Clinical trial results:
Feasibility study including a double blind (C)controlled study and an open label (C) controlled study for a larger randomised trial measuring the effect of oral vitamin D (I) on morbidity and mortality (O) in men and women aged 65-84 (P)

Summary

EudraCT number	2011-003699-34
Trial protocol	GB
Global end of trial date	22 March 2017

Results information

Result version number	v1 (current)
This version publication date	24 October 2019
First version publication date	24 October 2019

Trial information

Trial identification

Sponsor protocol code	QA343

Additional study identifiers

ISRCTN number	ISRCTN46328341
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	London School of Hygiene & Tropical Medicine
Sponsor organisation address	Keppel Street, London`, United Kingdom, WC1E 7HT
Public contact	Christine Rake, London School of Hygine & Tropical Medicine, CHRISTINE.RAKE@LSHTM.AC.UK
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 March 2017
Global end of trial reached?	Yes
Global end of trial date	22 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary aim of the feasibility study was to establish the procedures required to conduct the main trial and to determine the time taken to recruit and randomise 1,600 participants aged 65-84. The aims of the cluster randomisation of practices were to:
i) compare response (number randomised/number invited) and attrition (attendance at 2-year final visit) in blinded and open practices,
ii) compare allocated treatment compliance in participants on open label vitamin D and blinded participants, and
iii) compare contamination rates (the proportion taking > 400IU/day of vitamin D), particularly between open untreated controls and blinded participants.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. All subjects provided written informed consent before undergoing any study-related procedures. The study was reviewed and approved by a Research Ethics Committee (REC) and the Medicines & Healthcare products Regulatory Agency (MHRA). The principle discomfort of the study arose from giving blood samples; we sought to minimize this by employing GP research nurses who were competent phlebotomists. The principle risk (estimated at less than a 1 in 400 chance) arose from vitamin D−induced hypercalcaemia; we sought to minimize this by excluding those with elevated blood calcium level before randomisation; by excluding patients known to be at potentially increased risk of developing hypercalcaemia after vitamin D supplementation (e.g. those with hyperparathyroidism, sarcoidosis or baseline hypercalcaemia); by giving a dose of vitamin D that was sufficient to correct deficiency, but not sufficient to induce hypervitaminosis D; and by monitoring for hypercalcaemia post−randomisation, with unblinded review by data monitoring committee of accumulating data relating to adverse reactions. The proposed regimen of 100,000 IU vitamin D3 monthly (equivalent to 3300 IU per day) represented a dose that was at extremely low risk of inducing adverse effects, but which was sufficient to promote a clinical benefit.

Background therapy:

N/A

Evidence for comparator:

There is strong but not conclusive evidence that serum 25-hydroxyvitamin D (25(OH)D) should be at least 75 nmol/L for optimal health. Neither the vitamin D reference nutrient intake (RNI) (400IU/day) nor increased consumption of foods containing vitamin D will raise the majority of the UK population aged over 65 years above this level. Plausible effects of vitamin D deficiency include premature death and increased risks of pneumonia, cardiovascular disease, some cancers, dementia, falls and fractures. We therefore proposed the VIDAL (Vitamin D And Longevity) trial, a large randomised trial of high-dose monthly vitamin D3 for 5 years with all-cause mortality as the primary endpoint (20,000 participants aged 65-84 at entry). The VIDAL feasibility study was conducted to assess the feasibility of that larger main trial.
As well as demonstrating an expected increase in circulating 25-hydroxyvitamin D levels, the feasibility study sought to establish the study design and procedures required for the main trial. An important feature of the feasibility study was 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 the feasibility study was to ascertain recruitment levels, but the study also included 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 feasibility study therefore provides evidence on an important methodological issue in the design of pragmatic trials

in preventive medicine.

Actual start date of recruitment	27 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 11376
Worldwide total number of subjects	11376
EEA total number of subjects	11376

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	11376
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Baseline enrolment visits were conducted between 17/04/2013 and 11/12/2014 in 20 GP practices across England. The first patient was randomised on 09/05/2013, and the last patient was randomised on 15/01/2015.

