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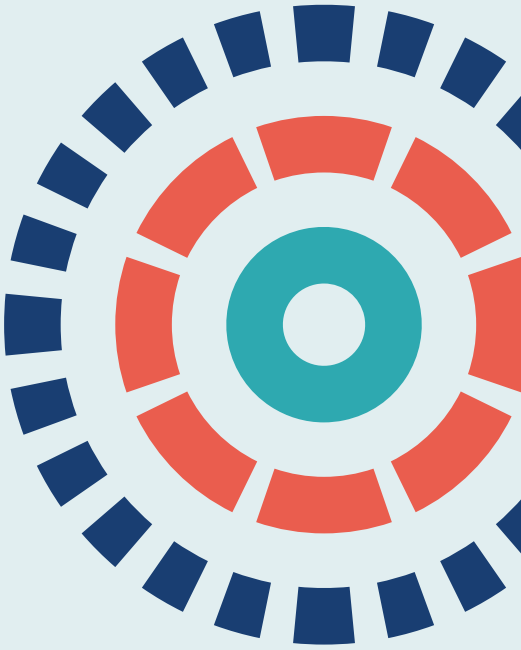

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High-dose oral vitamin D supplementation and mortality in people aged 65–84 years: the VIDAL cluster feasibility RCT of open versus double-blind individual randomisation

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Declared competing interests of authors: Irwin Nazareth was on the Health Technology Assessment (HTA) Commissioning Board from 2012 to July 2017. For the duration of the Vitamin D and Longevity (VIDAL) trial, Irwin Nazareth's PRIMENT Clinical Trials Unit was funded by the National Institute for Health Research (NIHR). He was a member of the HTA Disease Prevention Panel, a member of the HTA Commissioning Sub-board (Expression of Interest) and a member of the HTA Primary Care Themed Call. Benoit Aigret reported that Queen Mary University of London received a grant from the London School of Hygiene & Tropical Medicine to develop the VIDAL online application during the conduct of the study.

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This report

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Abstract

High-dose oral vitamin D supplementation and mortality in people aged 65–84 years: the VIDAL cluster feasibility RCT of open versus double-blind individual randomisation

Christine Rake,[1] Clare Gilham,[1] Laurette Bukasa,[1] Richard Ostler,[2] Michelle Newton,[3] James Peto Wild,[1] Benoit Aigret,[4] Michael Hill,[5] Oliver Gillie,[6] Irwin Nazareth,[7] Peter Sasieni,[4,8] Adrian Martineau[9] and Julian Peto[1]*

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Background: Randomised controlled trials demonstrating improved longevity are needed to justify high-dose vitamin D supplementation for older populations.

Objectives: To demonstrate the feasibility of a large trial ($n \approx 20{,}000$) of high-dose vitamin D in people aged 65–84 years through general practitioner (GP) practices, and to cluster randomise participating practices between open-label and double-blind randomisation to compare effects on recruitment, compliance and contamination.

Design: Twenty GP practices were randomised in matched pairs between open-label and double-blind allocation. Within each practice, patients were individually randomised to vitamin D or control (i.e. no treatment or placebo). Participants were invited to attend their GP practice to provide a blood sample and complete a lifestyle questionnaire at recruitment and again at 2 years. Randomisation by telephone followed receipt of a serum corrected calcium assay confirming eligibility (< 2.65 nmol/l). Treatment compliance was reported by quarterly follow-up forms sent and returned by e-mail or post (participant choice). GP visits and infections were abstracted from GP records. Hospital attendances, cancer diagnoses and deaths were ascertained by linkage to Hospital Episode Statistics and national registration through NHS Digital.

Setting: GP practices in England.

Participants: Recruitment opened in October 2013 and closed in January 2015. A total of 1615 registered patients aged 65–84 years were randomised: 407 to vitamin D and 421 to no treatment in open practices; 395 to vitamin D and 392 to placebo in blind practices.

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Interventions: There was a 24-month treatment period: 12 monthly doses (100,000 IU of vitamin D_3 or placebo as 5 ml oily solution) were posted after randomisation and at 1 year (100,000 IU per month corresponds to 3300 IU per day). Reminders were sent monthly by e-mail, text message or post.

Main outcome measures: Recruitment, compliance, contamination and change in circulating 25-hydroxyvitamin D [25(OH)D] from baseline to 2 years.

Results: Participation rates (randomised/invited) were 15.0% in open practices and 13.4% in double-blind practices ($p = 0.7$). The proportion still taking study medication at 2 years was 91.2% in open practices and 89.2% in double-blind practices ($p = 0.4$). The proportion of control participants taking > 400 IU vitamin D per day at 2 years was 5.0% in open practices and 4.8% in double-blind practices. Mean serum 25(OH)D concentration was 51.5 nmol/l [95% confidence interval (CI) 50.2 to 52.8 nmol/l] with 82.6% of participants < 75 nmol/l at baseline. At 2 years, this increased to 109.6 nmol/l (95% CI 107.1 to 112.1 nmol/l) with 12.0% < 75 nmol/l in those allocated to vitamin D and was unaltered at 51.8 nmol/l (95% CI 49.8 to 53.8 nmol/l) in those allocated to no vitamin D (no treatment or placebo).

Conclusions: A trial could recruit 20,000 participants aged 65–84 years through 200 GP practices over 2 years. Approximately 80% would be expected to adhere to allocated treatment (vitamin D or placebo) for 5 years. The trial could be conducted entirely by e-mail in participants aged < 80 years, but some participants aged 80–84 years would require postal follow-up. Recruitment and treatment compliance would be similar and contamination (self-administration of vitamin D) would be minimal, whether control participants are randomised openly to no treatment with no contact during the trial or randomised double-blind to placebo with monthly reminders.

Trial registration: Current Controlled Trials ISRCTN46328341 and EudraCT database 2011-003699-34.

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List of abbreviations

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
app	online application
AR	adverse reaction
BC	blind placebo control
BD	blind vitamin D
BMI	body mass index
BP	blood pressure
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
EDTA	ethylene diamine tetra-acetic acid
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GP	general practitioner
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
IDAOPI	Income Deprivation Affecting Older People Index
IMD	Index of Multiple Deprivation
MHRA	Medicines and Healthcare products Regulatory Agency
NIHR	National Institute for Health Research
OC	open control
OD	open-label vitamin D
QoL	quality of life
RCT	randomised controlled trial
SAE	serious adverse event
SST	serum separator tube
VDR	vitamin D receptor
VIDAL	Vitamin D and Longevity

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Plain English summary

High-dose vitamin D may reduce the risk of many diseases, but without large randomised controlled trials the evidence will remain inconclusive. We therefore proposed the Vitamin D and Longevity (VIDAL) trial, with 20,000 older people randomised to either no vitamin D medication or vitamin D medication for 5 years. The VIDAL feasibility study was conducted to establish the procedures required for the main trial, including assessment of recruitment, compliance (taking study treatment as directed) and contamination (how many control participants started taking vitamin D). This was done in two sets of general practitioner (GP) practices: (1) 'open' practices, in which participants knew their treatment allocation (2 years of 100,000 IU vitamin D monthly or no treatment), and (2) 'double-blind' practices, in which participants and their GPs did not know whether they were taking vitamin D or placebo oil.

We invited 11,376 men and women aged 65–84 years from 20 GP practices in England and 1615 (14%) took part. Ninety per cent of participants allocated to monthly oil took it for 2 years and few participants used vitamin supplements outside the trial, with no marked differences between open-label and double-blind arms. The best way to conduct the main trial will therefore depend on other considerations. A double-blind trial provides reliable evidence on effects where reporting could be influenced by you or your doctor knowing your treatment, which is important for many illnesses and any side effects of treatment. However, any long-term effects are likely to be considerably greater if treatment continues instead of stopping after 5 years when the main trial ends. An open trial is easier to conduct and, when it ends, those taking vitamin D can be offered a continuing supply so that the effect of lifelong treatment can be studied for major diseases and life expectancy, which are unlikely to be affected by individuals knowing whether or not they are taking vitamin D.

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Scientific summary

Background

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 (400 IU per day) nor the increased consumption of foods containing vitamin D will raise the majority of the UK population aged > 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 Vitamin D and Longevity (VIDAL) trial, a large randomised controlled trial of high-dose monthly vitamin D_3 for 5 years with all-cause mortality as the primary end point (20,000 participants aged 65–84 years at entry). The VIDAL feasibility study was conducted to assess the feasibility of that larger main trial.

Objectives

The primary objectives were to assess feasibility by randomising 1600 individuals aged 65–84 years through 20 participating general practitioner (GP) practices and to estimate the effects of trial design (open-label vs. double-blind randomisation) on recruitment, compliance and contamination. This was done by randomising the 20 practices in matched pairs between open allocation [randomising between an open-label vitamin D (OD) arm and an untreated open control (OC) arm] and double-blind allocation [randomising between a blind vitamin D (BD) arm and a blind placebo control (BC) arm].

Methods

Eligibility

Registered patients were considered for inclusion if they were aged 65–84 years and were willing to be randomised, were contactable by telephone, were able to receive recorded delivery post, were able to attend enrolment at the GP surgery and had GP notes available for the previous year. Exclusion criteria were:

- active tuberculosis, sarcoidosis, hyperparathyroidism, past or present nephrolithiasis, vitamin D intolerance, suspected hepatic or renal dysfunction, terminal illness, any malignancy other than non-melanoma skin cancer not in remission for ≥ 3 years, or any other condition that the GP or clinical principal investigator believed might compromise trial participation
- corrected serum calcium concentration of > 2.65 mmol/l
- taking dietary supplements or other medication containing > 400 IU (10 μg) per day of vitamin D
- concomitant therapy with 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 the first dose of investigational medicinal product.

Cluster randomisation of practices

The 20 participating GP practices were cluster randomised to open-label 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.

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Recruitment

After compiling a list of registered patients aged 65–84 years and excluding any who were deemed ineligible, the practice staff sent patient information booklets and invitations in batches by post. No reminders were sent. Those who responded were invited to attend their practice to verify eligibility, give written informed consent, have their blood pressure (BP) and body mass index (BMI) recorded, complete a short lifestyle questionnaire and provide a blood sample for calcium and 25(OH)D assay.

The web-based clinical data management system: the VIDAL online application

Participating practices accessed the VIDAL app (online application) during the baseline visit to create a participant record and enter identifying information and questionnaire responses when the informed consent documentation had been signed, and throughout the trial to update their records. The trials office accessed the VIDAL app to randomise participants and to manage and monitor study progress. The app sent monthly reminders to take medication (by automated telephone call, e-mail and/or text message). Quarterly questionnaires were either sent and received automatically by e-mail or printed and sent by post.

Randomisation, treatment and follow-up

When a corrected calcium result confirming eligibility (< 2.65 nmol/l) was received, the participant was telephoned by the trials office to confirm willingness to participate and was then immediately randomised by the VIDAL app. Participants allocated to study medication (BD, BC or OD arms) were sent 12 monthly doses of 100,000 IU (2.5 mg) vitamin D_3 or placebo in 5 ml oily solution by recorded delivery post immediately following randomisation and 1 year later. They received monthly reminders to take the study medication and 3-monthly questionnaires on treatment compliance, additional vitamin D intake (prescribed or self-administered) and adverse events. Apart from 121 participants who were telephoned in 2014 for an interim report (see *Contamination in open and placebo control participants*), OC participants were not re-contacted until 2 years later, when all participants were invited to attend their practice for repeat measurement of BP and BMI, blood sampling and the same lifestyle questionnaire. All participants were traced through Hospital Episode Statistics (HES) for hospital admissions and through national registers for cancer diagnoses and deaths. At the end of the trial, GP records of practice visits, diagnoses and prescriptions for the 2 years of the trial and the preceding year were downloaded and all baseline and follow-up serum samples were retrieved for 25(OH)D assay.

Results

There were 11,376 potential participants invited; 1673 participants attended the baseline visit and 1615 were randomised (target 1600). The participation rate (number randomised/number invited) was higher in open practices (15.0%, range 8.8–22.4%) than in blind practices (13.4%, range 7.7–26.4%), but this difference did not approach statistical significance owing to the wide variation between practices (Wilcoxon signed-rank test; $p = 0.7$). Of the randomised participants, 53.1% were male and virtually all (99.1%) were white. The overall participation rate of 14.2% (target 9%) was higher at age 65–79 years (14.6%: 1459/10,018) than at 80–84 years (11.5%: 156/1358). The percentage in each age group choosing e-mail rather than post for receiving and returning quarterly follow-up forms was 77.4% (483/624), 67.6% (345/510), 55.7% (181/325) and 36.5% (57/156) at ages 65–69, 70–74, 75–79 and 80–84 years, respectively, and was 55.7% (477/857) for men and 47.4% (359/758) for women. The numbers randomised were 395 to BD and 392 to BC in the 10 double-blind practices, and 407 to OD and 421 to untreated OC in the 10 open practices.

Mortality and serious adverse events

The trial was not powered to detect clinical effects or mortality differences. The number of deaths by allocated treatment was as follows: four (OC), eight (OD), three (BC) and five (BD). The numbers of serious adverse events (SAEs) reported (none of which was judged to be associated with treatment) were 13 (OC – SAEs not reported during trial), 48 (OD), 45 (BC) and 46 (BD). Emergency hospital admission was recorded in HES for 52 (OC), 47 (OD), 44 (BC) and 48 (BD) participants.

Compliance among participants allocated to study medication

Among participants allocated to study medication (BD, BC or OD), the proportion who were still taking allocated treatment declined from 95.7% at 6 months to 89.8% at 2 years. The proportion of surviving participants who attended the 2-year follow-up was similar for OD (93.2%) and blind practices (92.6%).

Contamination among open and placebo control participants

To obtain information on vitamin D consumption for an interim report, 121 participants randomised to no treatment in open practices (OC) before May 2014 were contacted by post, e-mail or telephone in December 2014. There was no other contact after randomisation with OC participants until they were invited to attend the 2-year final visit.

Information on vitamin D consumption at 2 years was obtained from 400 (95.9%) of the 417 OC survivors: 366 (87.8%) who attended the 2-year visit and a further 34 who were interviewed at 2 years by telephone but did not attend. Only 20 (5.0%) were taking > 400 IU of vitamin D per day (11 prescribed by the GP and nine self-administered), compared with 4.8% of placebo control participants in blind practices.

Baseline 25(OH)D levels

The mean baseline 25(OH)D level was higher in men [54.2 nmol/l, 95% confidence interval (CI) 52.3 to 56.1 nmol/l] than in women (48.5 nmol/l, 95% CI 46.6 to 50.3 nmol/l). The level was significantly associated with every variable except age and use of sun protection in a multivariate regression including sex, age, season, skin complexion, consumption of oily fish, travel abroad in last year, quality of life (QoL), latitude of practice, deprivation quintile, time outdoors, actively seeking suntan, sunbed use and use of sun protection (adjusted *p*-values: sex 0.003, age 0.6, deprivation 0.04, sun protection 0.3, sunbed use 0.02, all other variables $\leq$ 0.001).

Infections

The proportion of participants with two or more infections recorded in GP records during the trial was 10.2% in the control arms (OC and BC) and slightly but not significantly lower, at 9.1%, in the vitamin D arms (OD and BD). Among those with a baseline 25(OH)D of < 25 nmol/l, these proportions were 16.9% (control arms) and 9.8% (vitamin D arms), which was still a non-significant difference.

Change in 25(OH)D from baseline to 2-year follow-up

A similar and highly significant ($p < 0.0001$) effect of treatment on 25(OH)D levels was seen in both open and blind practices. At the 2-year visit, the mean 25(OH)D level and percentage of participants < 75 nmol/l by allocated treatment were 109.2 nmol/l and 11.0% (BD), 50.6 nmol/l and 83.1% (BC), 110.0 nmol/l and 13.0% (OD), and 53.0 nmol/l and 81.0% (OC). The increases over baseline in the mean level were 58.6 nmol/l in the blind practices and 58.0 nmol/l in the open practices, and the reductions in the percentage < 75 nmol/l were 72.1% and 68.0%, respectively. The percentage who were suboptimal [25(OH)D of < 75 nmol/l] declined from 83.6% at baseline to 12.1% at 2 years in those allocated to vitamin D and was unchanged at 81.9% in control participants (placebo or no treatment).

Conclusions

Recruitment and compliance were high and contamination in control participants was low, with no marked differences between open and blind practices. This confirms the feasibility of conducting the main trial with either open-label or double-blind randomisation (20,000 recruited through 200 GP practices with equal numbers at each age from 65 to 84 years).

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Recommendations for research

1. The main trial should be conducted, as it would constitute a major and perhaps decisive addition to the worldwide evidence on what the UK vitamin D reference nutrient intake should be for those aged ≥ 65 years.
2. The National Institute for Health Research (NIHR) Health Technology Assessment (HTA), in consultation with the relevant agencies, should review opportunities for reducing delays in Clinical Research Network funding approvals for multicentre population-based prophylactic trials, and for simplifying trial regulations for non-prescription treatments such as vitamin D for which extensive evidence on safety is already available.
3. Reports published after this trial began suggest that the treatment tested should be ≈4000 IU vitamin D daily rather than the monthly regimen we used.

Trial registration

This trial is registered as ISRCTN46328341 and EudraCT database 2011-003699-34.

Funding

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Chapter 1 Introduction

The number of people aged ≥ 80 years in the UK is projected to more than double, to 6 million, by mid-2037,[1] and interventions that improve quality as well as length of life are needed.[2] Cancer, cardiovascular disease, dementia, community-acquired pneumonia, falls and fractures account for much of the reduction in the quality of life (QoL) as well as overall mortality rates of older adults[3–7] and impose a huge economic burden on the NHS, social services and many families.[8] There is, therefore, a need for new interventions to prevent these conditions. A large and growing body of evidence identifies vitamin D supplementation as a promising candidate to reduce morbidity and mortality in the elderly.[9] Vitamin D is a pre-pro-hormone that is synthesised in the skin by ultraviolet B radiation in sunlight, which is a major source of vitamin D. Dietary sources are limited, with oily fish being the only significant contributor.[10] At the UK's latitude (50–58°N), sunlight can stimulate cutaneous vitamin D synthesis only between April and October.[11] Consequently, vitamin D insufficiency {defined as a serum 25-hydroxyvitamin D [25(OH)D] concentration of < 75 nmol/l} is very common, especially among older adults, who may spend less time outdoors and whose skin is less efficient at synthesising vitamin D.[9] Vitamin D insufficiency among older adults in the UK may therefore be an important and readily correctable risk factor for a variety of diseases. Offering a daily vitamin D supplement to all UK adults aged > 65 years would be inexpensive and safe and could result in significant and cost-effective improvements in QoL as well as longevity.

