI of all such notifications.

The online SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). Additional information should be added to the online record within 5 days if the event/reaction has not resolved at the time of initial reporting. However, hospitalisations for elective treatment of a pre-existing condition do not need to be reported as SAEs.

SAEs and SARs will be included in the annual development safety update reports (DSURs), but do not require expedited reporting.

### 7.3.4 Expedited reporting of SUSARs

SUSARs require expedited reporting by the Trial Coordination Centre via the LSHTM study sponsor to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Main Research Ethics Committee (MREC) according to the following timelines:

(i) Fatal and life-threatening events within 7 days of notification
(ii) Non-life threatening events within 15 days of notification.

All SUSARs occurring throughout the study will be recorded in the annual DSUR, which will be sent to MHRA, the MREC and the sponsor.

**Contact details for reporting SAEs/SARs/SUSARs in the event of failure of the online CRF:**

**Tel: 020 7927 2860 (Mon to Fri 09.00 – 17.00)**
**E-mail: VIDAL@LSHTM.AC.UK**

# 8. ASSESSMENT AND FOLLOW-UP

All study participants allocated to active treatment or placebo will be contacted at least once a month post-randomisation as outlined below. Those on open control will be contacted only at 24 months. The online CRF (VIDAL app) will send weekly reminders to each GP practice, listing all randomised participants with scheduled or overdue quarterly contact. The Trial Coordinating Centre will monitor adverse events, compliance and change of address online and telephone practices to give appropriate reminders.

**Automated phone call, e-mail or text message every month from months 1 to 24:**

All participants except those randomised to open control (no treatment) will be reminded to take their study medication every month by automated phone call, e-mail or text message generated by the online VIDAL app. No reply will be required from participants.

**E-mail or letter follow up at months 3, 6, 9, 12, 15, 18, 21 and 24:**

All participants except those randomised to open control (no treatment) will be contacted quarterly by e-mail or post (participant choice of medium) by the GP practice requesting a short reply by the same medium to record the dates on which the last 3 doses of study medication were taken or report reasons for non-compliance, to report any/no planned change of address, and to report any hospital admissions. The 3-monthly follow-up includes a reminder for participants to contact their GP if they are experiencing ongoing symptoms of hypercalcaemia (persistent nausea, vomiting, thirst, passing excessive amounts of urine or feeling generally unwell*).* All non-responders will be sent one reminder 3 weeks later and then telephoned by the GP practice staff if they have still not replied. Electronic responses will be recorded onto the VIDAL app by participants via a web-link supplied in the e-mail. Postal responses will be entered by the practice nurse on to the VIDAL app, and reminders will automatically be generated for outstanding items.

**GP practice visit at month 24:**

A repeat blood sample (9 ml lithium heparin vacutainer), blood pressure measurement, and responses to the same lifestyle questions will be obtained 24 months after randomisation for all 1600 participants to quantify differences in vitamin D status (circulating 25(OH)D level) between the intervention and control groups in the blinded and open-label studies.

Each GP practice will also examine all treatment packs brought in at the 2-year visit, cross-checking unused study oil bottles and the study oil dose dates recorded by each participant on the outside of the treatment pack against the compliance information supplied in the quarterly follow-up.

Summaries of GP records for all 1600 participants will also be extracted by the practice staff to obtain unbiased information about GP visits, prescriptions and infections over the preceding 3 years (1 year pre-randomisation and 2 years post-randomisation).

**Hypercalcaemia**

If a participant reports symptoms of hypercalcaemia during the study, a blood test to check for hypercalcaemia will be performed. If this initial test reveals hypercalcaemia, a repeat test will be performed. If the second test confirms hypercalcaemia, all further doses of IMP will be withheld, and appropriate management of hypercalcaemia will be instituted if necessary. IMP will be discontinued for any participant who develops hypercalcaemia confirmed on two blood tests during participation in the study.

**Automated follow-up**

All participants will be flagged for lifelong follow-up through national registers for death and cancer registration and tracing by NHS number linkage through the Hospital Episodes Statistics (HES) system for hospital admissions and diagnoses. The logistics of this flagging and linkage will be assessed in the feasibility study, but there will be too few such events for useful analysis in the feasibility study due to limited size and short follow-up.