Pre-assignment

Screening details:

The 20 GP practices were cluster randomised to open or double-blind individual randomisation within pairs matched approximately on size, whether urban or rural, ethnic mix and ward multiple deprivation index based on practice postcode. Within each practice, patients were individually randomised to vitamin D or control (no treatment or placebo).

Pre-assignment period milestones

Number of subjects started	11376
Number of subjects completed	1615

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not randomised to the trial: 9761

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Vitamin D (Blinded)

Arm description:

Study participants enrolled at the blinded GP practices received annual study medication packs each containing 12 monthly doses of study oil labelled as "vitamin D3 oil / placebo oil". The vitamin D (blinded) arm contained 12 bottles each containing 5.2 ml Vigantol® Oil (oily solution of vitamin D3, concentration 0.5 mg/ml). Bottles of study oil contained 5.2 ml to ensure delivery of 5 ml (2.5 mg of vitamin D3) because ~0.2 ml of the oily solution adheres and remains in the bottle.

Arm type	Experimental
Investigational medicinal product name	Vigantol® Oil
Investigational medicinal product code	A1 1 CC05 (cholecalciferol)
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Administered orally: 24 x 5 ml (= 24 x 2.5 mg) over two years.

Arm title	Placebo

Arm description:

Study participants enrolled at the blinded GP practices received annual study medication packs each containing 12 monthly doses of study oil labelled as "vitamin D3 oil / placebo oil". The placebo arm contained 12 bottles each containing 5.2 ml Miglyol® 812 oil.

Arm type	Placebo

Investigational medicinal product name	Miglyol® 812 Oil
Investigational medicinal product code	N/A
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Administered orally: 24 x 5 ml over two years

Arm title	Vitamin D (Open)

Arm description:

Study participants enrolled at the open GP practices received annual study medication packs each containing 12 monthly doses of study oil labelled as "vitamin D3 oil". The vitamin D (open) arm contained 12 bottles each containing 5.2 ml Vigantol® Oil (oily solution of vitamin D3, concentration 0.5 mg/ml). Bottles of study oil contained 5.2 ml to ensure delivery of 5 ml (2.5 mg of vitamin D3) because ~0.2 ml of the oily solution adheres and remains in the bottle.

Arm type	Experimental
Investigational medicinal product name	Vigantol® Oil
Investigational medicinal product code	A1 1 CC05 (cholecalciferol)
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Administered orally: 24 x 5 ml (= 24 x 2.5 mg) over two years.

Arm title	Open Control

Arm description:

Participants allocated to open control at randomisation are not sent any study oils, nor contacted during the follow-up period, but are invited back to the GP practice for a final study visit at 2-years.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1[1]	Vitamin D (Blinded)	Placebo	Vitamin D (Open)
Started	395	392	407
Completed	355	366	372
Not completed	40	26	35
Adverse event, serious fatal	5	3	8
Other reason	35	23	27

Number of subjects in period 1[1]	Open Control
Started	421
Completed	366
Not completed	55
Adverse event, serious fatal	4
Other reason	51

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The worldwide number of participants was the number of subjects invited to take part in the study, which was required for calculation of the first primary endpoint, "participation rates in blind versus open GP practices". The number of subjects reported to be in the baseline period equates to the number of participants actually randomised to the study, which is required for all other endpoints.

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	1615	1615	
Age categorical Units: Subjects			
65-69	624	624	
70-74	510	510	
75-79	325	325	
80-84	156	156	
Gender categorical Units: Subjects			
Female	758	758	
Male	857	857	
Ethnicity Units: Subjects			
White British	1563	1563	
White Irish	11	11	
White Other	26	26	
Caribbean	6	6	
Asian	6	6	
Mixed	3	3	

End points

End points reporting groups

Reporting group title	Vitamin D (Blinded)

Reporting group description:

Study participants enrolled at the blinded GP practices received annual study medication packs each containing 12 monthly doses of study oil labelled as "vitamin D3 oil / placebo oil". The vitamin D (blinded) arm contained 12 bottles each containing 5.2 ml Vigantol® Oil (oily solution of vitamin D3, concentration 0.5 mg/ml). Bottles of study oil contained 5.2 ml to ensure delivery of 5 ml (2.5 mg of vitamin D3) because ~0.2 ml of the oily solution adheres and remains in the bottle.