The diversity of the roles played by vitamin D in normal human physiology offers a plausible explanation of how a single micronutrient might ameliorate a heterogeneous collection of diseases. Humans evolved at equatorial latitudes in unlimited sunshine, and serum concentrations of the major circulating metabolite, 25(OH)D, are ≈115 nmol/l in people living traditional lifestyles near the equator,[12,13] which is three times the median level of 37 nmol/l among adults aged ≥ 65 years in the UK in January to March.[14] The enzyme that converts 25(OH)D to its active metabolite, the steroid hormone 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] or calcitriol, and the cognate receptor for that metabolite [the vitamin D receptor (VDR)] are expressed in the majority of human tissues,[10] not just those involved in calcium homeostasis, as was thought throughout much of the twentieth century. Ligation of VDR by calcitriol modifies expression of > 200 genes[15] to support a wide range of biological responses that may have an impact on the pathogenesis of many diseases as well as falls and fractures[16] (*Figure 1*).

In keeping with these biological actions, observational epidemiological studies have reported associations between low 25(OH)D levels and increased incidence of several cancers (particularly of the colon), cardiovascular disease, Alzheimer's disease and all-cause dementia, acute respiratory infection and risk of falls and fractures.[17–20] However, a recent systematic review of mortality studies[21] concluded that although all-cause mortality is consistently increased in people with 25(OH)D levels below about 75 nmol/l, several uncertainties remain. The optimal 25(OH)D level is ill-defined owing to imperfect assay methods; for cancers other than colon, survival after diagnosis rather than incidence may be affected; and effects on individual cancer types and subgroups of cardiovascular disease are unclear. Last but most important, reverse causation can be excluded only by large randomised controlled trials (RCTs). Published results of RCTs of vitamin D supplementation conducted to date are inconclusive and may be subject to publication bias. Some RCTs have reported protective effects for cancer incidence,[22] acute respiratory infections,[23–25] fractures[26] and falls[27] while others have not.[28–34] Many of these trials suffered from one or more of the following limitations:

- The dose of vitamin D administered was inadequate to elevate serum 25(OH)D concentration to > 75 nmol/l.[28–30]
- Vitamin D deficiency was not highly prevalent at baseline.[31]
- There was inadequate statistical power to detect modest but clinically significant effects of the intervention.[32]

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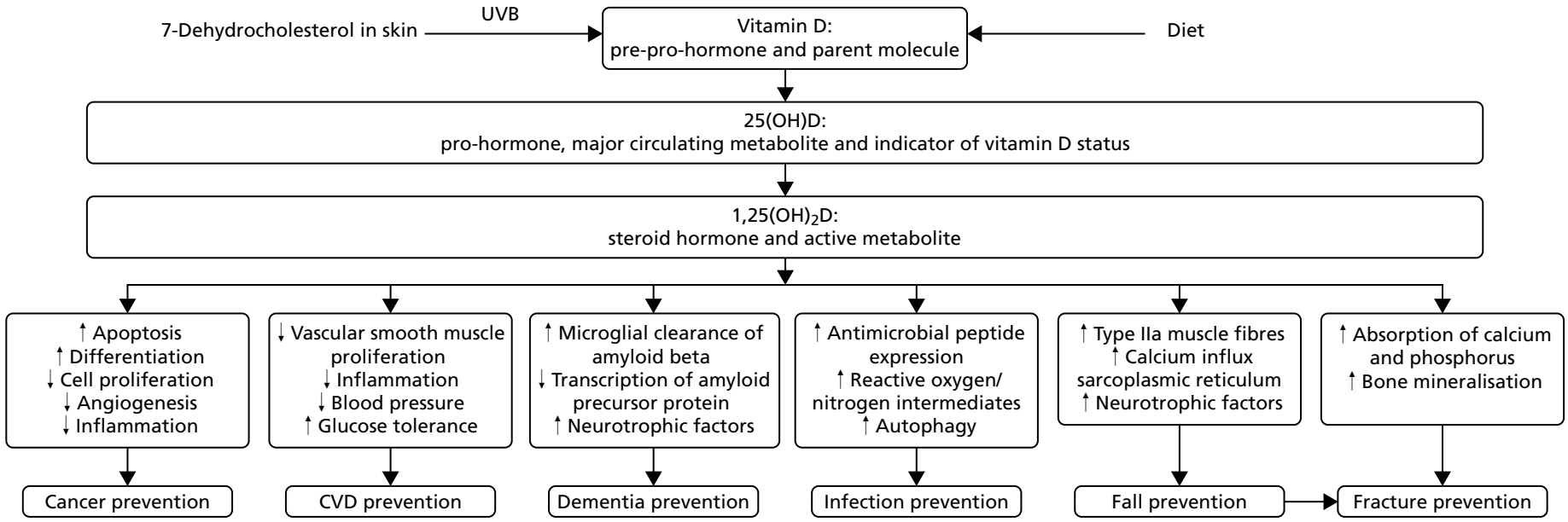

FIGURE 1 Mechanisms by which vitamin D may prevent cancer, cardiovascular disease, dementia, infections, falls and fractures. CVD, cardiovascular disease.

The promise of a potentially safe and cost-effective intervention to reduce the incidence of several diseases and prolong life has prompted a huge international research effort, particularly in the last decade. This has culminated in the establishment of four very large (> 5000 participants) RCTs of higher-dose vitamin D_3 in older adults – the so-called 'vitamin D megatrials', defined here as RCTs of higher-dose vitamin D_3 (≥ 2000 IU per day or equivalent) in older adults with a sample size of > 5000. The primary characteristics of these studies are summarised in PICO (Participants, Intervention, Comparator, Outcome) format in *Table 1*. Trials of lower doses[28,29] or of vitamin D_2 rather than vitamin D_3[35] have not been listed, as such regimens do not produce an adequate increase in 25(OH)D.

Why then does the UK need a 'vitamin D megatrial' of its own?

We propose two reasons:

1. The UK represents a setting with a high prevalence of vitamin D insufficiency, where supplementation could have maximal impact. Median serum 25(OH)D concentrations among older adults in the UK (37–49 nmol/l, depending on season) are significantly lower than in the countries where large trials are currently being conducted (New Zealand, 66 nmol/l;[36] Australia, 69 nmol/l;[37] Canada, 70 nmol/l;[38] USA, 57 nmol/l[39]). The efficacy of vitamin D supplementation is likely to depend on the prevalence of inadequate vitamin D status at baseline, so the results of the intervention studies conducted in these settings are likely to underestimate any effects that would be seen in older adults living in the UK and are less likely to achieve statistical significance. International differences in baseline vitamin D status may be partly attributable to the fact that many of the countries listed in *Table 1* are situated at lower latitudes than the UK and, therefore, their populations have greater exposure to sunshine of sufficient intensity to stimulate cutaneous vitamin D synthesis; moreover, many of these countries routinely fortify foods with vitamin D (e.g. milk in the USA, Canada and Finland is routinely vitamin D-fortified).
2. Conduct of a further large trial of daily vitamin D supplementation in the UK will add substantially to meta-analysis of these four megatrials to detect and estimate a modest but clinically significant effect of vitamin D on all-cause mortality among participants with low serum 25(OH)D, among whom any effect is likely to be concentrated. Apart from FIND (Finnish Vitamin D Trial)[40] in Finland, which stopped recruitment at 2500 participants (target 18,000 participants) with only 830 participants allocated to 3200 IU daily (see *Table 1* footnote), the proposed trial would provide the only evidence on the effects of a daily dose of the order of 4000 IU. Three trials (VIDA,[41,42] TIPS-3 and D-Health) are testing monthly dosing, which may be less effective. The VITamin D and OmegA-3 TriaL (VITAL), which tested 2000 IU daily, included only 3318 participants aged ≥ 75 years,[43] one-third of the number proposed in the VIDAL main trial.

The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme did not support our application in 2008 to conduct a large trial of vitamin D supplementation in older adults in the UK, but invited an application for this feasibility study to establish the procedures required to conduct the main trial. Funding was awarded in 2011 and recruitment began in 2013. An application for funding for the main trial was made again in January 2015 when recruitment was complete, but by that time the trials listed in *Table 1* were under way and the NIHR HTA programme decided that funding for a large British trial would not be reconsidered until the results of those trials become available. The results of the VITAL trial, which is the only large trial of daily high-dose vitamin D, are inconclusive for all-cause mortality [hazard ratio 2 to 5 years after entry 0.96, 95% confidence interval (CI) 0.84 to 1.11], so further evidence is now needed.[43]

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TABLE 1 Characteristics of vitamin D 'megatrials': RCTs of higher-dose vitamin D_3 (≥ 2000 IU per day or equivalent) in older adults with sample size > 5000[a]

Trial	Setting	Participants	Intervention	Comparator	Outcome (primary)	Status
VIDA	New Zealand	*n* = 5110, aged 50–84 years	100,000 IU vitamin D_3 monthly p.o.	Placebo	Incidence of cardiovascular disease over 5 years	Cardiovascular and bone outcomes reported[41,42]
VITAL	USA	*n* = 25,875 aged ≥ 50 years (male), ≥ 55 years (female)	2000 IU vitamin D_3 daily p.o. (2 × 2 factorial with omega-3)	Placebo	Incidence of cancer and cardiovascular disease (co-primary) over 5 years	Cardiovascular and cancer outcomes reported[43]
TIPS-3	Canada, India + nine other countries	*n* = 5713 aged ≥ 55 years (male), ≥ 60 years (female)	60,000 IU vitamin D_3 monthly p.o. (2 × 2 × 2 factorial with polypill and aspirin)	Placebo	Hip fracture (primary vitamin D outcome) over 5 years	Enrolling; due to report 2019
D-Health	Australia	*n* = 25,000 aged 60–79 years	60,000 IU vitamin D_3 monthly p.o.	Placebo	All-cause mortality over 5 years	Enrolling; due to report 2020

p.o., per os (by mouth).

a The original target for the FIND trial in Finland was 18,000, but recruitment ended in 2015 when 2500 had been randomised, with approximately 830 in each of the three arms: daily 3200 IU, 1600 IU or placebo.[40]

Chapter 2 Methods

Trial design

The Vitamin D and Longevity (VIDAL) feasibility trial was a four-arm multicentre RCT of 2 years' duration of subjects aged 65–84 years. Twenty general practitioner (GP) practices in England were cluster randomised in matched pairs to either double-blind or open-label study design. The GP practices were assigned to pairs matched approximately on size, whether urban or rural, ethnic mix and ward multiple deprivation index based on practice postcode. The practices in each pair were then randomly assigned to double-blind or open-label individual randomisation. In double-blind practices participants were individually randomised to blind vitamin D (BD) or blind placebo control (BC). In open-label practices individual randomisation of participants was to open-label vitamin D (OD) or untreated open control (OC).

Ethics and regulatory approval and research governance

Ethics approval for the study was given by the London–Chelsea National Research Ethics Service in February 2012 (reference number 11/LO/1989). Clinical trial authorisation for the study was given by the Medicines and Healthcare products Regulatory Agency (MHRA) in March 2012 (reference number 17072/0006/001-0001). Appropriate site-specific assessments were obtained from the primary care trusts to confer the required management permissions for the 20 participating GP practices. The trial was registered with the International Standard Randomised Controlled Trial Register under the reference number ISRCTN 46328341 and also with the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database under the reference number 2011-003699-34.

Patient and public involvement

Public opinion regarding the information being provided to participants of the trial was gauged in collaboration with Barts Clinical Trials Unit (CTU). The Queen Mary Trials Advisory Group provided valuable feedback on the patient invitation letter, information sheet and consent forms used in the trial. The lay member and consumer representative on the VIDAL Trial Management Group also contributed from the outset to the design of the feasibility study and provided feedback on trial management issues as they arose.

Eligibility

Members of the general population were recruited from 20 GP practices across England.

Inclusion criteria

Registered patients were considered for inclusion if they:

- were aged ≥ 65 years and ≤ 84 years at enrolment
- were contactable by telephone, able to receive recorded deliveries by post, able to attend enrolment at the GP surgery
- had GP notes available for the previous year.

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Exclusion criteria

The study design excluded anyone:

- with known active tuberculosis, sarcoidosis, hyperparathyroidism, past or present nephrolithiasis, vitamin D intolerance, referral for suspected hepatic or renal dysfunction, terminal illness or 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
- with any other condition that in the principal investigator's or chief investigator's judgement might compromise participant safety or compliance, interfere with evaluation or preclude completion of the study
- with a baseline corrected blood calcium level of > 2.65 mmol/l
- taking dietary supplements or other medication containing > 400 IU (10 µg) of vitamin D per day
- taking 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
- taking treatment with any other investigational medical product or device up to 4 months before first dose of the investigational medicinal product.

Recruitment procedure

Each of the 20 GP practices generated a list of registered patients aged 65–84 years. After excluding ineligible individuals, including those judged by the GP to lack the mental capacity to give informed consent or to be unsuitable for other reasons, study invitations were sent by post to potential participants.

Interested respondents were telephoned by a member of the research team at the GP practice to confirm eligibility and arrange a baseline assessment appointment at the GP practice, at which time informed consent was obtained from those agreeing to participate in the trial. Trial participants then provided information on current medications and conditions, diet (including dietary supplements), skin type and sun exposure, and QoL (see *Appendix 1*). Virtually all information was entered directly into case report forms (CRFs) accessed via the online clinical data management system [the VIDAL app (online application); see *Appendix 2*], with paper copies of all CRFs available as a back-up option. Systolic and diastolic blood pressure (BP), height, weight and waist circumference were recorded, and 12.5 ml of blood [9 ml ethylene diamine tetra-acetic acid (EDTA) vacutainer for measurement of 25(OH)D and 3.5 ml serum separator tube (SST) vacutainer for calcium assay] were obtained. The 3.5-ml aliquot was sent for corrected calcium assay at the practice's local laboratory to verify eligibility. The 9-ml aliquot was sent to the Clinical Trials Service Unit in Oxford for separation of buffy coat and storage in liquid nitrogen. Circulating 25(OH)D was assayed on all stored samples (baseline and 2-year follow-up) at the end of the study on the Cobas 6000 immunoassay (Roche Molecular Diagnostics, Pleasanton, CA, USA).

Informed consent

Informed written consent was obtained during the baseline assessment from eligible participants after an explanation of the aims, methods, anticipated benefits and potential hazards of the study. The original signed and dated consent forms were held at each GP practice, with copies sent to the participant and the Trial Coordination Centre. Patients ineligible for inclusion, based on the corrected blood calcium result, were informed of this by their GP or GP nurse, who also discussed whether or not any treatment was indicated.

Randomisation, concealment and blinding

Cluster randomisation of GP practices

Prior to study commencement, 20 GP practices were matched as closely as possible in pairs based on urban/rural location, deprivation [Index of Multiple Deprivation (IMD) of the ward of the GP practice based on the GP practice postcode], practice size and ethnic mix (non-white proportion). Practices were then randomised within each pair, one to the double-blind study and one to the open-label study, by the Biostatistician and Director of the Barts CTU, a UK Clinical Research Collaboration registered Trials Unit. Four GP practices (including both in one pair) withdrew after randomisation, so these were replaced and the three pairs were re-randomised.

Individual randomisation of eligible participants within the practices

Individual participants were subsequently randomised within GP practices using the VIDAL app developed by the Barts CTU. The VIDAL app generated a random sequence of allocations for each GP practice balanced in blocks of six or eight so that the next participant's allocation could not be predicted. Allocation of treatment was concealed from all participants, GP practices and researchers in the blind arm of the trial. Only the independent senior programmer at Barts CTU, who wrote the randomisation code on the VIDAL app, had access to this code.

On receipt of an eligible corrected blood calcium result and after verifying participant eligibility and consent, the Trial Coordination Centre telephoned potential participants to confirm their willingness to be randomised. Randomisation was then performed by the automated system on the VIDAL app.

Participants randomised to a treatment arm (BD, BC or OD) were then sent a 1-year supply of study medication by recorded delivery from the dispensing pharmacy. The second year's study medication was allocated automatically by the VIDAL app 1 year later and sent by the same procedure. Participants allocated to OC at randomisation received a letter from the Trial Coordinating Centre explaining that they would be recontacted at 2 years for a follow-up visit and a further blood sample.

The study participants who were enrolled at the blind practices received annual study medication packs, each containing 12 monthly doses of study oil labelled as 'vitamin D_3 oil/placebo oil'. Each pack contained 12 bottles containing either 5.2 ml cholecalciferol (Vigantol® Oil; Merck Serono GmbH, Germany) – an oily solution of vitamin D_3, concentration 0.5 mg/ml – or 5.2 ml placebo, a pharmacopoeia-listed mixture of palm oil and coconut oil containing medium-chain triglycerides (Miglyol® 812; Caesar & Loretz GmbH, Germany).

Study participants enrolled at open-label practices who were allocated to vitamin D (OD arm) received annual study medication packs each containing 12 monthly doses of study oil labelled as 'vitamin D_3 oil'. Each of the 12 bottles contained 5.2 ml, cholecalciferol.

The bottles of medication contained 5.2 ml to ensure delivery of 5 ml (2.5 mg of vitamin D_3) because $\approx$ 0.2 ml of the oily solution adheres to the sides of the bottle.