### 8.1 LOSS TO FOLLOW-UP

We expect the level of loss to follow-up (failure to contact non-responders by post or telephone) to be low. All participants will be consented at enrolment for flagging for lifelong follow-up through national registers for death and cancer registration and tracing by NHS number linkage through the Hospital Episodes Statistics (HES) system for hospital admissions and diagnoses.

### 8.2 TRIAL CLOSURE

The end of the study will be defined as the date of the final study visit of the final participant undergoing follow-up.

## 9. STATISTICS AND DATA ANALYSIS

All data required for analysing compliance and outcomes will be available from the online CRF (VIDAL app), together with the 25(OH)D results on the baseline and 2-year blood samples, and data extracted from GP notes or reported through flagging for hospital admissions (HES), cancer incidence and mortality.

### 9.1 SAMPLE SIZE

We will recruit 1,600 participants aged 65-84 through 20 GP practices (400 on open label vitamin D v. 400 open controls; 400 blinded to vitamin D v. 400 placebo). Our target is to randomise an average of 80 participants aged 65-84 per GP practice (at least 9% participation rate). It will be clear within the first six months if recruitment in some practices is falling well below this target. If this occurs, recruitment in other practices will continue after 80 participants have been randomized to achieve the overall target of 1,600 participants.

### 9.2 POWER

The main purpose of the feasibility study is to pilot the organisational procedures for the main trial, to demonstrate adequate recruitment, and to prepare us for any unexpected difficulties in running it. All eligible patients in each practice will therefore be invited, as would be required in the main trial. In addition, the number of practices involved must be large enough for them to be representative of the diversity of practices that may participate in the main trial, so that average recruitment (the proportion of those invited who are randomized) is a reliable estimate of what would be achieved in the main trial.

The proposed feasibility study (10 practices with placebo control and 10 with open control, with 80 participants per practice) also has adequate power to show a difference in recruitment depending on the design (open-label v. blinded).

The plan is to make comparisons between blinded and open control designs in 10 pairs of practices matched on distribution of socio-economic status, with a nominal two-sided alpha-level of 5%. Each practice will recruit approximately 80 participants. To estimate the power we simulated the number of patients that one would need to approach in each practice in order to recruit 80 participants (negative-binomial). We assumed the design would change the mean participation rate from 10% (range 2.5% to 17.5%) to 15% (5.7% to 24.3%). Under these assumptions the power to detect this difference would be 92%. (If there were no heterogeneity between practices, the overall recruitment rate would be estimated very precisely, e.g. 9% with standard error 0.2%.)

Additionally, to detect a difference of 10% in any binary outcome the trial will have (at least) 80% power (using a nominal 5% significance level) for any within practice comparison such as vitamin D v. placebo (400 per arm), and 70% power for any between practice comparison such as placebo v. open control (sign test with 10 pairs of practices; power = 70% for 0.45 v. 0.55, and 88% for 0.10 v. 0.20). The outcome might be reporting a respiratory infection (15% versus 25%) or compliance (85% versus 95%).

## 9.3 STATISTICAL ANALYSES

### 9.3.1 Main clinical analyses

The main analyses will be the matched-pair comparison of recruitment and overall compliance rates between blinded and open control designs. Details of additional vitamin D supplement use will be recorded at entry, and retrospectively at the 2-year final visit. Failure to report taking at least 19 doses of allocated IMP or to attend the 2-year final visit are included in the definition of non-compliance, so there will be no missing data for the main analyses.

Change in blood level of 25(OH)D from entry to exit will be analysed in relation to self-reported compliance. The effect of treatment on 25(OH)D level, both overall by allocated treatment and in compliant participants, will also be analysed in relation to the pre-treatment 25(OH)D level.

The principal economic issues in the feasibility study will be the overall additional trial costs in blinded practices, to be weighed against the advantages and disadvantages of placebo control in relation to possible bias in self-reporting of minor conditions and suspected side-effects, treatment compliance, and self-medication with vitamin D by controls. The feasibility of collecting appropriate resource use data will also be assessed, specifically the viability of linking HES data to NHS reference costs using Healthcare Resource Group (HRG) information in order to calculate NHS costs, and using participants' medical records to obtain information on the use of primary care services.