Reporting group title	Placebo

Reporting group description:

Study participants enrolled at the blinded GP practices received annual study medication packs each containing 12 monthly doses of study oil labelled as "vitamin D3 oil / placebo oil". The placebo arm contained 12 bottles each containing 5.2 ml Miglyol® 812 oil.

Reporting group title	Vitamin D (Open)

Reporting group description:

Study participants enrolled at the open GP practices received annual study medication packs each containing 12 monthly doses of study oil labelled as "vitamin D3 oil". The vitamin D (open) arm contained 12 bottles each containing 5.2 ml Vigantol® Oil (oily solution of vitamin D3, concentration 0.5 mg/ml). Bottles of study oil contained 5.2 ml to ensure delivery of 5 ml (2.5 mg of vitamin D3) because ~0.2 ml of the oily solution adheres and remains in the bottle.

Reporting group title	Open Control

Reporting group description:

Participants allocated to open control at randomisation are not sent any study oils, nor contacted during the follow-up period, but are invited back to the GP practice for a final study visit at 2-years.

Subject analysis set title	Subjects invited from "open" GP practices
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects from "open" GP practices who were invited to take part in the trial.

Subject analysis set title	Subjects invited from "blind" GP practices
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects from "open" GP practices who were invited to take part in the trial.

Subject analysis set title	Subjects randomised to all "blind" GP practices
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects that were randomised from "blind" GP practices

Subject analysis set title	All randomised participants allocated to vitamin D
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised participants allocated to receive vitamin D treatment (including both blind and open treatment groups).

Subject analysis set title	All randomised participants allocated to control group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised participants allocated to control groups (including both open and blind control groups).

Subject analysis set title	Randomised participants taking vitamin D supplements
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The number of randomised participants taking vitamin D supplements at baseline

Subject analysis set title	Randomised participants taking no vitamin D supplementation
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The number of randomised participants taking no vitamin D supplementation at baseline

Primary: Participation rates in blind versus open GP practices

End point title	Participation rates in blind versus open GP practices

End point description:

Proportion of invited participants who were randomised in each GP practice

End point type	Primary

End point timeframe:

Baseline

End point values	Subjects invited from "open" GP practices	Subjects invited from "blind" GP practices		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	828[1]	787[2]		
Units: percent				
arithmetic mean (full range (min-max))	15.0 (8.8 to 22.4)	13.4 (8.8 to 26.4)		

Notes:

[1] - 828 participants were randomised out of 5508 subjects invited across all "open" GP practices.

[2] - 787 participants were randomised out of 5868 subjects invited across all "blind" GP practices.

Statistical analyses

Statistical analysis title	Wilcoxon signed rank test

Statistical analysis description:

Wilcoxon signed rank test

Comparison groups	Subjects invited from "open" GP practices v Subjects invited from "blind" GP practices
Number of subjects included in analysis	1615
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7
Method	Wilcoxon signed rank test

Primary: Number of randomised participants returning for the 2 year visit by treatment group

End point title	Number of randomised participants returning for the 2 year visit by treatment group[3]

End point description:

Proportion of randomised participants returning for the 2-year visit in open control versus open treatment GP practices.

End point type	Primary

End point timeframe:

Attendance at the final 2-year visit.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a comparison of the treated versus untreated participants in the "open" GP practices. Those randomised in the "blinded" GP practices are excluded; therefore the endpoint should not report statistics for all of the arms in the baseline period.

End point values	Vitamin D (Open)	Open Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	399	417		
Units: percentage				
number (not applicable)	93.2	87.8		

Statistical analyses

Statistical analysis title	Chi-squared test

Statistical analysis description:

Chi-squared test

Comparison groups	Vitamin D (Open) v Open Control
Number of subjects included in analysis	816
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.008
Method	Chi-squared

Primary: Compliance of participants allocated to study medication

End point title	Compliance of participants allocated to study medication[4]

End point description:

Compliance of participants allocated to study medication: number of doses taken by study arm. Those randomised to receive no treatment in open GP practices are excluded.

End point type	Primary

End point timeframe:

Compliance of participants allocated to study medication over the 2 year trial period.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a comparison of open vitamin D versus all "blinded" GP practices. Those randomised to receive no treatment in the "open" GP practices are excluded; therefore the endpoint should not report statistics for all of the arms in the baseline period.