Follow-up

To obtain information on their vitamin D consumption for an interim report, 121 participants who were randomised to the no treatment arm in open practices (OC arm) before May 2014 were contacted by post, e-mail or telephone in December 2014. There was no other contact after randomisation with the OC participants until they were invited to attend the 2-year final visit. All other study participants (i.e. those allocated to active treatment or placebo) were contacted at least once per month post randomisation by their preferred medium, as described in the following paragraphs. Letters were sent by CFH Docmail Ltd (Radstock, UK) on behalf of the participating GP practices, with responses sent directly back to the study participant's GP practice.

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Automated telephone call, e-mail or text message every month from month 1 to month 24

All participants except those randomised to OC (no treatment) were reminded to take their study medication every month by automated telephone call, e-mail or text message generated by the VIDAL app.

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

All participants except those who were randomised to the OC (no treatment) arm were contacted quarterly either by post from their GP practice or by e-mail from the VIDAL app (depending on the participant's choice of medium). The participants were asked to send a short reply by the same medium. E-mails to the VIDAL app were recorded automatically. The reply recorded the dates on which the last three doses of study medication were taken or reasons for non-compliance, any planned change of address and any hospital admissions. The 3-monthly follow-up also included a reminder for participants to contact their GP if they were experiencing ongoing symptoms of hypercalcaemia (persistent nausea, vomiting, thirst, passing excessive amounts of urine or feeling generally unwell).

The Trial Coordinating Centre also monitored serious adverse events (SAEs), adverse reactions (ARs) and compliance during follow-up.

General practitioner practice visit at month 24

Two years after randomisation, all participants were invited to attend their GP practice for the 2-year visit to obtain a repeat blood sample for 25(OH)D assay, a BP measurement and responses to the same lifestyle questions as at baseline. Current consumption of any medication or supplement containing vitamin D was recorded to assess contamination.

Each GP practice also examined 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 exterior of the treatment pack against the compliance information supplied in the quarterly follow-up form.

Summaries of GP records for all randomised participants were extracted by the practice staff to obtain prospectively recorded information about GP visits, prescriptions and infections over the preceding 3 years (1 year pre randomisation and 2 years during the trial).

Automated follow-up

Cause-specific mortality, cancer incidence and hospital records were obtained by linking NHS number, date of birth and postcode to medical records held by NHS Digital on cancer registrations (provided by NHS Digital on behalf of Public Health England), deaths (from civil registration data and provided by NHS Digital on behalf of the Office for National Statistics) and the Hospital Episode Statistics (HES) database (from March 2012 to March 2017) on hospital admissions.[44]

Interim Data Monitoring Committee reports

A Data Monitoring Committee (DMC) was convened. Interim safety analyses were conducted twice during the feasibility study. The independent statistician conducted an analysis to compare the incidence of SAEs between intervention and control arms for review by the DMC. Had there been a significant difference ($p < 0.05$) in the incidence of fatal or life-threatening adverse events, the DMC would have been informed and would have discussed whether or not the sponsor and ethics committee should be consulted regarding stopping the trial, but this did not arise.

Trial outcomes

Primary outcomes

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 1600 participants aged 65–84 years. 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 blind and open practices
ii. compare allocated treatment compliance among open-label (OD) participants and blind (BC or BD) participants
iii. compare contamination rates (the proportion taking > 400 IU per day of vitamin D), particularly between open untreated control (OC) and blind (BC or BD) participants.

Secondary outcomes

i. Comparison of reported SAEs between vitamin D and control participants in blind practices provides a conventional safety measure. OC participants did not receive quarterly follow-ups and therefore did not report SAEs, which were recorded only retrospectively at the 2-year follow-up.
ii. Comparison of numbers of infections and GP visits between vitamin D and control participants (a) in blinded practices, and (b) in open-label practices. This provides an estimate of the bias in these measures with open-label randomisation.
iii. Blood 25(OH)D concentration at recruitment and at 2 years in relation to allocated treatment and other potential determinants of vitamin D status including self-reported sun exposure, latitude, consumption of oily fish and use of vitamin D supplements.
iv. Comparison of change in systolic and diastolic BP from recruitment to 2 years between the vitamin D arm and the control arm.

Sample size

The aim of the feasibility study was to recruit 1600 participants aged 65–84 years through 20 GP practices [400 on OD vs. 400 on OC; 400 in the blind vitamin D (BD) arm vs. 400 in the blind placebo control (BC) arm]. The target was to randomise an average of 80 participants aged 65–84 years per GP practice with at least 9% response (number randomised/number invited). If recruitment in some GP practices fell below this target, recruitment in other practices would be continued after 80 participants had been randomised to achieve the overall target of 1600 participants.

Power

The main purpose of the feasibility study was to pilot the organisational procedures for the main trial, to demonstrate adequate recruitment and compliance and to prepare for any unexpected difficulties in running the trial. The number of practices involved was considered large enough to be representative of the diversity of practices that may participate in the main trial, so that average participation (the proportion of those invited who are randomised) could be considered a reliable estimate of what would be achieved in the main trial.

The proposed feasibility study also had adequate power to detect a 5% difference in participation between open-label and blind practices with a nominal two-sided alpha level of 5%, comparing blind and open designs in 10 pairs of practices, with each practice recruiting 80 participants. To estimate the power, we simulated the number of registered GP practice patients who one would need to approach in each practice to recruit 80 participants (negative binomial). The cluster randomisation was powered to detect a change in the mean participation rate from 10% (range 2.5% to 17.5%) to 15% (5.7% to 24.3%). Under these assumptions the probability of detecting this difference at $p < 0.05$ would be 92%. (If there were no heterogeneity between practices the overall recruitment rate would be estimated more precisely, e.g. 9% with standard error 0.2%.)

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In addition, to detect a difference of 10% in any binary outcome, the trial had (at least) 80% power (using a nominal 5% significance level) for any overall comparison, such as vitamin D versus placebo (400 per arm), and 70% power for any between-practice comparison, such as BC versus OC (sign test with 10 pairs of practices; power = 70% for 0.45 vs. 0.55, and 88% for 0.10 vs. 0.20). The outcome might be reporting a respiratory infection (15% vs. 25%) or compliance (85% vs. 95%). The pre-specified definition of 'composite compliance' was that a randomised participant should attend the 2-year visit, and:

i. if allocated to vitamin D, report taking at least 19 (79%) of the 24 monthly doses of the allocated investigational medicinal product, or
ii. if allocated to no vitamin D (BC or OC), report taking a total of < 300,000 IU of vitamin D supplements over the 2 years of the study. (The current UK reference nutrient intake of 400 IU per day is 292,000 IU over 2 years.)

Statistical methods

All analyses were performed on an intention-to-treat basis using Stata® version 15 (StataCorp LP, College Station, TX, USA). Wilcoxon's signed-rank test was used for comparisons of blind versus open practices within matched pairs.

Response rates

The GP practices were able to provide anonymised data on the number of participants they approached to take part in the trial by 5-year age group and by sex. No further variables were available. From these totals, participation rates were calculated. Estimated numbers of replies are shown for two practices (1O and 3B) that did not record the number of reply slips, and for one (9B) that invited all 960 eligible patients, received 170 replies and stopped recruitment when 100 had attended the baseline visit. The numbers of replies at these three practices were estimated by assuming the same ratio of replies to baseline visits as at other practices with the same allocation (open or blind). The number of invitations required by practice 9B to give the estimated 108 replies was estimated as 960 × (108/170).

Compliance

Data from quarterly follow-ups and the 2-year visit were used to calculate the overall number of study medication doses taken. The percentage of participants taking all three doses was calculated in each quarter and tabulated by GP practice and treatment allocation. The proportion of participants taking at least one dose was also calculated in each quarter. Participants were defined as having stopped taking medication at the 2-year follow-up if they took fewer than two doses in the last quarter of the trial. The reasons for stopping study medication, as given on the withdrawal form, were tabulated by allocated treatment and study arm.

Contamination

The daily dose of any supplements containing vitamin D was self-reported at baseline and at the follow-up visit. Participants reporting taking cod liver oil were assumed to be consuming 200 IU per day of vitamin D. Details of prescriptions were also downloaded from GP records, but some did not record frequency, so daily dose could not always be calculated accurately. Doses of medication indicated from prescription data that could not be verified from self-reported medication data were assumed to be 800 IU per day. Self-reported and prescription data have been tabulated separately.

Summary measure of compliance

The single measure of 'composite compliance', defined above, was pre-specified to avoid multiple testing in the power calculation. This was calculated as described using the compliance and contamination data. Participants who died during the 2-year trial period were excluded from this analysis. The definition required control participants not to exceed 300,000 IU over the 2 years of the trial; however, a conservative approach

was taken such that any control participants who reported taking, or were prescribed, supplements exceeding 400 IU per day at either baseline or follow-up were considered non-compliant.

Deprivation

English indices of multiple deprivation (IMD) for 2015 were downloaded for each participant's home postcode.[45] These produce the IMD by small areas of approximately 650 households. We also used the Income Deprivation Affecting Older People Index (IDAOPI), grouping deciles of IDAOPI into quintiles.

Blood 25(OH)D

Mean blood 25(OH)D levels at baseline were categorised on demographic and lifestyle factors. Multivariate linear regression was used to calculate the adjusted means of 25(OH)D and trend *p*-values across categories for each factor (see *Table 14*). The adjusted means are the estimated marginal means, which are standardised to the observed distribution on all other variables. The suboptimal threshold was defined as blood 25(OH)D < 75 nmol/l.

Linear regression was used to assess change in blood 25(OH)D from baseline to the 2-year visit with respect to allocated treatment. As a secondary analysis, the change in season was also adjusted for, only slightly modifying the estimates. Vitamin D levels were lower in winter and spring and therefore a variable was constructed to represent change in season: summer/autumn to winter/spring, same season, winter/spring to summer/autumn.

Infections and GP visits

Data downloaded from GP notes were used to identify visits to the GP when an infection was diagnosed. Infections were categorised into five categories: upper respiratory, lower respiratory, urinary, skin/mucosal or soft tissue, and other. Multiple visits were combined by ignoring subsequent visits within the same category within 2 weeks. Infections were tabulated by allocated treatment and baseline blood 25(OH)D. Numbers of infections and visits were calculated in the year preceding the randomisation date and in the 2 years of the trial.

Cancer, mortality and hospital admissions data

Cancer incidence data were available until April 2017, just over 2 years after the last patient was randomised. The numbers of incident cancer diagnoses within 2 years of randomisation were tabulated; skin cancers and benign and in situ tumours were excluded. HES data[44] were complete until March 2017, providing complete data on emergency hospital admissions within 2 years of randomisation for all patients. Numbers of admissions by treatment arm were also available for the year preceding randomisation. Mortality data were available until February 2018, 3 years after the last patient was randomised.

Other measurements

Quality of life was measured at baseline and 2 years after randomisation using the standardised EuroQol-5 Dimensions, three-level version (EQ-5D-3L), health status instrument[46] consisting of two elements: (1) a simple descriptive profile comprising five dimensions (i.e. mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and (2) the EQ analogue scale, a single index value for health status. The descriptive dimensions each comprised three levels: no problems, some problems and extreme problems. These levels were assigned a score of 1, 2 and 3 respectively and a total score calculated from adding all five values, where a score of 5 equated to best possible health and a score of 15 equated to worst possible health. For the tables, these were categorised into five groups equating to a score of 5, 6, 7, 8 or ≥ 9. The EQ visual analogue scale records each respondent's self-rated health that day as a score between 1 and 100, where 1 is the worst imaginable health state and 100 is the best imaginable health state. This was adapted by asking participants to give a number between 1 and 100 instead of marking their score on a scale (see *Appendix 1*).

Changes in BP, height, weight, body mass index (BMI) and self-reported health score (given as a percentage) were calculated. Univariate linear regression models for each of these were fitted to estimated mean changes by allocated treatment.

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Chapter 3 Results

Recruitment

The CONSORT (Consolidated Standards of Reporting Trials) flow diagram summarising the number of individuals participating at each stage of the trial is shown in *Figure 2*. In addition to data collected from the participants at study visits, data regarding prescriptions, infections and GP visits were downloaded from each GP database. GP data were obtained for 1554 participants (96.2%) but this varied by GP practice.

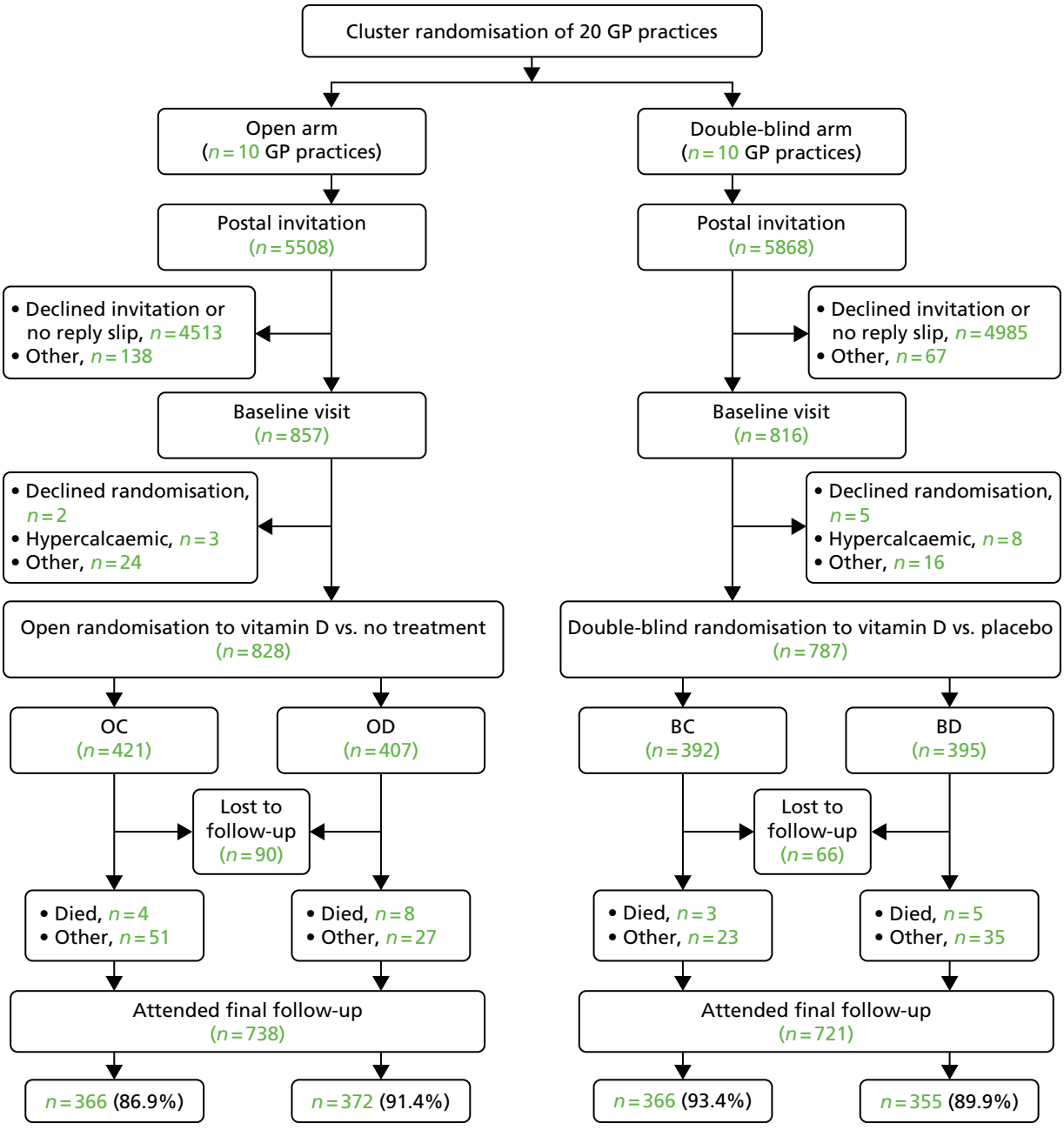

FIGURE 2 The VIDAL trial CONSORT flow diagram.

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Some practices did not provide data from patients who had moved GP or who had died, as these data were no longer available on their computer systems. *Figure 3* shows cumulative recruitment. The pilot practice began recruiting in April 2013. Main recruitment began in October 2013 and ended in January 2015 with 1615 participants randomised (the target was 1600 participants). The recruitment period for individual practices ranged from 4 to 12 months.

Table 2 shows the numbers of registered patients in each practice invited, replying, attending the baseline visit and randomised. GP practice codes indicate matched pair (0–9) and whether or not randomisation was open-label or blind (O or B).

The overall recruitment rate (number randomised/number invited) was 14.2%. The rate was higher in open (15.0%, range 8.8–22.4%) than in blind practices (13.4%, range 8.8–26.4%), but this did not approach statistical significance because of the wide variation between practices (Wilcoxon signed-rank test; $p = 0.7$). *Table 3* shows that the recruitment rate was lower ($p = 0.002$) in participants aged 80–84 years (11.5%) than in participants aged < 80 years (14.6%), and was lower in women than in men ($p = 0.002$).

Table 4 shows the 1615 randomised participants by age and sex. There were 857 (53.1%) men and 758 (46.9%) women, with similar age distributions. The majority (70.2%) were aged 65–74 years and only 9.7% were 80–84 years. Almost all were white (*Table 5*: 1600/1615). *Table 6* shows numbers by age and sex of those who chose to receive and return quarterly follow-ups by e-mail. The proportion choosing e-mail was higher among men and declined with age, from 77.4% in those aged 65–69 years to 36.5% in those aged 80–84 years. The proportion choosing e-mail for monthly reminders to take their study medication also declined with age, from 70.5% (440/624) of those aged 65–69 years to 33.3% (52/156) of those aged 80–84 years, most of whom (79.5%) requested a monthly telephone call. The proportion requesting text message reminders declined from 40.1% (250/624) in those aged 65–69 years to 9.0% (14/156) in those aged 80–84 years (more than one medium could be chosen).