### 9.3.2 Subgroup analyses

25(OH)D level (pre-treatment, and change after 2 years of treatment) will be analysed in sub-groups of 5-year age group and sex. The change in 25(OH)D level will also be analysed in relation to pre-treatment level, adjusted for the negative bias in this correlation. The overall recruitment rate among all registered patients in each practice will also be analysed in sub-groups of age and sex. (A tabulation by 5-year age group and sex of all registered patients will be obtained from each practice for this purpose.)

All analyses will be repeated in subgroups based on pre-treatment blood 25(OH)D level.

### 9.3.3 Interim reports

A Data Monitoring Committee will be convened (see section 12.1). Interim safety and recruitment analyses will be conducted annually for this feasibility study. The Trial Management Group will collate and clean data detailing all known serious adverse events to date in trial participants.. The trial statistician will then conduct an analysis to compare the incidence of SAEs between intervention and control groups, for review by the DMC. If there is a significant difference ($p<0.01$) in the incidence of fatal or life threatening adverse events an emergency meeting of the DMC will be convened and the Sponsor and Ethics Committee will be consulted to decide whether the trial should be stopped.

## 9.4 RECORD RETENTION AND ARCHIVING

Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

# 10. MONITORING

## 10.1 RISK ASSESSMENT

Because the dose administered (3,300 IU/day equivalent) will give less than the tolerable upper intake limit of 4,000 IU per day for vitamin D even in participants taking supplements delivering almost twice the UK RDA of 400 IU vitamin D per day (Institute of Medicine, 2011) this study should be considered low risk. Risk to study participants is further reduced by the effective exclusion of individuals with potential vitamin D hypersensitivity by eligibility criteria excluding individuals with baseline corrected calcium > 2.65 mmol/L, as well as those with known hyperparathyroidism or sarcoidosis. In view of the low risk nature of the study and the fact that most of the source data are collected online and immediately available to the Trial Coordinating Centre, virtually all monitoring will be done centrally by the Trial Coordinating Centre as outlined in sections 10.2 and 10.3 below.

## 10.2 MONITORING AT TRIAL COORDINATING CENTRE

Each GP practice will update the online CRF (VIDAL app) with details of new participants as they are enrolled into the trial (see section 5). The GP practice will also send copies of each participant's signed informed consent to the Trial Coordinating Centre. The Trial Coordinating Centre (and automated VIDAL app) will then confirm participant eligibility by (i) checking that the signed informed consent is satisfactorily completed, (ii) checking that the corrected serum calcium result has been entered on the website and is no higher than 2.65 mmol/L, and (iii) checking that the online lifestyle questions have been satisfactorily completed for each participant. Participants will then be contacted by the Trial Coordinating Centre to check that they are still willing to participate in the trial before being randomised as per section 5.1.5 of this protocol.

The online CRF (VIDAL app) will send weekly reminders to each GP practice, listing all randomised participants with scheduled or overdue quarterly follow-ups. The Trial Coordinating Centre will monitor adverse events, compliance and change of address online and telephone practices to give appropriate reminders. Copies of all postal communications and paper versions of baseline visit data from 10% of participants to each

GP practice will also be posted to the Trial Coordinating Centre for quality control purposes.

Following randomisation, the Trial Coordinating Centre staff will check, log on the VIDAL app, and file all returns received by post from participants confirming that they have received their correct medication pack (12 bottles labelled by month) and recording the date when their first dose was taken. Non-responders will be telephoned within 2 weeks to check receipt of medication. This process will be repeated when the treatment pack for the second year is sent. Following the second (2-year) visit to the GP practice, the Trial Coordinating Centre will monitor the VIDAL app to confirm that the repeat blood test was taken and the lifestyle questions were satisfactorily completed. Participating GP practices will also check the used treatment packs and unused study oil (brought in to the practice by each participant at their final visit). The practice will cross-check the study oil dose dates supplied on the front of the treatment packs against the dates provided in the 3-monthly follow-ups for consistency, querying any discrepancies with the patient. In addition, practices will also cross-check unused doses of study oil brought back by each participant against the quarterly follow-up compliance information.

All tracking and CRF data will be entered onto the VIDAL app as described in section 5. Data quality will be audited according to GCP guidelines, and an audit trail will be maintained of any change or correction to the electronic database. Data will be generated, recorded and reported in compliance with the protocol and with Good Clinical Practice.