End point values	Vitamin D (Open)	Subjects randomised to all "blind" GP practices		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	407	787		
Units: percentage				
number (not applicable)				
0-5 doses	4.4	3.6		

6-11 doses	2.2	3.9		
12-17 doses	2.0	2.7		
18-24 doses	91.4	89.8		

Statistical analyses

Statistical analysis title	Chi-squared test
Statistical analysis description:	
Chi-squared test	
Comparison groups	Vitamin D (Open) v Subjects randomised to all "blind" GP practices
Number of subjects included in analysis	1194
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3
Method	Chi-squared

Primary: Contamination rates among open untreated controls versus blinded participants

End point title	Contamination rates among open untreated controls versus blinded participants[5]
End point description:	
Contamination (proportion of participants taking >400IU/day of vitamin D): additional self-administered or GP prescribed daily vitamin D from all supplements being taken at the 2-year visit. Combined data from self-report and GP records.	
End point type	Primary
End point timeframe:	
Final 2-year visit	

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This is a comparison of open untreated controls versus all "blinded" GP practices. Those randomised to receive vitamin D in the "open" GP practices are excluded; therefore the endpoint should not report statistics for all of the arms in the baseline period.

End point values	Open Control	Subjects randomised to all "blind" GP practices		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	400	740		
Units: percent				
number (not applicable)	5.0	3.6		

Statistical analyses

Statistical analysis title	Chi-squared test
Statistical analysis description: Chi-squared test	
Comparison groups	Open Control v Subjects randomised to all "blind" GP practices
Number of subjects included in analysis	1140
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.27
Method	Chi-squared

Secondary: Serious Adverse Event (SAE) reporting in blind placebo versus blind treated groups

End point title	Serious Adverse Event (SAE) reporting in blind placebo versus blind treated groups[6]
End point description: Report of one or more Serious Adverse Events during the two year trial period, in blind placebo versus blind vitamin D groups.	
End point type	Secondary
End point timeframe: Two year trial period	

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This is a comparison of the placebo versus treatment groups within the "blinded" GP practices. Those randomised in the "open" GP practices are excluded; therefore the endpoint should not report statistics for all of the arms in the baseline period.

End point values	Vitamin D (Blinded)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	392		
Units: percent				
number (not applicable)	11.7	11.5		

Statistical analyses

Statistical analysis title	Chi-squared test
Statistical analysis description: Chi-squared test	
Comparison groups	Vitamin D (Blinded) v Placebo
Number of subjects included in analysis	787
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.9
Method	Chi-squared

Secondary: Baseline blood 25(OH)D level in treated versus control groups

End point title	Baseline blood 25(OH)D level in treated versus control groups

End point description:

Baseline blood 25(OH)D level in participants allocated to vitamin D versus control groups.

End point type	Secondary

End point timeframe:

Baseline

End point values	All randomised participants allocated to vitamin D	All randomised participants allocated to control group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	798	810		
Units: percent				
number (not applicable)	51.2	51.7		

Statistical analyses

Statistical analysis title	Two-sided t-test

Statistical analysis description:

Two-sided t-test

Comparison groups	All randomised participants allocated to vitamin D v All randomised participants allocated to control group
Number of subjects included in analysis	1608
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7
Method	t-test, 2-sided

Secondary: Treatment effects: two-year 25(OH)D level in treated versus control groups

End point title	Treatment effects: two-year 25(OH)D level in treated versus control groups

End point description:

Two-year blood 25(OH)D level in participants allocated to vitamin D versus control groups.