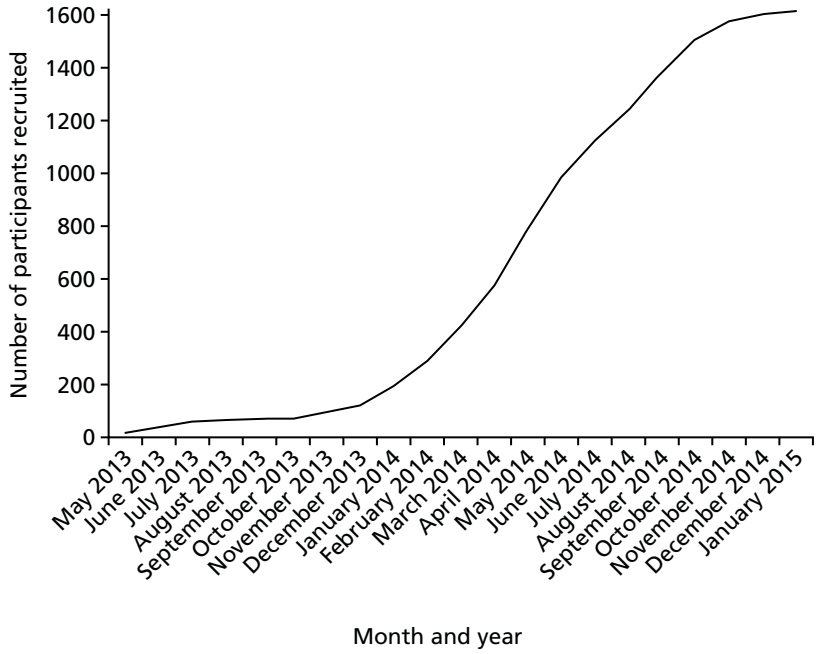

FIGURE 3 Cumulative VIDAL recruitment by month and year.

TABLE 2 Participation rates and numbers randomised by GP practice (estimated numbers in brackets). GP practice codes indicate matched pair (0–9) and allocated to open-label or blind individual randomisation (O or B)

GP practice	Number invited	Reply slips received	Attended baseline visit	Number randomised	% randomised	OC	OD	BC	BD
0B (pilot)	690	83	81	72	10.4			36	36
0O	348	95	80	78	22.4	42	36		
1B	659	81	80	79	12.0			39	40
1O	500	(97)	84	83	16.6	47	36		
2B	680	60	63	60	8.8			30	30
2O	316	77	67	60	19.0	28	32		
3B	476	(88)	81	73	15.3			35	38
3O	450	112	86	83	18.4	44	39		
4B	528	74	65	65	12.3			34	31
4O	616	64	57	54	8.8	28	26		
5B	375	129	102	99	26.4			48	51
5O	450	91	86	81	18.0	36	45		
6B	500	95	82	80	16.0			39	41
6O	705	78	78	76	10.8	38	38		
7B	1000	81	78	77	7.7			39	38
7O	805	176	159	156	19.4	79	77		
8B	350	84	84	84	24.0			43	41
8O	479	90	80	78	16.3	36	42		
9B	(610)	(108)	100	98	(15.5)			49	49
9O	839	115	80	79	9.4	43	36		
Total	11,376	1878	1673	1615	14.2	421	407	392	395

TABLE 3 Participation rates and numbers randomised by age group and sex

Participants	Number invited	Number randomised	% randomised
Age group (years)			
65–69	4599	624	13.6
70–74	3122	510	16.3
75–79	2297	325	14.2
80–84	1358	156	11.5
Sex			
Male	5631	857	15.2
Female	5745	758	13.2
Total	11,376	1615	14.2

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TABLE 4 Randomised individuals by age and sex

Age group (years)	Male, *n* (%)	Female, *n* (%)	All randomised, *n* (%)
65–69	341 (39.8)	283 (37.3)	624 (38.6)
70–74	253 (29.5)	257 (33.9)	510 (31.6)
75–79	177 (20.7)	148 (19.5)	325 (20.1)
80–84	86 (10.0)	70 (9.2)	156 (9.7)
Total	857 (100)	758 (100)	1615 (100)

TABLE 5 Randomised individuals by ethnicity

Ethnicity	*n* (%)
White British	1563 (96.8)
White Irish	11 (0.7)
White other	26 (1.6)
Caribbean	6 (0.4)
Asian	6 (0.4)
Mixed	3 (0.2)
Total	1615 (100)

TABLE 6 Proportion of those randomised choosing e-mail, text message or automated telephone call for their quarterly follow-ups and monthly reminders, by age group and sex (more than one could be chosen for monthly reminders)

	Males (years)				Females (years)			
Method	65–69	70–74	75–79	80–84	65–69	70–74	75–79	80–84
Quarterly follow-up, *n* (%)								
E-mail	274 (80.4)	182 (71.9)	114 (64.4)	37 (43.0)	209 (73.9)	163 (63.4)	67 (45.3)	20 (28.6)
Monthly reminder, *n* (%)								
E-mail	249 (73.0)	158 (62.5)	105 (59.3)	34 (39.5)	191 (67.5)	142 (55.3)	60 (40.5)	18 (25.7)
Text	135 (39.6)	84 (33.2)	38 (21.5)	10 (11.6)	115 (40.6)	85 (33.1)	27 (18.2)	4 (5.7)
Telephone	140 (41.1)	123 (48.6)	105 (59.3)	66 (76.7)	118 (41.7)	148 (57.6)	108 (73.0)	58 (82.9)
Total	341	253	177	86	283	257	148	70

Compliance

Tables 7 and *8* and *Figure 4* show compliance among the 1194 participants randomised to receive study medication (the blind treatment arms or the OD arm). Excluding participants who died during the trial period, 89.9% (1059/1178) were still taking medication at the end of the study, 91.2% in the OD arm and 89.2% in the blind treatment arms. All 24 doses of study medication were taken by 80.2% (625/779) of participants in the blind treatment arms and 83.2% (332/399) of those in the OD arm. Eleven participants in the blind treatment arms (1.5%) and four (1.0%) in the OD arm did not take any study medication from the outset. Compliance was higher among men than among women and among participants aged < 75 years: all 24 doses were taken by 86.6% of men and 79.0% of women aged < 75 years, and by 83.8% of men and 69.9% of women aged ≥ 75 years.

TABLE 7 Compliance of participants per quarter (percentage of those randomised taking all three monthly doses) by GP practice among 1194 patients taking study medication and number of participants attending the 2-year visit (of the 1595 still alive at the end of the trial)

			Compliance (% of randomised participants taking all three doses)								Attended the 2-year visit[a]
Practice	Total randomised	Randomised to treatment	3 month	6 month	9 month	12 month	15 month	18 month	21 month	24 month	*n* (%)
0B	72	72	95.8	93.1	88.9	90.3	88.9	86.1	84.7	80.6	64 (88.9)
0O	78	36	97.2	97.2	97.2	97.2	97.2	97.2	97.2	97.2	70 (89.7)
1B	79	79	96.2	96.2	94.9	93.7	92.4	89.9	88.6	89.9	74 (93.7)
1O	83	36	100.0	100.0	100.0	94.4	94.4	94.4	94.4	88.9	76 (91.6)
2B	60	60	100.0	98.3	98.3	98.3	98.3	95.0	91.7	90.0	54 (91.5)
2O	60	32	96.9	90.6	90.6	90.6	90.6	87.5	87.5	87.5	53 (88.3)
3B	73	73	98.6	98.6	91.8	90.4	89.0	89.0	89.0	87.7	64 (88.9)
3O	83	39	100.0	100.0	100.0	100.0	100.0	100.0	100.0	97.4	73 (89.0)
4B	65	65	96.9	93.8	89.2	83.1	81.5	81.5	81.5	80.0	52 (83.9)
4O	54	26	96.2	92.3	88.5	88.5	88.5	84.6	84.6	80.8	42 (79.2)
5B	99	99	100.0	99.0	98.0	97.0	94.9	93.9	93.9	93.9	96 (97.0)
5O	81	45	95.6	95.6	95.6	93.3	93.3	93.3	93.3	93.3	75 (93.8)
6B	80	80	98.8	95.0	95.0	92.5	92.5	91.3	90.0	88.8	73 (91.3)
6O	76	38	100.0	97.4	94.7	92.1	92.1	92.1	92.1	89.5	70 (93.3)
7B	77	77	98.7	98.7	98.7	97.4	97.4	97.4	96.1	96.1	75 (98.7)
7O	156	77	97.4	97.4	96.1	96.1	92.2	92.2	89.6	88.3	142 (92.2)
8B	84	84	97.6	94.0	94.0	90.5	84.5	84.5	83.3	82.1	75 (90.4)
8O	78	42	95.2	85.7	83.3	83.3	81.0	76.2	76.2	76.2	60 (82.2)
9B	98	98	99.0	96.9	96.9	95.9	95.9	94.9	93.9	90.8	94 (96.9)
9O	79	36	100.0	100.0	100.0	97.2	97.2	97.2	94.4	94.4	77 (98.7)
Total	1615	1194	98.1	96.2	94.8	93.3	92.0	91.0	90.0	88.7	1459 (91.5)

a Twenty deceased participants are excluded from the denominator.

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TABLE 8 Compliance of participants allocated to study medication: number of doses taken by study arm. Those randomised to receive no treatment in open practices are excluded

Total number of doses taken	Blind treatment arms, *n* (%)	OD, *n* (%)	Total, *n* (%)
0–5	28 (3.6)	18 (4.4)	46 (3.9)
6–11	31 (3.9)	9 (2.2)	40 (3.4)
12–17	21 (2.7)	8 (2.0)	29 (2.4)
≥ 18	707 (89.8)	372 (91.4)	1079 (90.4)
Total	787	407	1194

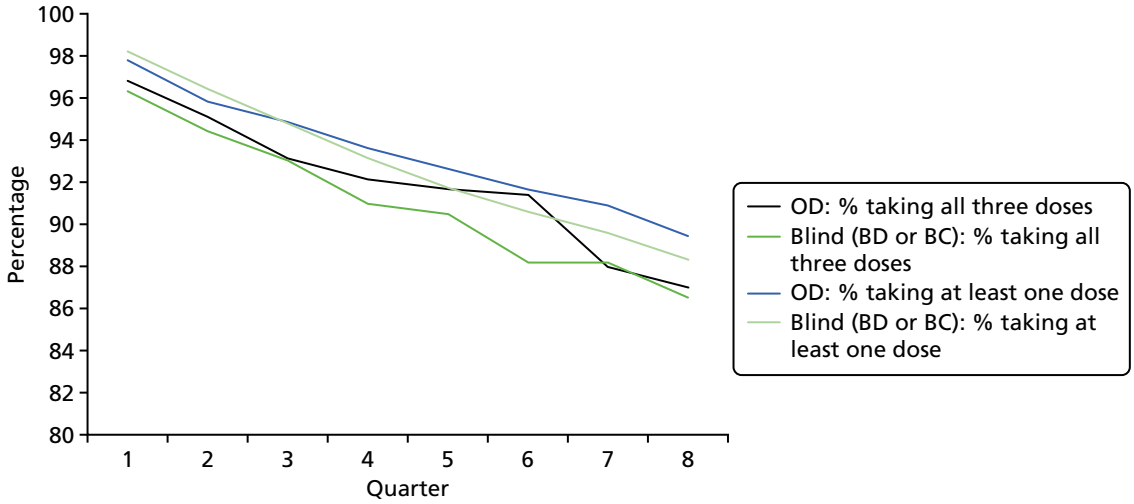

FIGURE 4 Compliance of participants taking study medication in each quarter (percentage of those randomised taking all three monthly doses vs. at least one dose) by randomisation method (blind or open-label).

Occasional doses were missed for various reasons and so a more useful measure of compliance is the date when a participant last took their study medication. Within 6 months of entry, 16 (4.0%) participants allocated to OD and 34 (4.4%) on blind treatment (BC or BD) had stopped taking study medication. The subsequent rate of decline (*Figure 5*), which was slightly lower, is likely to provide a better estimate of the proportion who would continue treatment in a longer trial. Among those compliant at 6 months, 6.2% (70/1128) stopped taking medication over the remaining 18 months of the trial [5.0% (19/383) on OD and 6.8% (51/745) on blind treatment; $p = 0.21$], which is an overall annual attrition of 4.1% per year. If this rate of attrition continued, 81.1% of all randomised participants would still be taking allocated medication at the end of a 5-year trial.

Treatment compliance and withdrawal

For mortality (the primary end point in the main trial for which this is the feasibility study), there were no withdrawals from follow-up, because all participants will continue to be followed up through NHS Digital unless they are censored at emigration. *Table 9* shows the reasons given by 13 (3.1%) of 421 OC participants who notified the practice that they wished to withdraw from the trial, either because they began taking > 400 IU per day of vitamin D or because they would not attend the 2-year follow-up (this includes two participants who started taking vitamin D during the trial but returned for the 2-year follow-up). *Table 9* also shows reasons for stopping treatment for 137 (11.5%) of 1194 participants allocated to treatment who stopped taking medication before the 2-year visit, including 16 participants who died and 45 participants who attended the 2-year visit. In the blind practices, 11.0% of participants stopped taking study medication compared with 8.8% of those allocated to vitamin D in open practices (Wilcoxon signed-rank test; *p*-value = 0.4). The proportion of participants who stopped their medication increased with the number of days spent in hospital over the 2-year trial period according to HES data:[44] 8.5% of those without hospital admissions, 27% (30/109) of those spending < 10 days in hospital and 53% (16/30) of those spending > 10 days in hospital.

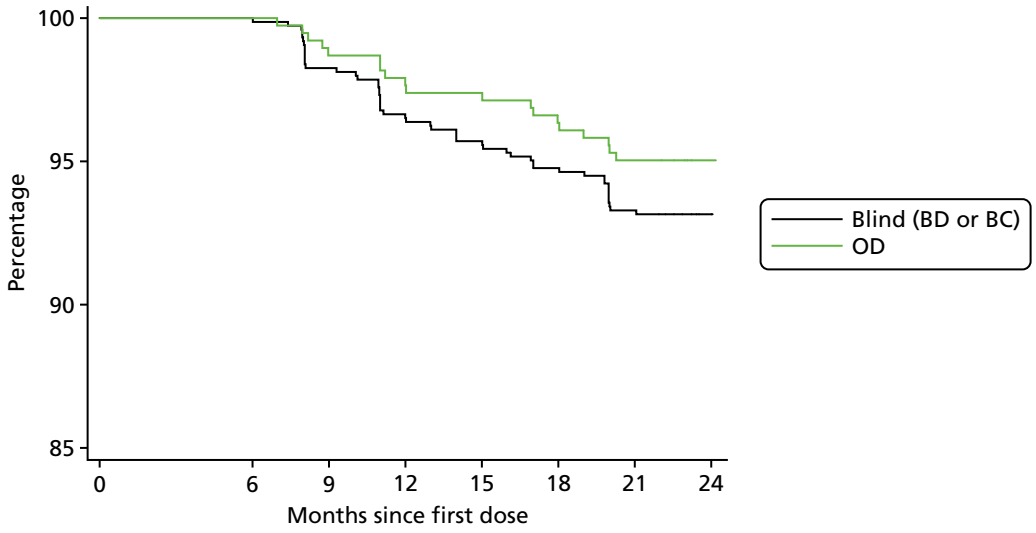

FIGURE 5 Proportion of participants who were compliant at 6 months still taking study medication over the remainder of the trial. Within 6 months of entry 4.0% of participants allocated to OD and 4.4% on blind treatment had stopped taking study medication.

TABLE 9 Reasons for 13 notified withdrawals in OC arm and reasons for stopping medication in treated participants as reported by participants

	Open practices		Blind practices		
Variable	**OC**	**OD**	**BC**	**BD**	**All blind patients**
Reason for withdrawal					
AR to oil	NA	11	7	7	14
Illness	3	8	4	12	16
Moved out of the area	4	4	6	6	12
Other reason	3	8	10	8	18
Decided to take vitamin D	2	0	1	1	2
Prescribed vitamin D	1	3	9	5	14
No reason given	0	1	1	8	9
Total stopping medication excluding deaths, *n* (%)		35 (8.8)	38 (9.8)	48 (12.3)	86 (11.0)
Deceased	4	8	3	5	8
Totals					
Randomised participants	421	407	392	395	787
Continued taking medication	NA	364	351	342	693

AR, adverse reaction; NA, not applicable.

Table 10 shows that 91.5% (1459/1595) of all surviving randomised participants returned for the 2-year visit. A viable blood 25(OH)D result was obtained for 1456 of them. As expected, a higher proportion of surviving participants in the three study medication arms than in the OC arm attended the 2-year visit (93.2% OD vs. 87.8% OC in open practices; $p = 0.008$) (92.6% BD and BC in blind practices). The proportion returning for the 2-year visit decreased with increasing number of days in hospital according to HES data:[44] 92.6% (1318/1424) of those without stays in hospital attended the follow-up visit compared with 79.9% (119/149) of those spending < 10 days in hospital and 52.4% (22/42) of those spending ≥ 10 days in hospital within the 2-year trial period.

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TABLE 10 Number of randomised participants returning for 2-year visit by treatment arm

	Open practices			
GP practice visit	OC	OD	Blind practices	Total
Baseline	421	407	787	1615
2-year visit	366	372	721	1459
% returning for 2-year visit[a]	87.8	93.2	92.6	91.5
Deceased	4	8	8	20

a Deceased participants are excluded from the denominator.

Contamination

Table 11 shows that almost one-quarter of participants (23.2%) reported taking self-administered daily supplements containing vitamin D at baseline, but the majority of these contained ≤ 200 IU (5 µg). GP notes abstracted at the end of the study revealed that an additional 17 (1.1%) participants were being prescribed medication containing vitamin D at baseline, including six at > 400 IU per day. These six, together with the three individuals who were taking > 400 IU (10 µg) per day (see *Table 11* footnote a), were missed by the practice nurse when eligibility was checked at baseline. At follow-up, the proportion reporting self-administered supplements containing vitamin D (16.5% overall) had fallen in the OD arm and in both blind treatment arms but remained unchanged in the OC arm. The proportion of individuals taking high-dose vitamin D increased in the OC arm and the blind treatment arm, but only four individuals reported taking > 1000 IU (25 µg) per day. At 2 years, 3.6% of participants with available data were receiving > 400 IU per day of additional vitamin D (1.1% self-administered, 2.2% prescribed). Contamination data were collected by telephone from 65 participants who did not attend the 2-year visit but remained unknown for 91 participants, including 20 who died during the trial and a further three who died before the telephone follow-up call.