### 10.3 MONITORING AT LOCAL SITE

This is a low risk study with minimal source data to verify. Most data obtained in the GP practices will be recorded directly onto the online CRF (VIDAL app), including email replies to 3-monthly follow-ups, which will be routed directly to the VIDAL App. Additional source data documents that will be retained at the GP practice will be signed consent, paper versions of the baseline visit data and communications from participants (postal, and copies of any e-mails), and from the GP practice to the Trial Coordinating Centre. Copies of all signed consent forms and the paper versions of baseline visit data and postal and e-mail communications from a random sample of participants, will be forwarded to the Trial Coordinating Centre for central monitoring purposes. The distribution of blood calcium results and SAEs will also be monitored at each site for unusual patterns. Following the initial training of practice staff from each site to establish and confirm procedures, monitoring at local sites will only take place if issues are identified through the central monitoring process.

## 11. REGULATORY ISSUES

### 11.1 CLINICAL TRIAL AUTHORISATION (CTA)

The trial will be conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations and subsequent amendments. An application for Clinical Trials Authorisation from the MHRA is approved (reference: 17072/0006/001-0001).

### 11.2 ETHICS APPROVAL

The Trial Coordinating Centre has obtained approval from the London - Chelsea Research Ethics Committee (REC reference: 11/LO/1989). The study must also be submitted for Site Specific Assessment (SSA) at each participating Primary Care Trust (PCT). The study will be conducted in accordance with the recommendations for physicians involved

in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

### 11.3 CONSENT

Consent to enter the study will be sought by the practice nurse from each participant only after an information leaflet has been sent and a minimum of 24 hours allowed for consideration, and a full explanation has been given at the visit to the GP practice. Signed participant consent will then be obtained, but participants will not be randomised until a subsequent telephone call from the Trial Coordinating Centre to confirm that they are still happy to participate. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. In these cases the participants remain within the study for the purposes of follow-up and data analysis, unless permission for this is specifically withdrawn.

### 11.4 CONFIDENTIALITY

Participants' identification data will be required for the registration process, for despatching the drugs, for follow-up, and for flagging purposes. The Trial Coordinating Centre will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

### 11.5 INDEMNITY

London School of Hygiene & Tropical Medicine holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

### 11.6 SPONSOR

London School of Hygiene & Tropical Medicine will act as the sponsor for this study. Delegated responsibilities will be assigned locally.

### 11.7 FUNDING

The NIHR Health Technology Assessment programme is funding this study.

### 11.8 AUDITS AND INSPECTIONS

The study may be subject to audit by the London School of Hygiene & Tropical Medicine under their remit as sponsor, the Trial Coordinating Centre and other regulatory bodies to ensure adherence to the protocol, GCP and all applicable regulatory requirements.

### 11.9 LEAD PRIMARY CARE TRUST (PCT) AND COMPREHENSIVE RESEARCH NETWORK (CLRN)

The lead Primary Care Trust (PCT) for this study is Camden PCT and the lead Comprehensive Local Research Network (CLRN) is the Central and East London CLRN.

## 12. TRIAL MANAGEMENT

The investigators and Trial Coordinator will constitute the Trial Management Group (TMG), which will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be co-ordinated through the Trial Coordinating Centre at the London School of Hygiene & Tropical Medicine. The Cancer Prevention Trials Unit at

Queen Mary University of London will provide a web-based system (the VIDAL app) to capture data electronically, incorporating a trial database and a system to carry out randomisations (see section 5.1.1). The specifications of the system will be defined by the Trial Coordinating Centre at the London School of Hygiene and Tropical Medicine and a service level agreement will be signed between the London School of Hygiene and Tropical Medicine and Queen Mary University of London to that effect.

## 12.1 DATA MONITORING COMMITTEE

a) A data monitoring committee (DMC), which will include an independent statistician, will be convened for the trial by the chairman (Professor Tim Peto, Oxford University) and will meet at least annually. The chairman of the DMC will keep a record of DMC communications and activities. The central responsibility of this DMC will be to make recommendations to the Sponsor and the Trial Management Group on the conduct of this trial, based on results of the monitoring procedures described above. Such recommendations could include continuing or terminating the trial, or modifying its protocol. Any such modifications should not violate the concepts behind the original study protocol. If changes in the study conduct are recommended by this DMC, sufficient information should be provided to allow the Sponsor and Trial Management Group to decide whether and how to implement them.

### 12.1.1 Maintenance of trial treatment randomisation codes and procedures for breaking codes

Nova Laboratories Ltd will provide a list of all treatment packs giving the pack codes and contents (whether vitamin D or placebo) to independent trialists at The Cancer Prevention Trials Unit at Queen Mary University of London, who will also have web access to a list of all randomised participants and their allocated treatments (see section 5.2). Staff at The Cancer Prevention Trials Unit at Queen Mary University of London may unblind a participant's allocation at the request of a GP according to the VIDAL Trial Standard Operating Procedure for emergency code breaking.

### 12.1.2 Monitoring procedures

The DMC will review accumulating data in an unblinded fashion in order to monitor safety, efficacy and quality of study conduct.

(a) Safety monitoring

At least annually, the Trial Management Group will collate and clean data detailing all known serious adverse events to date in trial participants, together with an updated HES download of all hospital admissions, and send these data to an independent statistician. The statistician will then conduct an analysis to compare the incidence of SAEs between intervention and control groups for review by the DMC, and the DMC will inform the Trial Management Group whether new findings for the subjects of the trial have changed the benefit / risk ratio of conducting the trial.

(b) Monitoring quality of study conduct

If the DMC observes problems with the study conduct (e.g. with respect to protocol adherence, recruitment or participant withdrawal), it should consider making recommendations to the investigators and the sponsor to improve the quality of the study.

### 12.1.3 Declaration of possible conflicts of interest of DMC members

The members of the DMC will have no involvements that might raise the question of bias in their reports to the sponsor or investigators in this study. Specifically, they will have no financial interest in the outcome of this study, and they will not be authors on publications arising from this study.

### 12.1.4 Frequency and format of DMC meetings

It is anticipated that the DMC will be able to conduct all of its business by email and telephone call, rendering a physical meeting between members, investigators and representatives of the sponsor unnecessary. The DMC will review safety analyses at least annually.

### 12.1.5 Communication Procedures

The DMC will communicate results of safety and efficacy analyses by email to the Trial Management Group. When a GP requests that a participant be unblinded, the Cancer Prevention Trials Unit at Queen Mary University of London will communicate directly with that GP by email or by telephone.

### 12.1.6 Documentation of the DMC activities

The DMC will keep a record of any safety and efficacy analyses performed, and the Cancer Prevention Trials Unit at Queen Mary University of London will keep a record of the circumstances in which it unblinded any participant's allocation.

## 13. PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Trial Coordinating Centre.

# 14. REFERENCES


**AHN, J., PETERS, U., ALBANES, D., PURDUE, M. P., ABNET, C. C., CHATTERJEE, N., HORST, R. L., HOLLIS, B. W., HUANG, W. Y., SHIKANY, J. M. & HAYES, R. B. 2008. Serum vitamin D concentration and prostate cancer risk: a nested case-control study. *J Natl Cancer Inst,* 100, 796-804.**

**AUTIER, P. & GANDINI, S. 2007. Vitamin D supplementation and total mortality - A meta-analysis of randomized controlled trials. *Archives of Internal Medicine,* 167, 1730-1737.**

**BISCHOFF-FERRARI, H. A., DAWSON-HUGHES, B., WILLETT, W. C., STAEHELIN, H. B., BAZEMORE, M. G., ZEE, R. Y. & WONG, J. B. 2004. Effect of vitamin D on falls - A meta-analysis. *Jama-Journal of the American Medical Association,* 291, 1999-2006.**

**BISCHOFF-FERRARI, H. A., GIOVANNUCCI, E., WILLETT, W. C., DIETRICH, T. & DAWSON-HUGHES, B. 2006. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes (vol 84, pg 18, 2006). *American Journal of Clinical Nutrition,* 84, 1253-1253.**

**BISCHOFF-FERRARI, H. A., SHAO, A., DAWSON-HUGHES, B., HATHCOCK, J., GIOVANNUCCI, E. & WILLETT, W. C. 2010. Benefit-risk assessment of vitamin D supplementation. *Osteoporos Int,* 21, 1121-32.**

**BISCHOFF-FERRARI, H. A., WILLETT, W. C., WONG, J. B., GIOVANNUCCI, E., DIETRICH, T. & DAWSON-HUGHES, B. 2005. Fracture prevention with vitamin D supplementation - A meta-analysis of randomized controlled trials. *Jama-Journal of the American Medical Association,* 293, 2257-2264.**

**BOUILLON, R., MOODY, T., SPORN, M., BARRETT, J. C. & NORMAN, A. W. 2005. NIH deltanoids meeting on Vitamin D and cancer conclusion and strategic options. *Journal of Steroid Biochemistry and Molecular Biology,* 97, 3-5.**

**BUSHINSKY, D. A. & MONK, R. D. 1998. Calcium. *Lancet,* 352, 306-311.**

**CANNELL, J. J., VIETH, R., UMHAU, J. C., HOLICK, M. F., GRANT, W. B., MADRONICH, S., GARLAND, C. F. & GIOVANNUCCI, E. 2006. Epidemic influenza and vitamin D. *Epidemiology and Infection,* 134, 1129-1140.**

**GIOVANNUCCI, E. 2005. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). *Cancer Causes Control,* 16, 83-95.**

**GIOVANNUCCI, E. 2009. Vitamin D and cardiovascular disease. *Curr Atheroscler Rep,* 11, 456-61.**

**GIOVANNUCCI, E., LIU, Y., HOLLIS, B. W. & RIMM, E. B. 2008. 25-hydroxyvitamin D and risk of myocardial infarction in men - A prospective study. *Archives of Internal Medicine,* 168, 1174-1180.**

**GIOVANNUCCI, E., LIU, Y., RIMM, E. B., HOLLIS, B. W., FUCHS, C. S., STAMPFER, M. J. & WILLETT, W. C. 2006. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst,* 98, 451-9.**

**GORHAM, E. D., GARLAND, C. F., GARLAND, F. C., GRANT, W. B., MOHR, S. B., LIPKIN, M., NEWMARK, H. L., GIOVANNUCCI, E., WEI, M. & HOLICK, M. F. 2007. Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis. *Am J Prev Med,* 32, 210-6.**

**GREENWALD, P., ANDERSON, D., NELSON, S. A. & TAYLOR, P. R. 2007. Clinical trials of vitamin and mineral supplements for cancer prevention'. *American Journal of Clinical Nutrition,* 85, 314S-317S.**

**HATHCOCK, J. N., SHAO, A., VIETH, R. & HEANEY, R. 2007. Risk assessment for vitamin D. *American Journal of Clinical Nutrition,* 85, 6-18.**

**HIRANI, V. & PRIMATESTA, P. 2005. Vitamin D concentrations among people aged 65 years and over living in private households and institutions in England: population survey. *Age and Ageing,* 34, 485-491.**

**HOLICK, M. F. 2007. Vitamin D deficiency. *N Engl J Med,* 357, 266-81.**

**IARC WORKING GROUP ON VITAMIN D 2008. Vitamin D and cancer. *WHO Press*.**

**INSTITUTE OF MEDICINE 2011. Dietary reference intakes for calcium and vitamin D.**

**JENAB, M., BUENO-DE-MESQUITA, H. B., FERRARI, P., VAN DUIJNHOVEN, F. J., NORAT, T., PISCHON, T., JANSEN, E. H., SLIMANI, N., BYRNES, G., RINALDI, S., TJONNELAND, A., OLSEN, A., OVERVAD, K., BOUTRON-RUAULT, M. C., CLAVEL-CHAPELON, F., MOROIS, S., KAAKS, R., LINSEISEN, J., BOEING, H., BERGMANN, M. M., TRICHOPOULOU, A., MISIRLI, G., TRICHOPOULOS, D., BERRINO, F., VINEIS, P., PANICO, S., PALLI, D., TUMINO, R., ROS, M. M., VAN GILS, C. H., PEETERS, P. H., BRUSTAD, M., LUND, E., TORMO, M. J., ARDANAZ, E., RODRIGUEZ, L., SANCHEZ, M. J., DORRONSORO, M., GONZALEZ, C. A., HALLMANS, G., PALMQVIST, R., RODDAM, A., KEY, T. J., KHAW, K. T., AUTIER, P., HAINAUT, P. & RIBOLI, E. 2010. Association between pre-diagnostic circulating vitamin D concentration and risk of colorectal cancer in European populations:a nested case-control study. *BMJ,* 340, b5500.**

**LIM, H. S., ROYCHOUDHURI, R., PETO, J., SCHWARTZ, G., BAADE, P. & MOLLER, H. 2006. Cancer survival is dependent on season of diagnosis and sunlight exposure. *International Journal of Cancer,* 119, 1530-1536.**

**MARTINEAU, A. R., WILKINSON, R. J., WILKINSON, K. A., NEWTON, S. M., KAMPMANN, B., HALL, B. M., PACKE, G. E., DAVIDSON, R. N., ELDRIDGE, S. M., MAUNSELL, Z. J., RAINBOW, S. J., BERRY, J. L. & GRIFFITHS, C. J. 2007. A single dose of vitamin D enhances immunity to mycobacteria. *Am J Respir Crit Care Med,* 176, 208-13.**

**RHODES, L. E., WEBB, A. R., FRASER, H. I., KIFT, R., DURKIN, M. T., ALLAN, D., O'BRIEN, S. J., VAIL, A. & BERRY, J. L. 2010. Recommended Summer Sunlight Exposure Levels Can Produce Sufficient (>= 20 ng ml(-1)) but Not the Proposed Optimal (>= 32 ng ml(-1)) 25(OH)D Levels at UK Latitudes. *Journal of Investigative Dermatology,* 130, 1411-1418.**

**SHARMA, O. P. 2000. Hypercalcemia in granulomatous disorders: a clinical review. *Curr Opin Pulm Med,* 6, 442-7.**

**STOLZENBERG-SOLOMON, R. Z., JACOBS, E. J., ARSLAN, A. A., QI, D., PATEL, A. V., HELZLSOUER, K. J., WEINSTEIN, S. J., MCCULLOUGH, M. L., PURDUE, M. P., SHU, X. O., SNYDER, K., VIRTAMO, J., WILKINS, L. R., YU, K., ZELENIUCH-JACQUOTTE, A., ZHENG, W., ALBANES, D., CAI, Q. Y., HARVEY, C., HAYES, R., CLIPP, S., HORST, R. L., IRISH, L., KOENIG, K., LE MARCHAND, L. & KOLONEL, L. N. 2010. Circulating 25-Hydroxyvitamin D and Risk of Pancreatic Cancer. *American Journal of Epidemiology,* 172, 81-93.**

**TRIVEDI, D. P., DOLL, R. & KHAW, K. T. 2003. Effect of four monthly oral vitamin D-3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *British Medical Journal,* 326, 469-472.**

**VIETH, R. 1999. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *American Journal of Clinical Nutrition,* 69, 842-856.**

# APPENDIX 1: SUMMARY OF INVESTIGATIONS, TREATMENT AND ASSESSMENTS

| | Visit 1<br>-4 weeks | Telephone Call<br>-1 week | IMP sent<br>0 Weeks | Post or email<br>Month 3 | Post or email<br>Month 6 | Post or email<br>Month 9 | Post or email<br>Month 12 | IMP sent<br>Month 12 | Post or email<br>Month 15 | Post or email<br>Month 18 | Post or email<br>Month 21 | Post or email<br>Month 24 | Visit 2<br>Month 24 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Sign consent forms** | X | | | | | | | | | | | | |
| **Eligibility checked** | X | | | | | | | | | | | | |
| **Give personal/medical details** | X | | | | | | | | | | | | X |
| **Complete online CRF** | X | | | | | | | | | | | | X |
| **Blood pressure, waist circumference, height and weight measured** | X | | | | | | | | | | | | X |
| **Give blood sample** | X | | | | | | | | | | | | X |
| **Confirm eligibility and willingness to be randomised** | | X | | | | | | | | | | | |
| **Randomisation, IMP sent, (unless open control), medication receipt confirmed** | | | X | | | | | X | | | | | |
| **Monthly reminder to take study medication** | | | **Automated phone call, e-mail or text every month from month 1 - 24 to remind participants to take their study medication** | | | | | | | | | | |
| **Take study medication** | | | **Study medication taken every month from when it is received at week 0 and month 12 (24 times in total)** | | | | | | | | | | |
| **Confirm medication taken** | | | | X | X | X | X | X | X | X | X | X | X |


VIDAL

# APPENDIX 2: FLOWCHART FOR SAFETY REPORTING