End point type	Secondary

End point timeframe:

Two year final visit

End point values	All randomised participants allocated to vitamin D	All randomised participants allocated to control group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	722	726		
Units: percent				
number (not applicable)	109.6	51.8		

Statistical analyses

Statistical analysis title	Two-sided t-test
Statistical analysis description: Two-sided t-test	
Comparison groups	All randomised participants allocated to control group v All randomised participants allocated to vitamin D
Number of subjects included in analysis	1448
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	t-test, 2-sided

Secondary: Vitamin D supplementation and blood 25(OH)D level

End point title	Vitamin D supplementation and blood 25(OH)D level
End point description: Effect of vitamin D supplementation on average blood 25(OH)D level among all participants at baseline	
End point type	Secondary
End point timeframe: Baseline	

End point values	Randomised participants taking vitamin D supplements	Randomised participants taking no vitamin D supplementation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	390	1218		
Units: percent				
number (not applicable)	65.5	47.0		

Statistical analyses

Statistical analysis title	Linear regression

Statistical analysis description:

Linear regression

Comparison groups	Randomised participants taking vitamin D supplements v Randomised participants taking no vitamin D supplementation
Number of subjects included in analysis	1608
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	Regression, Linear

Secondary: Number of infections in 2-year trial period in treated versus control groups

End point title	Number of infections in 2-year trial period in treated versus control groups

End point description:

Number of infections during the 2-year trial period as reported from GP notes for all study participants, comparing controls (untreated or placebo) against vitamin D (open or blind). All infections included (upper and lower respiratory infections, urinary tract infections, skin/mucosal or soft tissue infections and other infections).

End point type	Secondary

End point timeframe:

Two year trial period

End point values	All randomised participants allocated to vitamin D	All randomised participants allocated to control group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	798	810		
Units: percent				
number (not applicable)				
0 infections	73.2	72.0		
1 infection	17.7	17.8		
2 infections	6.1	5.9		
3 infections	1.7	2.2		
4+ infections	1.2	2.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of GP appointments in 2-year trial period by treatment group

End point title	Number of GP appointments in 2-year trial period by treatment group

End point description:

Number of GP appointments during the 2-year trial period as reported from GP notes for all study participants by treatment group.

End point type	Secondary

End point timeframe:

Two year trial period

End point values	Vitamin D (Blinded)	Placebo	Vitamin D (Open)	Open Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	383	384	386	401
Units: percent				
number (not applicable)	12.2	12.9	12.6	12.9

Statistical analyses

No statistical analyses for this end point

Secondary: Change in systolic blood pressure across 2-year trial period in treated and control groups

End point title	Change in systolic blood pressure across 2-year trial period in treated and control groups

End point description:

Change in systolic blood pressure from recruitment to 2 years between vitamin D (open label and blind) and control (untreated and placebo) groups.

End point type	Secondary

End point timeframe:

Two year trial period

End point values	All randomised participants allocated to vitamin D	All randomised participants allocated to control group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	726	732		
Units: percent				
number (not applicable)	1.21	0.14		

Statistical analyses

Statistical analysis title	Linear regression

Statistical analysis description:

Linear regression

Comparison groups	All randomised participants allocated to vitamin D v All randomised participants allocated to control group
Number of subjects included in analysis	1458
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2
Method	Regression, Linear

Secondary: Change in diastolic blood pressure across 2-year trial period in treated and control groups

End point title	Change in diastolic blood pressure across 2-year trial period in treated and control groups

End point description:

Change in diastolic blood pressure from recruitment to 2 years between vitamin D (open label and blind) and control (untreated and placebo) groups

End point type	Secondary

End point timeframe:

Two year trial period

End point values	All randomised participants allocated to vitamin D	All randomised participants allocated to control group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	726	732		
Units: percent				
number (not applicable)	0.63	-0.55		

Statistical analyses

Statistical analysis title	Linear regression

Statistical analysis description:

Linear regression

Comparison groups	All randomised participants allocated to vitamin D v All randomised participants allocated to control group
Number of subjects included in analysis	1458
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.03
Method	Regression, Linear

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study medication to the end of study.

Adverse event reporting additional description:

Serious adverse events and adverse reactions were detected either through routine clinical contact with the participant at the GP practice, participant response to quarterly follow-up communications or final visit questions, or linkage with NHS digital to hospital admissions, cancer diagnoses and mortality data.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Vitamin D (Blinded)

Reporting group description:

Study participants enrolled at the blinded GP practices received annual study medication packs each containing 12 monthly doses of study oil labelled as "vitamin D3 oil / placebo oil". The vitamin D (blinded) arm contained 12 bottles each containing 5.2 ml Vigantol® Oil (oily solution of vitamin D3, concentration 0.5 mg/ml). Bottles of study oil contained 5.2 ml to ensure delivery of 5 ml (2.5 mg of vitamin D3) because ~0.2 ml of the oily solution adheres and remains in the bottle.