Composite compliance

'Composite compliance', as defined in *Chapter 2*, *Methods*, was calculated for all participants who did not die within 2 years of randomisation. All between-practice differences were tested using Wilcoxon's signed-rank test with 10 matched pairs of practices. Among the control participants, a significantly higher proportion were compliant in blind practices than in open practices (89.7% BC vs. 83.0% OC; $p = 0.01$). This difference was a result of the lower attendance among untreated OCs at the follow-up visit (94.1% BC vs. 87.8% OC; $p = 0.01$), as the proportions exceeding the permitted total dose of vitamin D supplements (300,000 IU over 2 years) were similar. There was an opposite but non-significant difference for the composite compliance variable among those allocated to vitamin D, with higher compliance among open practices (91.0% OD vs. 86.9% BD; $p = 0.07$) owing to slightly higher attendance at the follow-up visit (93.2% OD vs. 91.0% BD) and a slightly higher proportion taking at least 19 doses (92.7% OD vs. 89.2% BD). These opposite effects led to similar overall composite compliance of 88.3% (688/779) in the blind practices and 86.9% (709/816) in the open practices ($p = 0.43$).

Safety

At least one SAE was reported during the 2-year trial period for 11.6% of participants allocated to study medication (*Table 12*), the majority of which resulted in hospitalisation. None of the 184 reported SAEs was judged to be associated with the study medication. There were no significant differences between the SAEs reported between the vitamin D arms and the blind placebo arm. Only seven SAEs were not a cancer diagnosis, did not necessitate hospitalisation and did not result in death. The SAEs were not reported during the trial by patients in the untreated OC arm of the study, as they did not return quarterly follow-up forms.

TABLE 11 Contamination: additional self-administered or GP prescribed daily vitamin D from all supplements being taken at baseline and at the 2-year visit (combined data from self-report and GP records)

Daily vitamin D in addition to study medication	Open practices		Blind practices			Total
	OC	OD	BC	BD	All blind	
Baseline visit						
None	327	305	297	295	592	1224
Self-administered						
≤ 200 IU	75	76	73	78	151	302
201–400 IU	15	23	14	17	31	69
401–1000 IU	1[a]	0	2	0	2[a]	3
GP prescribed						
≤ 400 IU	1	3	4	3	7	11
> 400 IU	1		2	2	4	5
Dose NK[b]	1					1
% > 400 IU	0.7	0.0	1.0	0.5	0.8	0.6
2-year visit						
None	304	318	304	297	601	1223
Self-administered						
≤ 200 IU	54	46	36	47	83	183
201–400 IU	18	10	9	10	19	47
401–1000 IU	8	2	4	3	7	17
> 1000 IU	1	1[c]	2	0	2[d]	4
GP prescribed						
≤ 400 IU	4	2	6	4	10	16
> 400 IU	10	2	6	3	9	21
Dose NK[b]	1	3	6	3	9	13
% > 400 IU among responders	5.0	2.1	4.8	2.5	3.6	3.6
Totals at 2-year visit						
Attended 2-year visit	366	372	366	355	721	1459
Telephoned at 2 years	34	12	7	12	19	65
No data	17	15	16	23	37	71
Deceased	4	8	3	5	8	20
All randomised participants	421	407	392	395	787	1615

NK, not known.

a These three participants were taking 400 IU of vitamin D per day. Two were also taking cod liver oil and one was taking a multivitamin supplement containing 400 IU of vitamin D. These additional supplements were missed by the practice staff when checking eligibility at the baseline visit. (The protocol specified a daily maximum of 400 IU in addition to study treatment.)

b Assumed to be > 400 IU per day.

c This participant randomised to take OD stopped taking study medication after 2 months because of an AR to the oil and began taking vitamin D (1200 IU per day).

d Two participants in the BC arm stopped taking study medication after 8 months. One had been prescribed vitamin D (5000 IU) by their GP and one believed they were on placebo and started taking vitamin D (2500 IU).

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TABLE 12 The SAEs and ARs reported by patients and practices during the 2-year trial period and emergency hospitalisations from HES data

	Open practices		Blind practices		
SAEs, hospital admissions and ARs	OC	OD	BC	BD	Total
SAEs					
Number of SAEs					
None reported	408	359	347	349	1463
1 reported	13	43	37	36	129
2 reported	0	3	6	8	17
3 reported	0	1	1	1	3
4 reported	0	1	1	1	3
Total	421	407	392	395	1615
Reporting ≥ 1 SAE, *n* (%)	13 (3.1)	48 (11.8)	45 (11.5)	46 (11.7)	152 (9.4)
Reporting ≥ 1 life-threatening SAE, *n* (%)	6 (1.4)	10 (2.5)	7 (1.8)	11 (2.8)	34 (2.1)
Participants with ≥ 1 SAE resulting in disability, *n* (%)	3 (0.7)	8 (2.0)	2 (0.5)	3 (0.8)	16 (1.0)
Participants with ≥ 1 SAE not defined as cancer or resulting in death or hospitalisation,[a] *n* (%)	0 (0.0)	0 (0.0)	2 (0.5)	3 (0.8)	5 (0.3)
Reporting ≥ 1 SAE requiring hospitalisation, *n* (%)	7 (1.7)	43 (10.6)	40 (10.2)	41 (10.4)	131 (8.1)
Source of notification for participants with non-fatal SAEs					
Quarterly follow-up	NA	31	35	35	101
GP practice during trial	0	3	4	4	11
At 2-year follow-up	7	5	2	1	15
Hospital admissions from HES data[44]					
Reporting ≥ 1 SAE requiring hospitalisation, *n* (%)	52 (12.4)	47 (11.5)	44 (11.2)	48 (12.2)	191 (11.8)
ARs					
Participants reporting ARs to study oil,[b] *n* (%)	NA	12 (2.9)	4 (1.0)	5 (1.3)	21 (1.8)
Possible		6	2	2	10
Probable		2	2	1	5
Definite		0	0	1	1
Not assessable		4	0	1	5

NA, not applicable.
a These would not be known via HES or cancer/death registration.
b ARs include five participants with diarrhoea, four with nausea, four with skin reactions and eight with other symptoms. The AR that was definitely related was 'bad taste in the mouth'. The probably related ARs were two participants reporting diarrhoea, two reporting nausea and one with skin rash.

Rates of emergency hospitalisation from HES data[44] are slightly higher than the self-reported episodes for the patients allocated to study medication (11.6% vs. 10.4%), and much higher for OCs (12.4% vs. 1.7%), as expected. There were no significant differences in the hospitalisation rate between the open and blind arms of the trial (11.8% in both arms spent at least one night in hospital). Very few participants were hospitalised for > 30 days in total during the 2 years following randomisation [8/813 (1.0%) in the control arms and 7/802 (0.9%) in the vitamin D arms]. *Table 12* shows that the notification source for 116 (91.3%) of the 127 patients with SAEs other than death was self-report on quarterly follow-up forms (*n* = 101) or retrospective report at the 2-year follow-up (*n* = 15). GPs reported only an additional 11 non-fatal SAEs

(8.7%), and none in OCs. ARs were rare, with a non-significantly higher rate on OD (2.9%) than on BD (1.1%) (Wilcoxon signed-rank test; $p = 0.13$). Neither SAEs nor ARs were significantly related to treatment in blind practices.

Quality of life

The self-assessed QoL score at baseline decreased with age, as expected (see lifestyle questionnaire in *Appendix 1*). At baseline, 23.9% of individuals reported problems with mobility, 3.1% reported problems with self-care, 11.1% reported problems performing usual activities, 41.4% reported some pain and 12.5% reported some anxiety or depression. Overall, 49% of individuals reported no problems with mobility, self-care or performing usual activities and did not report pain, discomfort, anxiety or depression (*Table 13*). The lowest QoL scores (reflecting some trouble with four or five of the indicators or extreme trouble with two or more indicators) were reported by 4% of the population overall, but this varied by GP practice (0–17%).

Serum 25(OH)D concentrations

Blood samples valid for 25(OH)D analysis were collected for 1608 participants at baseline and 1448 participants at the year 2 visit. (Four baseline samples were not received at the laboratory and three were insufficient.) Overall, 82.6% of participants had baseline 25(OH)D below the 75 nmol/l threshold. Baseline levels by demographic and lifestyle factors reported at baseline are shown in *Table 14*. Levels decreased with increasing age [p(trend) = 0.01] and were lower in women ($p < 0.0001$). Average levels were highest in summer and autumn, lower in winter and even lower in spring ($p < 0.0001$) and increased with skin darkness from the fairest skin to participants who reported that they rarely burn and always tan (olive skin) ($p < 0.0001$). The small number of participants who described their skin colour as brown or black had lower levels than those with olive skin. Average levels increased with frequency of eating oily fish, although the mean level of 66 nmol/l in participants who reported eating oily fish more than four times a week was still below the adequacy threshold of 75 nmol/l. Levels were lower in participants living at higher latitude ($p = 0.03$ adjusted for IDAOPI deprivation score). The three right-hand columns in *Table 14* show adjusted means and significance levels from a multiple regression including all variables in the table. The trend of reduced 25(OH)D with increasing age was virtually eliminated after adjustment for all variables [p(trend) 0.01 unadjusted, 0.6 adjusted]. The magnitude and significance of trends for other variables were slightly weakened or unaffected by adjustment.

TABLE 13 Self-assessed QoL at baseline by age

	Age (years)				
QoL score, *n* (%)	65–69	70–74	75–79	80–84	Total
5 (best health)	349 (55.9)	252 (49.4)	131 (40.3)	56 (35.9)	788 (48.8)
6	157 (25.2)	126 (24.7)	90 (27.7)	44 (28.2)	417 (25.8)
7	73 (11.7)	82 (16.1)	59 (18.2)	21 (13.5)	235 (14.6)
8	27 (4.3)	29 (5.7)	34 (10.5)	23 (14.7)	113 (7.0)
≥ 9 (worst health)	18 (2.9)	21 (4.1)	11 (3.4)	12 (7.7)	62 (3.8)
Total	624 (100)	510 (100)	325 (100)	156 (100)	1615 (100)

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TABLE 14 Baseline blood 25(OH)D levels (nmol/l) and baseline questionnaire items in 1608 trial participants with baseline blood samples. Adjusted means were estimated in a multivariate regression including all variables in the table

	Univariate analysis						Multivariate regression		
Demographic and lifestyle factors	*n*	Mean	25th percentile	Median	75th percentile	Unadjusted *p*-value	Adjusted mean	95% CI	Adjusted *p*-value[a]
Male	852	54.2	33.7	50.3	69.5	< 0.001	53.2	51.6 to 54.9	0.003
Female	756	48.5	29.1	44.3	64.3		49.6	47.8 to 51.3	
Blind practices	781	50.2	29.9	45.9	64.4	0.07	50.1	48.2 to 52.0	0.06
Open practices	827	52.7	32.3	48.6	68.8		52.9	51.0 to 54.7	
Season recruited									
Summer (June–August)	495	59.5	39.9	56.2	75.1	< 0.001	58.1	55.9 to 60.2	< 0.001
Autumn (September–November)	244	58.0	41.0	56.4	71.7		56.4	53.4 to 59.5	
Winter (December–February)	257	47.1	28.0	42.7	62.3		50.5	47.5 to 53.6	
Spring (March–May)	612	44.3	25.0	39.9	56.7		44.7	42.8 to 46.6	
Complexion									
Very fair	80	39.4	22.3	37.9	52.1	< 0.001	49.3	43.8 to 54.7	0.001
Fair	279	46.8	28.0	41.6	62.5		49.1	46.2 to 52.0	
Pale	397	48.0	29.5	45.6	62.6		47.9	45.5 to 50.3	
Olive	805	56.2	36.1	52.8	71.3		54.4	52.7 to 56.1	
Brown/black	45	49.0	22.5	41.8	59.7		51.2	44.1 to 58.2	
Eating oily fish									
Less than once per week	598	48.7	27.3	44.5	64.3	< 0.001	49.7	47.7 to 51.6	0.001
Once per week	599	52.1	33.3	47.3	67.1		51.3	49.3 to 53.2	
2 or 3 times per week	382	53.9	34.4	50.6	69.1		53.8	51.4 to 56.2	
≥ 4 times per week	29	65.9	36.6	59.8	82.1		64.1	55.2 to 72.9	
Travel abroad in previous year									
No	704	44.3	25.6	40.9	58.8	< 0.001	46.8	45.0 to 48.7	< 0.001
Yes	902	57.2	37.3	53.1	72.4		55.2	53.6 to 56.8	

Demographic and lifestyle factors	Univariate analysis						Multivariate regression		
	n	Mean	25th percentile	Median	75th percentile	Unadjusted *p*-value	Adjusted mean	95% CI	Adjusted *p*-value[a]
QoL score									
5 (best)	785	55.6	36.5	51.6	70.1	< 0.001	53.7	52.0 to 55.5	< 0.001
6	414	51.6	30.8	46.9	67.9		51.4	49.0 to 53.7	
7	235	44.4	24.6	38.6	60.9		47.0	43.9 to 50.2	
≥ 8 (poorest)	174	42.5	24.3	38.7	56.2		47.8	44.1 to 51.5	
Age (years)									
65–69	621	53.2	35.0	49.8	67.9	0.013	51.5	49.6 to 53.4	0.6
70–74	509	51.9	30.8	47.6	66.4		52.2	50.1 to 54.3	
75–79	324	49.5	28.3	43.7	65.3		50.9	48.3 to 53.6	
80–84	154	47.7	25.7	43.3	67.2		50.3	46.5 to 54.2	
Latitude									
51°	878	53.8	32.2	49.7	69.4	< 0.001	53.8	52.2 to 55.4	< 0.001
52°	220	48.8	29.6	44.4	63.5		50.6	47.0 to 54.2	
54°	427	49.5	31.6	46.0	65.4		47.5	45.0 to 49.9	
55°	83	44.7	22.8	42.2	55.4		50.5	45.0 to 55.9	
Quintile deprivation score									
1 (lowest)	91	39.1	19.9	32.4	51.7	< 0.001	47.3	42.2 to 52.4	0.04
2	137	47.7	29.1	43.1	63.7		48.2	44.1 to 52.3	
3	289	53.3	34.1	50.4	67.9		51.8	49.0 to 54.6	
4	431	52.0	31.1	47.4	68.3		52.3	50.0 to 54.6	
5 (highest)	660	52.9	32.5	48.6	67.6		52.2	50.3 to 54.0	

continued

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TABLE 14 Baseline blood 25(OH)D levels (nmol/l) and baseline questionnaire items in 1608 trial participants with baseline blood samples. Adjusted means were estimated in a multivariate regression including all variables in the table (*continued*)

	Univariate analysis						Multivariate regression		
Demographic and lifestyle factors	*n*	Mean	25th percentile	Median	75th percentile	Unadjusted *p*-value	Adjusted mean	95% CI	Adjusted *p*-value[a]
Time spent outdoors per day (hours)									
< 1	309	37.6	23.0	33.3	48.4	< 0.001	42.1	39.2 to 44.9	< 0.001
1–2	543	48.8	29.6	45.6	64.0		49.9	47.9 to 52.0	
3–4	332	54.5	34.7	50.6	69.3		53.3	50.7 to 55.9	
≥ 4	422	62.8	42.3	59.7	78.8		59.0	56.7 to 61.4	
Use sun protection									
Never	192	50.4	29.8	43.4	64.1	0.3	51.0	47.5 to 54.6	0.3
Rarely	143	49.7	30.2	44.1	63.0		49.5	45.5 to 53.6	
Sometimes	392	51.5	32.4	48.3	67.5		51.1	48.6 to 53.5	
Often	879	52.1	30.9	48.0	67.8		52.1	50.5 to 53.8	
Actively seek suntan									
Never	1006	47.9	28.6	43.5	62.8	< 0.001	48.6	47.1 to 50.2	< 0.001
Rarely	242	50.6	32.2	49.1	65.3		51.0	48.0 to 54.1	
Sometimes	215	58.9	38.6	52.6	74.3		58.0	54.7 to 61.2	
Often	143	67.4	46.3	63.0	83.2		62.8	58.7 to 66.8	
Sunbed use in past year									
Never	1592	51.4	30.9	47.1	66.4	0.009	51.4	50.2 to 52.6	0.02
1–9 times	10	65.8	48.6	68.1	79.1		59.9	44.9 to 74.9	
≥ 10 times	4	79.1	51.2	80.1	107.0		76.7	52.9 to 100.5	

CI, confidence interval.
a For all ordinal variables, *p*-values for trends are given.

Treatment effects

Figure 6 and *Table 15* show blood 25(OH)D levels at baseline and at 2 years in control participants and in those randomised to receive vitamin D. The mean blood 25(OH)D levels at follow-up were 109.6 nmol/l in those allocated to vitamin D and 51.8 nmol/l in control participants. The proportion ≥ 75 nmol/l was 16.4% at baseline and 88.0% at 2 years in the vitamin D treatment arms but remained unchanged in the control arms (18.3% at baseline, 17.9% at 2 years). The proportion ≥ 75 nmol/l at 2 years was 51.7%

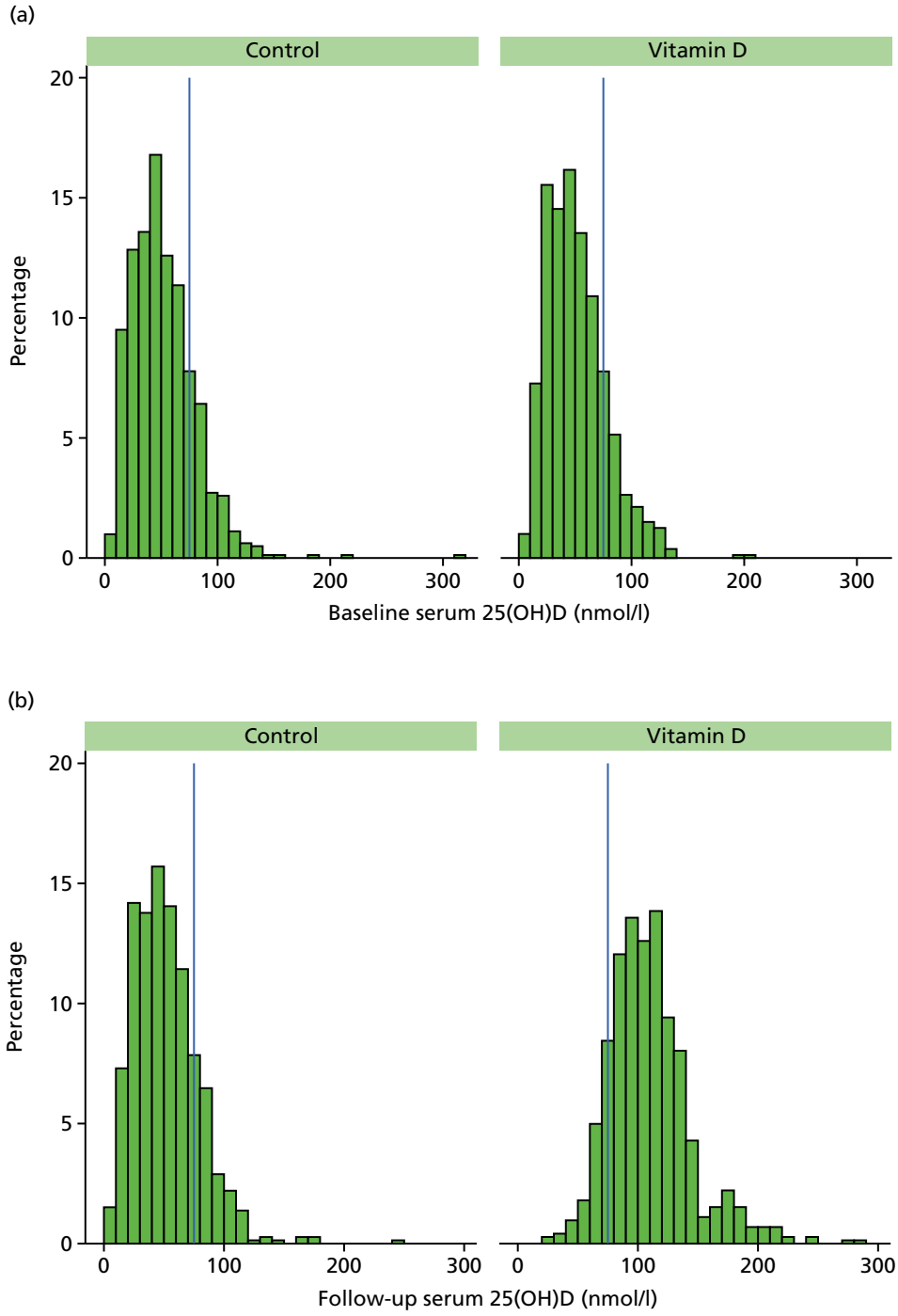

FIGURE 6 Baseline blood 25(OH)D levels by treatment arm at (a) baseline and (b) 2 years. The vertical line shows the suboptimal 75 nmol/l threshold.

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TABLE 15 Blood 25(OH)D levels at baseline ($n = 1608$) and follow-up ($n = 1448$)

	Open practices, *n* (%)		Blind practices, *n* (%)	
Blood 25(OH)D (nmol/l)	OC	OD	BC	BD
Baseline				
0–24	65 (15.4)	66 (16.3)	71 (18.3)	56 (14.3)
25–49	153 (36.3)	147 (36.2)	146 (37.5)	166 (42.4)
50–74	126 (29.9)	120 (29.6)	101 (26.0)	112 (28.6)
75–99	56 (13.3)	51 (12.6)	48 (12.3)	36 (9.2)
100–149	19 (4.5)	21 (5.2)	21 (5.4)	21 (5.4)
≥ 150	2 (0.5)	1 (0.3)	2 (0.5)	1 (0.3)
All participants				
< 75	344 (81.7)	333 (82.0)	318 (81.8)	334 (85.2)
≥ 75	77 (18.3)	73 (18.0)	71 (18.3)	58 (14.8)
Total participants	421 (100.0)	406 (100.0)	389 (100.0)	392 (100.0)
2-year visit				
0–24	50 (13.7)	0 (0.0)	67 (18.5)	1 (0.3)
25–49	130 (35.7)	6 (1.6)	134 (37.0)	5 (1.4)
50–74	115 (31.6)	42 (11.4)	100 (27.6)	33 (9.4)
75–99	57 (15.7)	106 (28.7)	38 (10.5)	114 (32.3)
100–149	10 (2.8)	180 (48.8)	20 (5.5)	168 (47.6)
≥ 150	2 (0.6)	35 (9.5)	3 (0.8)	32 (9.1)
All participants				
< 75	295 (81.0)	48 (13.0)	301 (83.2)	39 (11.1)
≥ 75	69 (19.0)	321 (87.0)	61 (16.9)	314 (89.0)
Compliant[a]				
< 75		43 (12.0)	289 (83.3)	30 (8.9)
≥ 75		314 (88.0)	58 (16.7)	306 (91.1)
Non-compliant[b]				
< 75		5 (41.7)	12 (80.0)	9 (52.9)
≥ 75		7 (58.3)	3 (20.0)	8 (47.1)
Total participants	364 (100.0)	369 (100.0)	362 (100.0)	353 (100.0)

a Still taking study medication at the end of the trial.
b Stopped taking study medication. A 2-year blood sample was not taken for the majority of the participants who stopped their medication: 31/43 in the OD arm, 26/41 in the BC arm and 36/53 in the BD arm.

(15/29) in non-compliant participants allocated to vitamin D. Among those allocated to vitamin D, mean blood levels decreased with time since last dose from 117.6 nmol/l in those tested within a month of last dose (220 participants) to 108.4 nmol/l in those tested 1–3 months after last dose (463 participants) and 80.0 nmol/l in those tested ≥ 4 months after last dose (38 participants).

Figure 7 shows that vitamin D levels increased for almost all (99.3%) of those randomised to receive vitamin D. The estimated mean increase was 57.9 nmol/l (95% CI 56.3 to 59.4 nmol/l) in the vitamin D arms compared with 0.2 nmol/l (95% CI –1.4 to 1.7 nmol/l) in the control arms. *Figure 8* shows the change in each arm and *Figure 9* shows the smaller change in non-compliant (OD and OB) participants who took vitamin D for < 2 years.

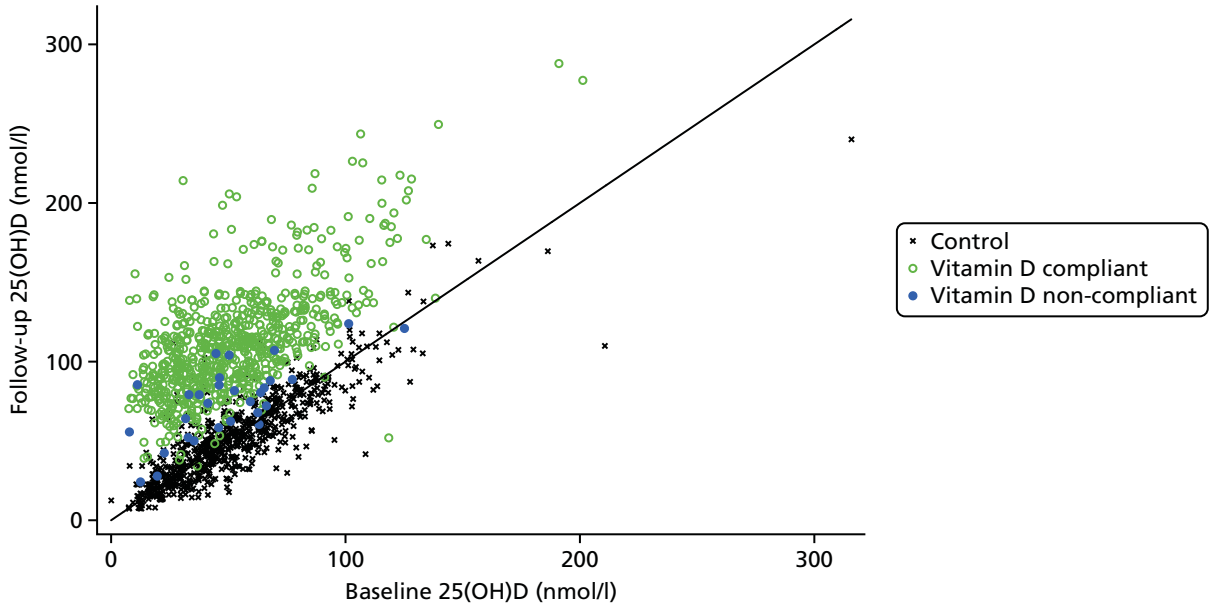

FIGURE 7 Baseline and follow-up blood 25(OH)D levels by allocated treatment arm in 1444 participants who provided two blood samples. Participants stopping their vitamin D medication early are shown as solid blue points.

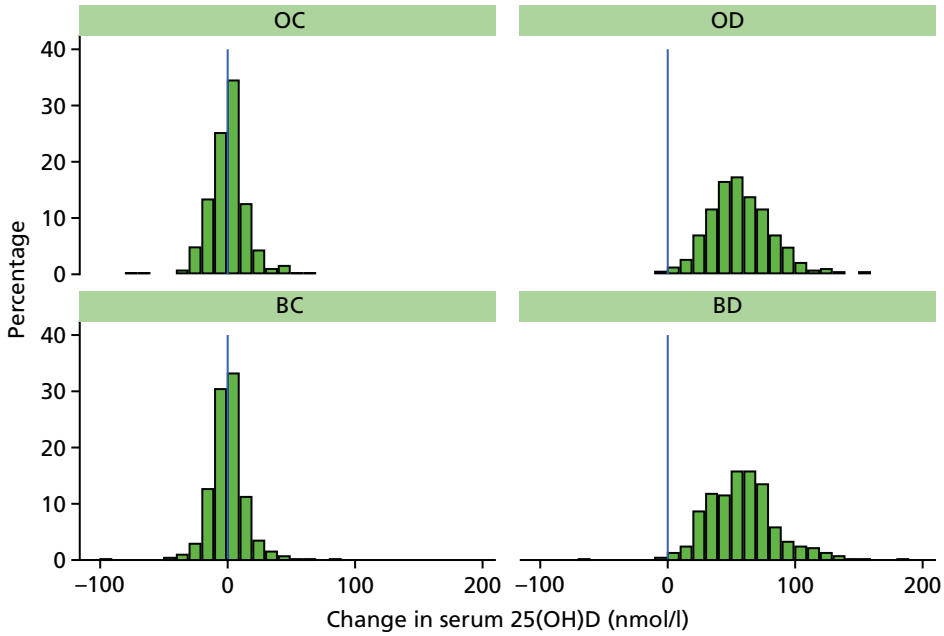

FIGURE 8 Change from baseline to 2 years in blood 25(OH)D levels by treatment arm in 1444 participants who provided two blood samples. No change is denoted by the vertical line at zero.

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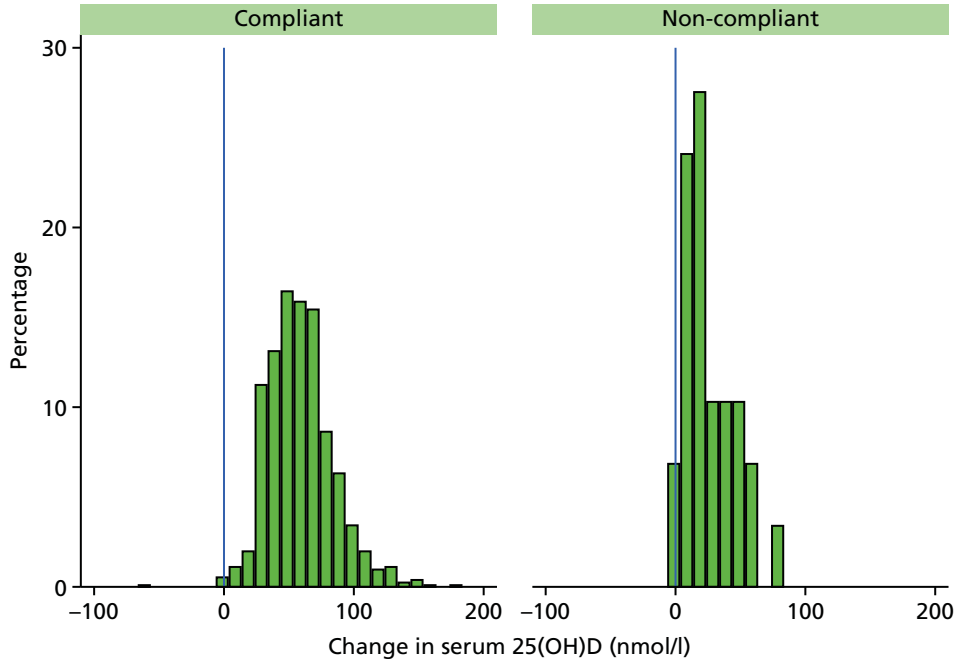

FIGURE 9 Change in blood 25(OH)D levels in those allocated to take vitamin D who were compliant and those who stopped taking their medication (non-compliant, $n = 41$).

TABLE 16 Change in season between baseline and follow-up visit for those with two blood samples ($n = 1444$)

Season change between visits	Control	Vitamin D	Total
Summer/autumn to winter/spring, *n* (%)	154 (21.3)	144 (20.0)	298 (20.6)
Same season, *n* (%)	507 (70.0)	528 (73.3)	1035 (71.7)
Winter/spring to summer/autumn, *n* (%)	63 (8.7)	48 (6.7)	111 (7.7)
Total	724	720	1444

A larger proportion of participants in the control arms had their year 2 visit in winter/spring and baseline visit in summer/autumn than those in the vitamin D arms (8.7% vs. 6.7%, respectively) (*Table 16*), so the change in season was adjusted for yielding an estimated mean increase of 57.8 nmol/l (95% CI 56.1 to 59.5 nmol/l) in the vitamin D arms compared with 0.3 nmol/l (95% CI –1.4 to 2.0 nmol/l) in the control arms. In the control arms, the effect of season change was fairly small with an estimated increase of 5.7 nmol/l (95% CI 3.0 to 8.3 nmol/l) for those whose baseline blood was taken in winter/spring and follow-up was taken in summer/autumn. Conversely, the estimated decrease in vitamin D levels in control participants whose blood samples were taken in summer/autumn at baseline and winter/spring at follow-up was 8.8 nmol/l (95% CI 4.9 to 12.6 nmol/l).

Table 17 shows significantly lower blood 25(OH)D levels at baseline in all participants and at follow-up among control participants who did not take supplements containing vitamin D ($p < 0.0001$). The mean blood 25(OH)D (nmol/l) was 47.0 (95% CI 45.5 to 48.5) among those not taking supplements compared with 65.5 (95% CI 62.8 to 68.1) among those taking supplements at baseline, and similar results were seen at follow-up among the control participants. However, this higher level was still below the optimal threshold of 75 nmol/l. Additional supplementation did not change the blood 25(OH)D levels among those randomised to take vitamin D.

TABLE 17 Blood 25(OH)D levels at baseline and follow-up in relation to daily vitamin D from all supplements being taken at baseline and at the 2-year visit (combined data from self-report and GP records – doses from GP notes as defined in *Table 11*)

Daily vitamin D supplements	*n*	< 75 nmol/l, *n* (%)	Mean	25th percentile	Median	75th percentile
Baseline						
None	1218	1055 (86.6)	47.0	28.4	42.4	61.4
≤ 400 IU	381	268 (70.3)	65.3	47.8	61.2	79.3
> 400 IU	9	6 (66.7)	71.5	52.8	66.1	81.7
Total	1608	1329 (82.6)	51.5	30.9	47.4	66.6
Follow-up visit						
OC						
None	278	234 (84.2)	49.3	30.5	46.5	62.3
≤ 400 IU	67	49 (73.1)	64.1	48.6	64.1	78.7
> 400 IU	19	12 (63.2)	68.3	50.6	65.2	80.9
Total	364	295 (81.0)	53.0	34.1	50.6	68.4
OD						
None	304	44 (14.5)	108.1	83.7	107.2	126.4
≤ 400 IU	58	3 (5.2)	121.6	96.2	116.0	132.6
> 400 IU	7	1 (14.3)	99.1	79.2	80.6	120.0
Total	369	48 (13.0)	110.0	85.3	108.5	127.0
BC						
None	298	256 (85.9)	46.6	26.4	42.5	62.9
≤ 400 IU	50	36 (72.0)	68.7	47.7	59.8	77.0
> 400 IU	14	9 (64.3)	71.6	62.2	68.0	87.3
Total	362	301 (83.1)	50.6	29.4	46.3	67.2
BD						
None	284	32 (11.3)	108.3	86.9	105.3	124.2
≤ 400 IU	60	7 (11.7)	113.6	91.9	103.3	128.4
> 400 IU	9	0 (0.0)	106.2	102.9	106.5	111.4
Total	353	39 (11.0)	109.2	88.6	104.9	123.7
All control participants						
None	576	490 (85.1)	47.9	28.3	44.7	62.6
≤ 400 IU	117	85 (72.7)	66.1	48.6	62.0	77.0
> 400 IU	33	21 (63.6)	69.7	61.1	67.4	84.1
Total	726	596 (82.1)	51.8	32.0	48.2	67.3
All allocated to vitamin D						
None	588	76 (12.9)	108.2	85.7	106.5	125.7
≤ 400 IU	118	10 (8.5)	117.5	92.9	109.9	132.6
> 400 IU	16	1 (6.3)	103.1	81.8	103.0	115.7
Total	722	87 (12.0)	109.6	87.4	107.0	126.1

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Tables 18 and *19* show the number of infections during the 2-year trial period as reported from GP notes for all patients, comparing control participants (untreated or placebo) with vitamin D participants (open-label or blind). The overall number of infections during the 2-year trial period did not differ between control and vitamin D arms (see *Table 19*): 28.0% of those in the control arms had at least one infection compared with 26.8% in the vitamin D arms. A slightly higher proportion of control participants with low blood 25(OH)D had at least one infection during the trial period compared with those allocated vitamin D (31.6% vs. 25.9% in the < 25 nmol/l group and 29.1% vs. 28.4% in the 25–49 nmol/l group).

There were no significant differences between the treatment arms in changes from baseline to follow-up for systolic BP and BMI (*Table 20*). A small increase in diastolic BP and a small decrease in health score were seen among those allocated to take vitamin D ($p = 0.03$ and $p = 0.04$, respectively). No significant differences were seen between the treatment arms regarding changes in the five indices of QoL (*Table 21*). On average, participants lost 0.47 cm in height and 0.55 kg in weight over the 2 years of the trial.

TABLE 18 Number of infections during the 2-year trial period in GP records

	Number of infections in 2 years, *n* (%)					
Type of infection	0	1	2	3	≥ 4	Total
All infections						
Control	585 (72.0)	145 (17.8)	48 (5.9)	18 (2.2)	17 (2.1)	813
Vitamin D	587 (73.2)	142 (17.7)	49 (6.1)	14 (1.7)	10 (1.2)	802
Upper respiratory infections						
Control	753 (92.6)	57 (7.0)	2 (0.2)	1 (0.1)	0 (0.0)	813
Vitamin D	743 (92.6)	53 (6.6)	3 (0.4)	2 (0.2)	1 (0.1)	802
Lower respiratory infections						
Control	735 (90.4)	57 (7.0)	17 (2.1)	3 (0.4)	1 (0.1)	813
Vitamin D	733 (91.4)	53 (6.6)	11 (1.4)	2 (0.2)	3 (0.4)	802
Urinary tract infections						
Control	772 (95.0)	27 (3.3)	9 (1.1)	1 (0.1)	4 (0.5)	813
Vitamin D	774 (96.5)	25 (3.1)	2 (0.2)	0 (0.0)	1 (0.1)	802
Skin/mucosal or soft tissue infections						
Control	744 (91.5)	54 (6.6)	8 (1.0)	7 (0.9)	0 (0.0)	813
Vitamin D	738 (92.0)	51 (6.4)	10 (1.2)	1 (0.1)	2 (0.2)	802
Other infections						
Control	770 (94.7)	36 (4.4)	6 (0.7)	1 (0.1)	0 (0.0)	813
Vitamin D	761 (94.9)	35 (4.4)	6 (0.7)	0 (0.0)	0 (0.0)	802

TABLE 19 Number of infections during the 2-year trial period by baseline blood 25(OH)D

Type of infection	Arm	Baseline blood 25(OH)D (nmol/l), *n* (%)				Total, *n* (%)
		< 25	25–49	50–74	≥ 75	
Any infections						
At least one infection	Control	43 (31.6)	87 (29.1)	60 (26.4)	37 (25.0)	227 (28.0)
	Vitamin D	35 (25.7)	85 (28.4)	61 (26.9)	33 (22.3)	214 (26.4)
At least two infections	Control	23 (18.9)	27 (8.6)	23 (9.9)	10 (7.6)	83 (10.4)
	Vitamin D	12 (9.8)	33 (10.5)	19 (8.2)	9 (6.9)	73 (9.1)
Upper respiratory infections						
At least one infection	Control	10 (7.4)	20 (6.7)	15 (6.6)	15 (10.1)	60 (7.4)
	Vitamin D	8 (5.9)	21 (7.0)	19 (8.4)	10 (6.8)	58 (7.2)
At least two infections	Control	1 (0.8)	0 (0.0)	1 (0.4)	1 (0.8)	3 (0.4)
	Vitamin D	2 (1.6)	1 (0.3)	3 (1.3)	0 (0.0)	6 (0.8)
Lower respiratory infections						
At least one infection	Control	18 (13.2)	28 (9.4)	23 (10.1)	9 (6.1)	78 (9.6)
	Vitamin D	13 (9.6)	31 (10.4)	19 (8.4)	6 (4.1)	69 (8.5)
At least two infections	Control	5 (4.1)	6 (1.9)	9 (3.9)	1 (0.8)	21 (2.6)
	Vitamin D	5 (4.1)	6 (1.9)	4 (1.7)	1 (0.8)	16 (2.0)
Urinary tract infections						
At least one infection	Control	12 (8.8)	13 (4.3)	9 (4.0)	6 (4.1)	40 (4.9)
	Vitamin D	5 (3.7)	10 (3.3)	8 (3.5)	5 (3.4)	28 (3.5)
At least two infections	Control	5 (4.1)	4 (1.3)	3 (1.3)	2 (1.5)	14 (1.8)
	Vitamin D	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	3 (0.4)
Skin/mucosal or soft tissue infections						
At least one infection	Control	16 (11.8)	27 (9.0)	18 (7.9)	8 (5.4)	69 (8.5)
	Vitamin D	14 (10.3)	24 (8.0)	18 (7.9)	8 (5.4)	64 (7.9)
At least two infections	Control	4 (3.3)	6 (1.9)	4 (1.7)	1 (0.8)	15 (1.9)
	Vitamin D	3 (2.5)	5 (1.6)	2 (0.9)	3 (2.3)	13 (1.6)
Other infections						
At least one infection	Control	7 (5.1)	18 (6.0)	10 (4.4)	8 (5.4)	43 (5.3)
	Vitamin D	5 (3.7)	17 (5.7)	11 (4.8)	8 (5.4)	41 (5.1)
At least two infections	Control	3 (2.5)	3 (1.0)	1 (0.4)	0 (0.0)	7 (0.9)
	Vitamin D	0 (0.0)	3 (1.0)	2 (0.9)	1 (0.8)	6 (0.8)
Participants, n						
	Control	136	299	227	148	810
	Vitamin D	122	313	232	131	798

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TABLE 20 Blood pressure, height, weight, BMI and health score at baseline and follow-up

Health measures	Control ($n = 732$)	Vitamin D ($n = 726$)	Treatment difference	95% CI	*p*-value
Change in systolic BP (mmHg)	0.14	1.21	1.07	–0.75 to 2.88	0.2
Change in diastolic BP (mmHg)	–0.55	0.63	1.19	0.11 to 2.26	0.03
Change in height (cm)	–0.46	–0.48	–0.02	–0.26 to 0.22	0.9
Change in weight (kg)	–0.70	–0.39	0.31	–0.19 to 0.81	0.2
Change in BMI (kg/m^2)	–0.10	0.01	0.10	–0.09 to 0.30	0.3
Change in health score (out of 100)	0.33	–1.12	–1.45	–2.82 to –0.08	0.04

TABLE 21 Changes in health state as measured using the QoL questionnaire

	Experiencing changes in health state, *n* (%)					
	Control			Vitamin D		
QoL indices	*N* (%)	Worsened	Improved	*N* (%)	Worsened	Improved
Mobility						
No problem at baseline	560 (76.6)	82 (14.6)	NA	575 (79.1)	91 (15.8)	NA
Problems at baseline	171 (23.4)	0	52 (30.4)	152 (20.9)	0	50 (32.9)
Self-care						
No problem at baseline	712 (97.4)	17 (2.4)	NA	704 (96.8)	15 (2.1)	NA
Problems at baseline	19 (2.6)	0	8 (42.1)	23 (3.2)	1 (4.3)	10 (43.5)
Usual activities						
No problem at baseline	644 (88.1)	69 (10.7)	NA	665 (91.5)	63 (9.5)	NA
Problems at baseline	87 (11.9)	2 (2.3)	42 (48.3)	62 (8.5)	2 (3.2)	33 (53.2)
Pain/discomfort						
No problem at baseline	438 (59.9)	115 (26.3)	NA	438 (60.2)	135 (30.8)	NA
Problems at baseline	293 (40.1)	15 (5.1)	104 (35.5)	289 (39.8)	12 (4.2)	99 (34.3)
Anxiety/depression						
No problem at baseline	654 (89.5)	71 (10.9)	NA	628 (86.4)	59 (9.4)	NA
Problems at baseline	77 (10.5)	6 (7.8)	33 (42.9)	99 (13.6)	3 (3.0)	43 (43.4)

NA, not applicable.

Table 22 shows the number of GP appointments recorded in the GP notes during the year before randomisation and during the 2-year trial period. There was a mean of 5.7 appointments in the year preceding randomisation with no significant differences between the treatment arms (i.e. 5.5 appointments in the OC arm, 5.4 in the OD arm and 5.9 in both blind treatment arms). The mean number of appointments per year increased to 6.3 during the trial, with no significant differences either between year 1 and year 2 or between treatment arms.

TABLE 22 Number of GP appointments in the year prior to randomisation and during the 2-year trial period from GP records

	Open practices, *n* (%)		Blind practices, *n* (%)		
Number of GP appointments	OC	OD	BC	BD	Total, *n* (%)
Total participants	421	407	392	395	1615
No data[a]	20	21	8	12	61
1 year prior to randomisation					
0–5 appointments	218 (54.4)	208 (53.9)	195 (50.8)	189 (49.4)	810 (52.1)
5–9 appointments	112 (27.9)	108 (28.0)	117 (30.5)	110 (28.7)	447 (28.8)
10–14 appointments	45 (11.2)	45 (11.7)	42 (10.9)	56 (14.6)	188 (12.1)
≥ 15 appointments	26 (6.5)	25 (6.5)	30 (7.8)	28 (7.3)	109 (7.0)
Mean	5.5	5.4	5.9	5.9	5.7
Median	4	4	4	5	4
Year 1 of trial					
0–5 appointments	194 (48.4)	176 (45.6)	193 (50.3)	198 (51.7)	761 (49.0)
5–9 appointments	122 (30.4)	114 (29.5)	104 (27.1)	117 (30.6)	457 (29.4)
10–14 appointments	53 (13.2)	66 (17.1)	52 (13.5)	39 (10.2)	210 (13.5)
≥ 15 appointments	32 (8.0)	30 (7.8)	35 (9.1)	29 (7.6)	126 (8.1)
Mean	6.4	6.5	6.4	5.8	6.3
Median	5	5	4	4	5
Year 2 of trial					
0–5 appointments	195 (48.6)	190 (49.2)	186 (48.4)	184 (48.0)	755 (48.6)
5–9 appointments	109 (27.2)	115 (29.8)	121 (31.5)	115 (30.0)	460 (29.6)
10–14 appointments	63 (15.7)	51 (13.2)	36 (9.4)	51 (13.3)	201 (12.9)
≥ 15 appointments	34 (8.5)	30 (7.8)	41 (10.7)	33 (8.6)	138 (8.9)
Mean	6.5	6.1	6.5	6.4	6.4
Median	5	5	5	5	5
2-year trial period					
0–5 appointments	93 (23.2)	83 (21.5)	92 (24.0)	94 (24.5)	362 (23.3)
5–9 appointments	98 (24.4)	89 (23.1)	100 (26.0)	101 (26.4)	388 (25.0)
10–14 appointments	74 (18.5)	81 (21.0)	73 (19.0)	75 (19.6)	303 (19.5)
15–19 appointments	56 (14.0)	53 (13.7)	49 (12.8)	40 (10.4)	198 (12.7)
≥ 20 appointments	80 (20.0)	80 (20.7)	70 (18.2)	73 (19.1)	303 (19.5)
Mean	12.9	12.6	12.9	12.2	12.6
Median	10	11	9.5	9	10

a No data; participants' records not available from the GP practice, including removal because of death or moving from the area.

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Table 23 shows the mortality and cancer incidence for the 1615 participants in the trial. All were flagged with NHS Digital, providing complete follow-up data. The overall death rate was 4.2% in the vitamin D treatment arms and 2.8% in the untreated control arms ($p = 0.12$), with a cancer incidence rate over 2 years of 2.6% in those allocated to vitamin D and 3.1% among those allocated to the control arms ($p = 0.6$). Cause of death is shown in the lower part of the table. This is not yet available for the most recent deaths (5/57).

TABLE 23 Mortality, cancer incidence and cause of death by treatment allocation

Follow-up	OC, *n* (%)	OD, *n* (%)	BC, *n* (%)	BD, *n* (%)	Total, *n* (%)
Total participants	421 (100)	407 (100)	392 (100)	395 (100)	1615 (100)
Alive at follow-up[a]	408 (96.9)	389 (95.5)	382 (97.4)	379 (96.0)	1158 (96.5)
Died within 2 years of randomisation	4 (1.0)	8 (2.0)	3 (0.8)	5 (1.3)	20 (1.2)
Died between 2 and 4 years after randomisation	9 (2.1)	10 (2.5)	7 (1.8)	11 (2.8)	37 (2.3)
Total deaths	13 (3.1)	18 (4.4)	10 (2.6)	16 (4.1)	57 (3.5)
Cancer incidence within 2 years of randomisation	15 (3.6)	12 (3.0)	10 (2.6)	9 (2.3)	46 (2.8)
	Control, *n* (%)	**Vitamin D, *n* (%)**			
Total participants	813 (100)	802 (100)			
Cause of death					
Cancer	5 (0.62)	14 (1.75)			
Circulatory	7 (0.86)	12 (1.50)			
Other	8 (0.98)	6 (0.75)			
Not known	3 (0.37)	2 (0.25)			
Total deaths	23 (2.83)	34 (4.24)			

a Mortality follow-up until February 2018, approximately 4 years after the last patient was randomised.

Chapter 4 Discussion

The primary aims of this study were (1) to demonstrate the feasibility of achieving adequate recruitment through GP practices in a larger trial (20,000 participants) of prolonged high-dose vitamin D in people aged 65–84 years with mortality as the primary outcome and (2) to compare the effects of open and double-blind randomisation on recruitment, contamination (self-administered or prescribed vitamin D consumption in control participants) and treatment compliance assessed both by self-report and by blood 25(OH)D concentration at the 2-year final visit, particularly the proportion in whom this figure is < 75 nmol/l. The proportion of participants with blood 25(OH)D concentration of < 75 nmol/l was 81.8% at baseline, which confirmed the high prevalence of suboptimal vitamin D status in this age group in the UK. This decreased to 22.0% at the final 2-year assessment in participants allocated to vitamin D (see *Table 15*) and was not significantly altered from baseline in control participants. The only substantial difference between the protocol in this feasibility study and that proposed for the main trial is the regimen of vitamin D. We used 100,000 IU monthly, but reports published after we began recruitment suggest that daily dosing is likely to prove superior.[47,48] Therefore, we propose a daily dose of 4000 IU, which was shown to achieve substantially higher serum 25(OH)D levels than 2000 IU per day in a recent study.[49,50]

We believe that this is the first such trial in which open-label and double-blind randomisation have been compared by cluster randomisation. Strong opinions are held on the relative merits and disadvantages of open-label and blind allocation, and we held divergent views on the best approach for evaluating the effects of long-term vitamin D on overall mortality. Therefore, we decided that randomised evidence was needed to inform the choice of protocol for the main trial and that the best way to obtain this was by cluster randomisation of GP practices between open-label and double-blind randomisation. The 20 GP practices were situated throughout England in areas ranging from wealthy to relatively deprived.

Preliminary procedures

Study approvals occupied almost 3 years (July 2011–May 2014) before recruitment could begin at all GP practices. Research Ethics Committee and MHRA approvals were straightforward, and the major delay was in obtaining approvals for NHS research and development and service support costs in each Clinical Research Network. In view of this experience, a formal review of the costs and benefits of expediting these processes for non-commercial population-based trials of this sort might be evaluated in consultation with the relevant agencies. Protracted correspondence and discussions with NHS Digital also delayed linkage to HES and other databases to obtain follow-up data for death, cancer registration and hospital admissions. Our application to NHS Digital underwent 13 revisions for these linkages. A major focus was the wording of our informed consent, which had been reviewed and approved both by our patient advisory group and by senior staff at the Health and Social Care Information Centre before the trial began. Requested amendments included the wording of the London School of Hygiene & Tropical Medicine's Data Protection Act registration, and the VIDAL trial website's description of fair processing, linkage processes, data flow, research outputs, the target audience and benefits to health and social care.

Recruitment

Recruitment in the pilot practice (practice 0B) began in April 2013 and was completed in September 2013. Procedures modified over this period included improvements to the web-based clinical data management system (the VIDAL app, see *Appendix 2*). The recruitment period in the other 19 practices ranged from 4 to 12 months, and the last participant was randomised in January 2015. Participation was better than expected, with one in seven (14.2% compared with the protocol target of 9%) of all invited eligible patients aged 65–84 years being randomised. Despite the matching of practice pairs on region and social deprivation,

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recruitment varied widely within matched pairs (see *Table 2*), and the slightly higher overall recruitment in open practices (15.0% of invited patients randomised) than in blind practices (13.4% randomised) did not approach statistical significance.

Compliance

The proportion of participants allocated to a treatment arm who took all three doses of study medication was 88.7% in the last 3 months of the trial (see *Table 7*). The proportion was slightly, but not significantly, higher for OD participants than for blind participants throughout (see *Figure 4*), and this non-significant trend was also seen in the total number of doses taken (see *Table 8*) and in the proportion of participants compliant at 6 months who were still taking study medication over the remainder of the trial (see *Figure 5*).

Feasibility of the main trial

The recruitment target in the VIDAL main trial is 20,000 participants aged 65–84 years with equal numbers in each 5-year age group (i.e. 200 practices recruiting an average of 100 participants with 25 in each age group). The recruitment rate was 11.5% at age 80–84 years and higher at < 80 years (see *Table 3*), so this uniform age distribution could be achieved if the average number of registered patients aged 80–84 years in participating practices was 220 and all were invited. The average number of registered patients aged 80–84 years per practice in England is 190, so this should be easily achievable by targeting larger practices.

The proportions of participants choosing e-mail for quarterly follow-up at ages 65–69, 70–74, 75–79 and 80–84 years were 77.4%, 67.6%, 55.7% and 36.5%, respectively (see *Table 6*). The corresponding participation rates (see *Table 3*) imply that in a trial restricted to participants willing to be contacted by e-mail, the participation rates at ages 65–69, 70–74, 75–79 and 80–84 years would be 10.5%, 11.0%, 7.9% and 4.2%, respectively. To recruit an average of 25 patients in each age group, the following numbers of patients would need to be invited on average per practice: 240 patients aged 65–69 years; 230 aged 70–74 years; 320 aged 75–79 years; and 600 aged 80–84 years. The average numbers of registered patients per practice in England in these age groups are 380, 300, 250 and 190, respectively. The main trial could thus be restricted to participants willing to receive and reply to follow-ups by e-mail for those aged < 75 years, or < 80 years if larger practices were targeted, but postal contact would be required for many participants aged 80–84 years to recruit equal numbers in each age range.

A limitation of this study was the virtual absence of recruits of Asian, African or Caribbean origin (see *Table 5*). Our protocol for the main trial specifies that practices in areas with large numbers of people from these ethnic groups should be invited to participate, but we have no information on the participation rate that could be achieved in such practices.

A further limitation is the monthly dosing regimen, which we would not now recommend. The suggestion that daily dosing may be clinically more effective than our monthly regimen was published during the trial.[47,48] A feasibility study of daily vitamin D_3 supplementation among men and women aged > 65 years at a GP practice in Oxfordshire (the 'BEST-D' study)[49,50] showed that allocation to 4000 IU of daily vitamin D increased 25(OH)D on average by 80 nmol/l and 88% of participants achieved plasma levels of 25(OH)D > 90 nmol/l. Compliance levels were comparable to those in the current feasibility study, and we would therefore recommend that daily regimen in the main trial.

Our recruitment, compliance and contamination results are based on patients from the 20 participating practices and are inevitably limited to the 2-year treatment duration of the trial. We have no direct evidence of differences between these selected practices and the 200 practices that would be required for the main trial, or on changes that would occur over the 5-year treatment period of the main trial.

Contamination in untreated open control participants

Table 11 shows that only 20 (5.0%) of the 400 untreated control participants who were interviewed at 2 years (366 who attended the 2-year visit and 34 non-attenders who were telephoned) reported taking > 400 IU of vitamin D per day (11 prescribed and nine self-administered), and only one was taking > 1000 IU per day. This very low level of self-reported contamination is confirmed by their blood 25(OH)D levels, which were similar to their baseline results (see *Table 15* and *Figure 6*). Significant contamination was thus negligible over the 2 years since randomisation, during which time they were not contacted. We have no reason to think that contamination was much more common among the 17 (4.1% of 417 2-year survivors allocated to OC) who could not be contacted 2 years after randomisation.

Open versus placebo-controlled trial designs

Compliance and contamination

The only significant difference between BCs and OCs was in the proportion attending the 2-year visit (94.1% and 87.8%, respectively; $p = 0.01$), and hence in 'composite compliance' ($p = 0.01$). Contamination was negligible among open untreated control participants, and treatment compliance was equally high for those in the OD arm and the blind treatment arms. Any real effect of 5 years of vitamin D on mortality will thus be estimated with similar power by open or by placebo-controlled randomisation, so the choice between these trial designs will be determined by other considerations.

Simplicity and cost

The advantages of open allocation with an untreated control arm include simplicity and lower trial costs. The costs of recruitment are the same for open and blind allocation, and the main additional expenditure with placebo control would be a doubling of trial office staff costs associated with participant contact and follow-up during the trial plus the costs of manufacturing, labelling, dispensing and delivering placebo. The savings that could be achieved in an open trial of 5 years duration might be substantially greater if aspects of monitoring required for a placebo-controlled trial could be reduced. We have shown that contact with participants allocated to vitamin D could be conducted entirely by e-mail for those aged < 80 years, with automated text and/or e-mail reminders to take study medication and report suspected adverse effects. Those on OD should perhaps be recalled every few years for serum calcium assay, and a sample of a few hundred in each arm should be recalled at 5 years to confirm the high compliance and low contamination seen in this trial. However, little useful additional information is obtained by recalling all participants for a final visit either for the primary aim, the analysis of mortality by allocated treatment, or for cancer incidence and reasons for hospitalisation, which were captured more completely by linkage with national databases (cancer registration and HES[44]). SAEs were reported retrospectively and incompletely by GPs; 96.2% (177/184) of SAEs were deaths or cancer diagnoses or involved hospitalisation (see *Table 12*). Our results show that these outcomes will be obtained more completely and reliably by linkage to NHS Digital databases than by GP or patient report, with no evidence of bias as a result of open randomisation. Moreover, in the large trial, for which this is a feasibility study, cancer diagnosis and hospitalisation should be included as primary end points and would therefore not be classed as SAEs. The accumulated evidence of the safety of high-dose vitamin D will be augmented by other ongoing trials with more detailed clinical monitoring. The possibility of adverse effects in those allocated to vitamin D can be managed, as in this trial, by self-report and GPs who are aware that their patient is taking study medication.

Extending treatment beyond 5 years

An important potential advantage of open allocation is that when the trial ends (subject to an application for extended funding) a further 5-year supply can be offered to participants allocated to vitamin D without recontacting control participants, provided this is specified at the outset in the patient information. A continued supply of vitamin D could be offered to those on active treatment following unblinding at the end of a 5-year double-blind trial, but power might be compromised by increased contamination in those who are informed that they have been taking placebo for 5 years, and the theoretical advantage of placebo control would be lost

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for the comparison of subsequent mortality. If the effects of vitamin D on mortality are transient and confined to the period of treatment, as was seen for simvastatin (Zocor©; Merck Serono GmbH, Darmstadt, Germany),[51] any effect on long-term mortality would be much larger for ≥10 years than for 5 years of treatment. This would reinforce the arguments rehearsed earlier (see *Chapter 1 Introduction*) for the value of a large UK trial. A trial in which the majority of treated participants continue to take high-dose vitamin D is the only way to observe the effects of continuing treatment beyond 5 years. Ongoing double-blind trials cannot answer this important question and, if the effect on mortality is transient, they will also have substantially lower power to achieve statistical significance. If confirmed, the 4% reduction in overall mortality seen in the VITAL trial (hazard ratio 2–5 years after entry 0.96, 95% CI 0.84 to 1.11) might justify vitamin D supplementation, but it did not approach statistical significance.[43]

The advantages of placebo control are well known. They include unbiased evidence on potential ARs and on any diagnoses that might be influenced by participants or clinicians knowing that high-dose vitamin D is being taken. A substantial placebo effect on lifestyle behaviour and hence health is, in principle, possible if implausible. Many researchers are therefore suspicious of all open trials irrespective of the end point. Perhaps the strongest reason for insisting on placebo control is the guarantee of universal acceptance of the results on incidence of non-fatal diseases and, hence, their inclusion in meta-analyses of ongoing trials. This is reflected in the Cochrane risk-of-bias tool, which downgrades quality of evidence by at least one step for RCTs when a placebo is not used.

Some co-authors felt a priori that the scientific advantages of a blind design were so great that it should be replaced by an open design only if it were shown to be substantially (and significantly) inferior in the cluster randomised comparison of participation, compliance and contamination. That has not happened, so those co-authors believe that the results reinforce the case for placebo control. Other co-authors think that an open design is simpler, substantially cheaper and facilitates extending treatment beyond 5 years and, therefore, believed a priori that the absolute need for a blind design exists only when the primary outcome is subjective. This group argued that it was only necessary to show that the open design was not inferior in terms of participation, compliance, non-contamination and retention. This trial has shown the open design to be essentially equivalent in these areas, so those co-authors believe that the main trial should use an open design.

Chapter 5 Conclusions

The study was designed to (1) assess the feasibility of conducting a large trial of vitamin D in healthy adults aged 65–84 years (n = 20,000 with equal numbers aged 65–69, 70–74, 75–79 and 80–84 years) recruited through 200 GP practices and (2) compare the effects of open-label and placebo-controlled randomisation on recruitment, compliance and contamination. Our conclusions are therefore restricted to these issues. The study was not powered to detect clinical effects of vitamin D other than elevation of blood 25(OH)D, which was the only substantial and statistically significant clinical effect observed.

Recruitment

The overall participation rate (the proportion of invited patients who were randomised) was 14.2% overall (the protocol target was 9%) and 11.5% at age 80–84 years, with no evidence of a difference between open and blind practices. This confirms the feasibility of the main trial as planned.

Compliance and contamination

Treatment compliance was high among participants openly allocated to vitamin D and among those on blind treatment, and contamination was quantitatively negligible in all arms including the open untreated control arm. A trial of 5 years of treatment would thus be equally powerful whether open or blind, so the choice of design depends on other considerations.

For the main end points (overall mortality, cancer diagnosis and reasons for hospital admission), the advantages of open-label randomisation with follow-up by linkage to national registers are:

- A potentially substantial increase in power if those still on medication at 5 years were offered a continued supply of vitamin D, maintaining a large difference in blood 25(OH)D between treated and control participants beyond the initial 5 years of the trial. This might not be feasible in a double-blind trial when treatment is unblinded after 5 years, and in any case results beyond 5 years would not be placebo controlled.
- A lower cost, as control participants would not be recontacted after randomisation and would not be given any medication.

The main advantages of placebo control are:

- Reliable evidence on side effects and any potentially subjective outcomes.
- Lifestyle changes that are affected by treatment allocation might in principle influence health, so any effect observed in an open trial could be a biased estimate of the pharmacological effect of vitamin D.

Research recommendations

1. Having established the feasibility of a large UK vitamin D trial, our main recommendation is that it should begin as soon as possible, irrespective of the pending results of ongoing trials, which are likely to be inconclusive for the reasons shown in *Table 1* [bolus dosing or daily regimens ≤ 2000 IU, and higher population 25(OH)D levels than in the UK]. A substantial body of evidence from different populations will be required to decide whether or not, at what dose and for whom, this mass medication should be recommended, and results from a UK trial would be the most relevant. Increasing publicity about the potentially large benefits may make it increasingly difficult to recruit for such a trial. If the evidence from ongoing trials is encouraging but not strong enough to justify recommending mass medication, or to

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determine both the optimal dose and the blood 25(OH)D level below which it is worthwhile, these issues may never be satisfactorily resolved.

2. The decision on whether randomisation should be open-label, blind or a mixture of the two in a large vitamin D trial with mortality as the primary outcome will depend strongly on a priori assumptions. The NIHR HTA might consider its view on this separately from assessing specific applications to conduct such a trial.
3. The NIHR HTA in consultation with the relevant agencies might review opportunities for reducing delays in Clinical Research Network funding approvals for multicentre population-based prophylactic trials, for simplifying trial regulations for non-prescription treatments, such as vitamin D, for which extensive evidence on safety is already available, and for arranging linkage to HES and other NHS Digital databases for all non-commercial medical research.

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Contributions of authors

Christine Rake (Trial Manager) managed all aspects of the conduct of the study and contributed to the design of the study and writing the report.

Clare Gilham (Medical Statistician) performed the majority of the statistical analyses and contributed to the interpretation of data and writing the report.

Laurette Bukasa (Trial Administrator) contributed to the conduct of the study, trial management, data collection and data analysis.

Richard Ostler (Senior Programmer) designed the dedicated online trial management system and contributed to trial oversight via the Trial Management Group.

Michelle Newton (Trial Administrator) contributed to the conduct of the study and data collection.

James Peto Wild (Trial Administrator) contributed to the conduct of the study, data collection and database implementation.

Benoit Aigret (Barts CTU Head) contributed to protocol development and trial oversight via the Trial Management Group and as Operation Lead of Barts CTU.

Michael Hill (Oxford Clinical Trials Service Unit Laboratory Scientific Director) provided technical support in planning and throughout the trial on sample receipt, storage and analysis.

Oliver Gillie (Medical Journalist) was our lay member and contributed to the design of the study and trial oversight via the Trial Management Group.

Irwin Nazareth (Professor of Primary Care and Population Sciences) was delegate clinical chief investigator, hosted the pilot GP practice and assisted with GP practice selection and trial oversight via the Trial Management Group.

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Peter Sasieni (Professor of Biostatistics and Cancer Epidemiology) contributed to protocol development and trial oversight via the Trial Management Group and as Director of Barts CTU, which developed the online trial management system.

Adrian Martineau (Clinical Professor of Respiratory Infection and Immunity) was the clinical chief investigator and contributed to the design of the study, trial oversight and writing the report.

Julian Peto (Professor of Epidemiology) was the chief investigator with overall responsibility for the design and supervision of the study, the statistical analysis and writing the report.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Lifestyle and quality of life questions

Lifestyle questions:

Diet:

How often do you eat oily fish (examples of oily fish are: tuna, sardines, mackerel, eel, salmon, trout)?

Less than Once a week		Once a week		2-3 times a week		4+ Times a week	

1. SUPPLEMENTS CONTAINING VITAMIN D:

Do you take any supplements containing Vitamin D? Yes ☐ No ☐

Please list any supplements containing vitamin D below, stating the dose of vitamin D taken and the year the patient started taking the supplement. Please include all supplements that include any vitamin D (eg cod liver oil, multi-vitamins), but only give the dose of vitamin D taken.

NB. If the supplement contains vitamin D, check patient does not exceed 400 IU / 10 micrograms daily or 2800IU / 70 micrograms weekly (see eligibility criteria)

Please circle one option for both Units and Frequency for each supplement.

1) Name of supplement _____ Daily dose _____ Units: IU/ mcg/ g/ mg /mls /Other

Frequency: Per Week/Per Day Year Started Taking_____

2) Name of supplement _____ Daily dose _____ Units: IU/ mcg/ g/ mg /mls /Other

Frequency: Per Week/Per Day Year Started Taking_____

3) Name of supplement _____ Daily dose _____ Units: IU/ mcg/ g/ mg /mls /Other

Frequency: Per Week/Per Day Year Started Taking_____

4) Name of supplement _____ Daily dose _____ Units: IU/ mcg/ g/ mg /mls /Other

Frequency: Per Week/Per Day Year Started Taking_____

5) Name of supplement _____ Daily dose _____ Units: IU/ mcg/ g/ mg /mls /Other

Frequency: Per Week/Per Day Year Started Taking_____

IMPORTANT NOTE: Patients must NOT take in excess of 400 IU / 10 micrograms of vitamin D daily (or 2800IU / 70 micrograms of vitamin D weekly) from all sources. Please confirm that this limit is not exceeded when vitamin D from both dietary supplements and medications are combined (i.e Yes, limit exceeded or No, limit not exceeded):

Yes ☐ No ☐

NB TICKING "YES" INDICATES THAT THE PARTICIANT VITAMIN D INTAKE EXCEEDS THE ALLOWED DOSE. IF THIS IS CORRECT THEN THE PARTICIPANT CANNOT TAKE PART IN THE TRIAL

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2. SUPPLEMENTS THAT DO NOT CONTAIN VITAMIN D:

Do you take any dietary supplements? Yes ☐ No ☐

Please list supplements that do not contain vitamin D below (with the year the patient started taking the supplement). We do not require the dose of supplements which do not contain any vitamin D.

1) Name of supplement _____ Year Started Taking_____

2) Name of supplement _____ Year Started Taking _____

3) Name of supplement _____ Year Started Taking _____

4) Name of supplement _____ Year Started Taking _____

5) Name of supplement _____ Year Started Taking _____

Skin type and Sun Exposure:

How long per day do you usually spend outdoors during the daylight hours (please tick one box for each row)?

	No time	Under 15 minutes	15 – 30 mins	30 – 60 mins	1 - 2 hours	3 - 4 hours	Over 4 hours
...last month?							
...in Summer?							
...in Winter?							

Have you travelled abroad in the last year? Yes ☐ No ☐

If you have answered YES please provide details below:

Destination	Duration of stay	Month of return to UK

How many times have you used a sun bed in the last year?

Please tick one box:

Never ☐ 1- 9 times ☐ Over 10 Times ☐

In sunny weather, both in the UK and in other countries do you...

Please tick one box on each line

	Often	Sometimes	Rarely	Never
a) Protect your skin from the sun, for example with clothing or sun cream	☐	☐	☐	☐
b) Get blistering after being burned in the sun?	☐	☐	☐	☐
c) Actively seek a suntan?	☐	☐	☐	☐

Which one of the 6 categories below best describes your skin type and your skin's response to the midday sun in summer months? (Please circle one)

Category	Response
1	I have extremely fair skin. I always burn and never tan.
2	I have fair skin. I always burn and sometimes tan.
3	I have pale coloured skin. I sometimes burn and always tan.
4	I rarely burn and always tan.
5	I have a moderately pigmented brown skin which never burns and always tans.
6	I have markedly pigmented black skin which never burns and always tans.

Please turn to next page for Quality of Life CRF

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Quality of Life Questionnaire

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

On a scale of 1 to 100 where 1 is worst imaginable health state and 100 is best imaginable health state, how good or bad is your health state today ☐ (1.0 – 100.0)

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Please ensure that the information recorded in all paper CRFs is entered onto the online VIDAL application as soon as possible, if not the same day.

Appendix 2 The web-based clinical data management system: the VIDAL online application

The VIDAL app was the web-based clinical data management system developed specifically to streamline data capture and management for the VIDAL feasibility study. It was designed to be able to accommodate the 200 practices and 20,000 participants required for the main trial, to eliminate costly administration, transport and postal fees, and to optimise the process of data acquisition and data management.

The functions of the VIDAL app were to provide:

- secure online access
- current GP practice and trials office contact details
- access to all current study documents (in the online library)
- access to online CRFs for local GP staff to create, complete and view participant data
- participant accessible follow-up data entry forms (CRFs)
- trials office access to view participant and GP practice data
- participant randomisation into the trial
- online tools for ordering and tracking study medication
- tracking tools for recording blood sample dispatch and receipt
- automated e-mail, text message and telephone call alerts and reminders for participants, GP practices and trials office staff
- online tools for mail merging and printing study letters and prescriptions and logging reply slips and consent forms
- reports to monitor participant progress and compliance through the trial
- timely completion of online SAE and AR CRFs.

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