Reporting group title	Placebo

Reporting group description:

Study participants enrolled at the blinded GP practices received annual study medication packs each containing 12 monthly doses of study oil labelled as "vitamin D3 oil / placebo oil". The placebo arm contained 12 bottles each containing 5.2 ml Miglyol® 812 oil.

Reporting group title	Vitamin D (Open)

Reporting group description:

Study participants enrolled at the open GP practices received annual study medication packs each containing 12 monthly doses of study oil labelled as "vitamin D3 oil". The vitamin D (open) arm contained 12 bottles each containing 5.2 ml Vigantol® Oil (oily solution of vitamin D3, concentration 0.5 mg/ml). Bottles of study oil contained 5.2 ml to ensure delivery of 5 ml (2.5 mg of vitamin D3) because ~0.2 ml of the oily solution adheres and remains in the bottle.

Reporting group title	Open Control

Reporting group description:

Participants allocated to open control at randomisation are not sent any study oils, nor contacted during the follow-up period, but are invited back to the GP practice for a final study visit at 2-years.

Serious adverse events	Vitamin D (Blinded)	Placebo	Vitamin D (Open)
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 395 (11.65%)	45 / 392 (11.48%)	48 / 407 (11.79%)
number of deaths (all causes)	5	3	8
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
All SAEs	Additional description: All SAEs		

subjects affected / exposed	46 / 395 (11.65%)	45 / 392 (11.48%)	48 / 407 (11.79%)
occurrences causally related to treatment / all	0 / 59	0 / 56	0 / 56
deaths causally related to treatment / all	0 / 5	0 / 3	0 / 8

Serious adverse events	Open Control		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 421 (3.09%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
All SAEs	Additional description: All SAEs		
subjects affected / exposed	13 / 421 (3.09%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 4		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Vitamin D (Blinded)	Placebo	Vitamin D (Open)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 395 (1.27%)	4 / 392 (1.02%)	12 / 407 (2.95%)
General disorders and administration site conditions			
All ARs	Additional description: All ARs		
subjects affected / exposed	5 / 395 (1.27%)	4 / 392 (1.02%)	12 / 407 (2.95%)
occurrences (all)	5	4	12

Non-serious adverse events	Open Control		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 421 (0.00%)		
General disorders and administration site conditions			
All ARs	Additional description: All ARs		
subjects affected / exposed	0 / 421 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 October 2012	Include a reminder on the 3-monthly follow-up for participants to contact their GP if they are experiencing symptoms of hypercalcaemia. Allow CCI to send signed prescriptions directly to pharmacy and GP nurses to send ICF to TCC by any medium.
24 October 2012	Administrative changes: Amending protocol and supporting document terminology for consistency; paper administration of the baseline visit; modification of the lifestyle questions, invitation letter and quarterly follow-up; amendment of previous errors on the PIS and 2-year appointment letter; asking GP practices (instead of TCC) to check study oil dates on the used medication packs brought in to the final practice visit; modifying the remit of the DMC; modifying the format of the unique VIDAL ID; and modifying the verification procedure for the calcium blood test result. Request by TCC of an anonymised version of the quarterly pre-consent spreadsheet, for the purpose of monitoring response rates and reasons for non-participation by 5-year age-group and sex. Other changes: Inclusion of blood pressure as an additional outcome. Increasing the volume of blood taken for the calcium blood test (from 3ml to 3.5ml) for logistical reasons. Initial recording of SAEs by the practice nurse as well as PI (subject to review and confirmation by the PI).
30 May 2013	Removal of existing sites/PIs and addition of new sites/PIs.
10 September 2013	Text on IMP bottle and carton labels altered to confirm study oil should be taken orally once a month; Insert added with instructions in IMP delivery pack; Certificate of Analysis for extended shelf life of vigantol oil.
20 September 2013	Change of PI at four participating sites.
27 September 2013	Change of PI at one participating site.
04 February 2014	Removal of existing sites/PIs and addition of new sites/PIs.
08 May 2014	Removal of existing site/PI and addition of new site/PI.
01 July 2014	Minor edits to the statistical section of the protocol and addition of a contamination communication.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported