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Vitamin D supplementation compared to placebo in people with First Episode psychosis - Neuroprotection Design (DFEND): a protocol for a randomised, double-blind, placebo-controlled, parallel-group trial

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Abstract

Background: People experiencing their first episode of psychosis often have vitamin D deficiency, with observational studies reporting an association between low vitamin D concentrations and poorer subsequent health outcomes. Vitamin D deficiency in neonates and children have been linked to later increased risk of schizophrenia and psychotic-like experiences. This trial aims to examine the effect of high dose vitamin D supplementation on outcomes in early psychosis. We hypothesise that vitamin D supplementation will be associated with better mental health outcomes.

Methods: The DFEND study is a multicentre, double blind, placebo-controlled, parallel-group trial of vitamin D supplementation in people with early psychosis. Patients with an ICD-10 diagnosis of functional psychosis will be randomised on a 1:1 basis to receive either 120,000 IU/month of vitamin D (cholecalciferol) or matched placebo for six months. The primary outcome is the total Positive and Negative Syndrome Scale (PANSS) score at six-month follow-up in all patients. Secondary outcomes include assessment of mood (Calgary Depression Scale), general function (Global Assessment of Functioning), cardiovascular risk (body mass index, waist circumference, c-reactive protein, cholesterol and HbA1c) and vitamin D levels at six-month follow-up. Additionally, three and six-month PANSS total scores will be analysed in the subgroup of those with inadequate vitamin D levels at baseline.

Discussion: The DFEND study is the first study aimed at examining whether vitamin D supplementation in early psychosis is associated with better mental health outcomes. The findings of this study will help resolve the clinical equipoise regarding the benefits and cost-effectiveness of routine vitamin D supplementation in people with psychosis.

Trial Registration: ISRCTN, ISRCTN12424842. Registered 25 February 2015, https://www.isrctn.com/ISRCTN12424842

Keywords: psychosis, first episode, vitamin D, 25OHD, randomised controlled trial, Positive and Negative Syndrome Scale, mental health

Background

Vitamin D is a fat-soluble secosteroid obtained largely through sun exposure and, to a lesser extent, food sources such as oily fish (e.g. mackerel) and egg yolk. The best-known role of vitamin D is in regulating bone health, being essential for the regulation of calcium in the body, but latterly important additional functions have been identified. These include links between brain function and vitamin D [1, 2] with in vitro and animal experiments demonstrating a neuroprotective effect [3]. In rodents, developmental vitamin D deficiency alters a wide range of outcomes in the adult brain, including neurotransmitters relevant to schizophrenia [4, 5], while vitamin D deficiency during adulthood has been associated with changes in behaviour and brain neurochemistry [6]. In animal models, vitamin D is neuroprotective, preventing neuronal damage from inflammation and oxidative stress [7], and inducing nerve growth factor [8]. Greater ischemic brain damage in stroke is seen in vitamin D deficient rodents [9]. The long term adverse neurobehavioural effects of maternal immune activation in offspring can be attenuated by administration of 1-, 25-hydroxyvitamin D3 [10]. With respect to neuropsychiatric disorders, a randomised control trial of vitamin D supplementation in those with established Parkinson's disease showed a slower progression compared with placebo over a 12 month follow-up [11]. Based on these findings, the hypothesis has been proposed that vitamin D deficiency during adulthood may worsen brain-related outcomes in those with prior neuropsychiatric disorders [12].

Schizophrenia is more common in people born in winter and spring months [13] and at higher latitudes [14], both conditions in which exposure to the sun, and so vitamin D production, is limited. In addition, dark-skinned individuals living in cold (i.e., less sunny) countries have an increased risk of schizophrenia [15]. McGrath et al. have hypothesised that low vitamin D in early life may be linked to the risk of later development of schizophrenia [16]. Indeed, a large Danish study found a higher relative risk of developing schizophrenia in adult life in neonates with low vitamin D levels [17]. Similarly, low total vitamin D_3 levels during childhood are associated with a higher risk of psychotic experiences during adolescence [18]. A recent meta-analysis reported that an overall prevalence of vitamin D deficiency in patients with schizophrenia of 65% and that people with vitamin D deficiency were 2.16 times at risk of developing the condition [19]. Diet appears to have an effect also: a large population-based study of Swedish women (n = 33,623) reported an association between low dietary vitamin D intake and an increased risk of psychotic-like experiences [20]. The evidence therefore suggests that low vitamin D disrupts early brain development and may also influence later brain function.

Vitamin D deficiency is commonly defined in the UK as having levels of 25 hydroxyvitamin D (25OHD) less than 25 nmol/L, insufficiency as between 25-50 nmol/L and sufficiency as greater than 50 nmol/L [21]. Those with established psychosis in the UK are highly likely to be vitamin D deficient, with only 14% having sufficient vitamin D levels [22]. This is true even in the early stages of psychosis. Crews et al. examined vitamin D status in 69 people with their first episode of psychosis (FEP) along with 69 controls of similar age, sex and ethnicity [23]. Over a third had a vitamin D deficiency while an additional 25% had a vitamin D insufficiency. Overall, the people with FEP had a nearly three-fold greater risk of vitamin D deficiency than comparators. Higher vitamin D levels at presentation were associated with lower "total" and negative symptoms of psychosis a year later [24]. The deficiency in vitamin D seems to be unrelated to other vitamins and minerals. A meta-analysis of nutritional deficiencies in FEP showed strongest evidence for vitamin D deficiency and some evidence for low vitamin C and folate in FEP, but no evidence for deficiencies in vitamins A and E, or in minerals [25].

People with severe mental illnesses such as schizophrenia and schizoaffective disorder experience poor physical health and high rates of premature death [26]. They have higher rates of cardiometabolic risk including diabetes, hypertension and central obesity [27-29]. Low vitamin D levels have been associated with cardiometabolic risk in both the general population [30, 31] and in people with established psychosis [22]. Large population-based, placebo-controlled studies are currently underway that will examine the influence of vitamin D supplement on general health including cardiometabolic outcomes [32].

Despite research suggesting that vitamin D has been linked to brain function and schizophrenia, little high-quality evidence is available on the impact of vitamin D supplementation on outcomes for people with psychosis. Whilst several studies have used vitamin D supplements in people with psychosis [33-35], these largely focused on physical health outcomes and 25OHD concentrations, and employed uncontrolled research designs. However, one recent randomised controlled trial (RCT) in Israel aimed to explore whether vitamin D supplementation of 14,000 IU per week for 8 weeks improves outcomes in clozapine-treated patients with chronic schizophrenia, finding no improvement on mental health, cognitive or metabolic outcomes [36]. To our knowledge, there have been no trials examining vitamin D supplementation in FEP. If vitamin D is able to confer a positive neuroprotective impact and improve outcomes in psychosis, the first episode may be the ideal window of opportunity.

Clinical equipoise therefore persists as to whether routine vitamin D supplementation in early psychosis would be of benefit to mental or physical health outcomes.

This paper describes the study protocol for the DFEND Study ("Vitamin D supplementation compared to placebo in people presenting with their First Episode of psychosis Neuroprotection Design"), which is a randomised, double-blind, placebo-controlled, parallel-group trial evaluating the impact of 6 months of vitamin D supplementation on Positive And Negative Syndrome Scale (PANSS) outcomes in people with early psychosis.

Method/Design

Aims/Objectives

The primary objective of the trial is to determine whether adding monthly supplementation of 120,000 IU of vitamin D_3 (cholecalciferol) to standard treatment is more efficacious than placebo in improving outcomes (PANSS) at six-month follow-up in people with FEP. Secondary objectives are to examine PANSS total score at 3 months, PANSS sub-scores at 3 and 6 months, along with a broader range of clinically relevant outcomes including Global Assessment of Function (GAF), the Calgary Depression Scale (CDS), cardiovascular risk markers and 25-hydroxyvitamin D (25OHD) concentrations.

Setting

The study will take place in English Mental Health Trusts part of the National Health Service (NHS) in the United Kingdom (UK). Participants will be identified and recruited from clinical mental health services, including early intervention services, home treatment teams, general and forensic inpatient units and outpatient community teams. The study is sponsored jointly by Kings College London (London, UK) and the South London and Maudsley NHS Foundation Trust (London, UK).

Ethics

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of the International Conference on Harmonisation and Good Clinical Practice (ICH-GCP) [37] and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

The protocol and related documents have been approved centrally by the National Research Ethics

Committee – London Dulwich (REC reference number 14/LO/1588), and by the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation (reference 14523/0261/001-004). Recruitment will not begin at study sites until local approvals have been obtained. It has also been approved by the Health Research Authority (HRA, reference IRAS 147978) and registered online (ISRCTN12424842, https://doi.org/10.1186/ISRCTN12424842, registered: 25/02/2015, accessed 28/01/2019).

Eligibility Criteria

The study population is patients experiencing FEP, defined as presenting to health services with symptoms of psychosis within the last three years. A minimum level of symptoms or PANSS score is not required to take part, and patients can be enrolled during a period of stable remission. Patients must have capacity to give written consent which is determined by the delegated team members in conjunction with treating clinicians if needed.

Inclusion Criteria

- Aged between 18-65 years old including women of child-bearing age
- Having a diagnosis of functional psychosis defined according to ICD-10 criteria for psychosis (codes F20-29 and F30-33)
- Willing to agree to refrain from taking multivitamin or non-study vitamin D supplements that exceed 400IU/day throughout the study
- Willing to give a blood vitamin D sample at baseline
- Patients who are able to and have given written informed consent

Exclusion Criteria

- Known intolerance of vitamin D2 or D3 or known allergy to any of the trial medications
- Taking vitamin D supplements at a dose exceeding 400IU/day
- Having taken cardiac glycosides, calcium channel blockers, or oral, intramuscular, or intravenous corticosteroids, bendroflumethiazide, isoniazid, or rifampicin in the past month
- Known active tuberculosis, sarcoidosis, hypo or hyperparathyroidism, past or present nephrolithiasis (renal stones), suspected or diagnosed hepatic or renal dysfunction, any malignancy other than non-melanoma skin cancer not in remission for ≥ 3 years, calcium disorders
- Baseline corrected serum calcium > 2.6mmol/L
- Known history of hypercalcaemia

- Pregnant or breast-feeding women and women planning a pregnancy
- Lacking the capacity to provide written informed consent
- Insufficient English to complete the core assessments with the available assistance

Outcomes/measures

All outcome measures and time points are specified in Figure 1.

Primary outcome

The primary outcome is symptom severity, as assessed via PANSS total scores at 6 months after randomisation[38]. The PANSS assesses symptom severity across three domains: positive symptoms (7 items), negative symptoms (7 items) and general psychopathology (16 items) [38]. A total PANSS score is derived by summing scores across the three domains. Scores range from 30 to 210, with higher scores depicting greater symptom severity. The reliability (α coefficients = 0.73, 0.83, and 0.79 for the positive, negative, and general psychopathology scales, respectively)[38]. All researchers will undergo thorough two stages of in-house PANSS training. Firstly, trainee researchers will watch and rate two PANSS training videos on two separate occasions, followed by feedback and discussion with the trial manager. Secondly, trainee researchers will shadow an experienced member of the team and observe real-world PANSS interviews, after which they will rate the interview to become familiar with the rating scale. Researchers will then be permitted to conduct the PANSS assessments independently. Researchers will also be required to attend regular 6 monthly training to maintain reliability throughout the trial.

Secondary outcomes

The following clinically-relevant outcome measures will be compared between the trial arms:

- Positive and Negative Syndrome Scale (PANSS) at 3 months
- PANSS subscores at 3 and 6 months (Positive Scale, Negative Scale and General Psychopathology Scale)
- Global Assessment of Functioning (GAF)[39, 40] at 6 months: the assessment is used to rate the social, occupational and psychological functioning of adults. It is divided into two ratings, symptoms and disability, with one score for each. Reliability measured by intra-class coefficients (ICC) range from 0.81 to 0.94 [41-43]
- Calgary Depression Scale (CDS)[44] at 6 months. This scale rates the depression symptoms on a 9-point scale (α = 0.79)[45]

- Cardiovascular risk factors at 6 months: waist circumference, body mass index, C-reactive protein (CRP), haemoglobin A1c (HbA1c) and total cholesterol

We will examine all these outcomes in (a) all participants and (b) in a subgroup of patients with suboptimal vitamin D concentrations at baseline. We will also measure the efficacy of vitamin D supplementation at 6 months indicated by 25OHD blood concentration level.

Exploratory measures include inflammatory/ immune markers as well as genetic markers, processed in collaboration with the BioResource for Mental and Neurological Health based at the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre (London, UK). Participants will be asked to give written consent to have their blood specimens stored for future research, which will be subject to new ethics approvals.

Outcomes will be measured by objective face-to-face interviews, information in medical notes or self-report. All participants will be assessed at baseline and 6 months. Additional safety measures will take place at 3 months (see Figure 1).

Figure 1. SPIRIT figure. DFEND time schedule of enrolment, interventions, and assessments

	STUDY PERIOD								
	Enrolment	**Allocation**	**Post-allocation**						**Close-out**
TIMEPOINT	***-2 weeks***	**0**	***Month 1***	***Month 2***	***Month 3***	***Month 4***	***Month 5***	***Month 6***	***28 days after last dose***
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
INTERVENTIONS:									
Vitamin D or Placebo			←	—	—	—	→		
ASSESSMENTS:									
Sociodemographics	X								

NOS (Duration of untreated psychosis)	X								
Medical history	X								
Current medications	X		X	X	X	X	X	X	X
Vitamin D supplementation check	X		X	X	X	X	X	X	
Anthropometrics	X							X	
Blood sample for vitamin D levels	X							X	
Blood sample: clinical, genetic, including calcium	X							X	
Urine pregnancy test	X		X	X	X	X	X	X	
Smoking habits questionnaire	X							X	
PANSS	X				X			X	
GAF	X							X	
CDS	X							X	
OPCRIT	X								
Sun exposure questionnaire	X							X	
IPAQ	X							X	
SIMPAQ	X							X	
Fitzpatrick Skin Type questionnaire	X							X	
Vitamin D food frequency questionnaire	X							X	
Patient medication guess form				X	X	X	X	X	X
Service contact form								X	
Adverse events			X	X	X	X	X	X	X
Blood sample: safety – calcium and albumin check*					X				

* Blood sampling for calcium levels (including parathyroid hormone test if hypercalcaemic) will always be done at Month 3, but can be done at all monthly visits if patient reports nausea and vomiting.

NOS: Nottingham Onset Schedule, PANSS: Positive and Negative Symptom Scale, GAF: Global Assessment Functioning, CDS: Calgary Depression Scale, OPCRIT: Operational Criteria, IPAQ: International Physical Activity Questionnaire, SIMPAQ: SIMple Physical Activity Questionnaire

Participant timeline

The end of the trial will be defined as the last patient last post-6-month visit telephone call.

Sample size

The sample size is based on PANSS Total score in FEP patients collected as part of the Physical health and substance Use Measures in first episode Psychosis study (PUMP) [46] study (n = 190), where the mean (and standard deviation) score was 58.1 (15.0) units. Based on the number of new cases presenting to FEP services, and annual counts of FEP patients recruited into similar studies, we predicted a recruitment and randomization rate of 120 patients per year (i.e. 240 over two years). For the primary outcome (six-month follow-up), we assumed a 20% attrition proportion. After 20% attrition, the effective sample size is 192 (96 in each trial arm).

For the power analyses, we modelled two plausible scenarios using 80% and 90% power respectively, with alpha=0.05 for both scenarios. Based on alpha = 0.05 and power = 80%, samples between 200 and 180 participants will be able to confidently detect mean PANSS total score group differences of between 6 and 6.3 units. This equates to a standardised effect of size of approximately 0.4 to 0.42. Considering 90% power with the same power assumptions, we will be able to detect mean PANSS total score group differences of between 6.9 and 7.3 units (standardised effect size from 0.46 to 0.49).

As a secondary objective we also wish to estimate the average treatment effect in those participants with low vitamin D deficiency at baseline. We assume 60% of the FEP population has vitamin D concentrations below 50 nmol/L at baseline [23]. At 6 months after 20% attrition and 60% who meet the vitamin D threshold, this will result in a projected sample size of 115. Based on alpha = 0.05 and power = 80%, samples between 120 and 100 participants will be able to confidently detect mean PANSS total score trial arm differences of between 7.7 and 8.5 units (ES 0.52-0.57). Considering 90% power with the same power assumptions, we will be able to detect mean PANSS total score group differences of between 8.95 and 9.8 units (ES 0.60 to 0.65).

Recruitment

To be eligible for entry into the trial individuals who experienced their first presentation to health services with psychosis within the last three years must satisfy all eligibility criteria. Researchers will visit wards and community services to speak with staff and will meet interested patients face-to-face

or contact them by telephone. Once a patient has agreed to meet for a first appointment, an International Council on Harmonisation – Good Clinical Practice (ICH-GCP) trained clinician (research nurse, doctor or allied health professional) will be responsible for obtaining written informed consent. Eligibility will be confirmed by an ICH-GCP trained doctor for all trial participants prior to randomisation. Recruitment strategies will involve liaising with consultants throughout the Trust to inform about the study, visiting in-patient wards, attending physical health clinics in community settings and reaching out to care coordinators about their patients.

Randomisation

An online randomisation service will be provided by King's Clinical Trials Unit (KCTU, King's College London, London, UK). Randomisation will take place after collection of baseline measures. Randomisation will be stratified according to ethnicity (2 levels: White, Other), at a 1:1 ratio with randomly varying block sizes of 2-4. While there are no known predictors of PANSS scores in our target population, blood vitamin D concentrations vary by ethnicity [47], and we hypothesize that blood vitamin D concentration mediates any effect of vitamin supplement.

Intervention

All eligible patients will be randomised to receive either vitamin D3 (cholecalciferol) 120,000 IU (equivalent to 4000 IU per day) or placebo once monthly for a maximum of 6 months in a 1:1 ratio. We selected a monthly dosing design to help with adherence because this clinical group may already have a high tablet burden and are routinely assessed at intervals.

Vitamin D will be given as the drug Vigantol® which contains vitamin D3 (cholecalciferol) in oil. The placebo will be achieved by using an organoleptically matched triglyceride oil (Miglyol® 812 oil). Both active and placebo will be primarily packaged in identical sealed glass bottles (fill volume of 8mL). Active and placebo treatment will be administered orally as 6mL dose given in a graduated oral syringe by a trained researcher. Both will be administered at six monthly visits.

Guy's & St Thomas' Pharmacy Manufacturing unit (London, UK) is responsible for arranging the manufacture of the investigational medicinal product, randomised labelling, packaging and final Qualified Person (QP) release for clinical trial use.

No restrictions are placed on prior or concomitant interventions (medications or therapies, rescue or subsequent treatments) allowed, other than we ask the participants to refrain from taking vitamin D supplements (including multivitamins that contain vitamin D) that exceed 400IU/day for the duration of the trial.

Assignment of intervention

Each active and placebo investigational medicinal product (IMP) bottle will have a unique identification number. Each patient will be assigned a separate unique Patient Identification Number (PIN) which will be used throughout the duration of their treatment. Once the PIN is entered, the randomization algorithm will randomly allocate the patient to a study arm and notify the unblinded members of staff. Pharmacy staff will then assign a unique IMP bottle to the participant for a specific monthly visit. Only pharmacy staff dispensing the IMP and pharmacy monitor (clinical research associate) will be unblinded. The blinded members of staff will include all research teams at site level including Chief Investigator, the study site Principal Investigator, researchers undertaking assessments at each time point, and trial statisticians. Participants will remain in their allocated treatment arm for the duration of the study, even if IMP is discontinued.

Emergency code-break

Emergency code break and medical information will be provided by ESMS Global Ltd (London, UK). Each randomised subject will be provided with a patient card detailing code break telephone numbers and emergency contact details. Subjects will be requested to carry this card with them at all times whilst participating in the trial. Only healthcare professionals who have direct responsibility for the care of the trial participant, clinical trial investigators, pharmacists and the King's Health Partners Clinical Trials Office (KHP-CTO) staff are authorised to request unblinding.

Data collection and management

The trial data will be held in a customised electronic database (Infermed MACRO, Elsevier ltd, version 4, London, UK) created and maintained by the KCTU. All source data will be collected directly on to paper source data worksheets and then entered into an online electronic case report form (eCRF). The data entry screens will resemble the paper source document forms as closely as possible to minimise transcription error. MACRO allows for data entry checks thereby enhancing data accuracy. Data can be extracted from the database for checks and analysis. All personal information collected on DFEND trial participants and on potential participants will be treated as confidential and will be handled according to GCP guidelines, associated standard operating procedures, and in accordance with the Data Protection Act 1998 and European General Data Protection Regulations [48]. All electronic files containing personal information will be held only on password-protected computers. The computers themselves will be kept securely. All other trial information such as the trial master file (TMF), source notes and data keys will also be stored in a lockable, fireproof facility and only accessed by delegated DFEND trial staff.

Statistical analysis

Full details of the statistical analyses will be specified in a statistical analysis plan written in collaboration with the trial statisticians.

Descriptive analyses, recruitment rate, consent rate, loss to follow-up, departures from randomised treatment and the prevalence of serious adverse events post-randomisation will be reported and summarised by treatment arm over the course of the study. All causes of withdrawal from randomised treatment will be reported.

Analyses will be carried out by the trial statistician who will remain blinded until all analyses are completed. The analysis of the secondary outcome of blood sampling vitamin D concentrations at 6 months will be carried out after all other analyses are completed as there is a high expectation that mean concentration will be higher in the intervention group.

Intention-to-treat analysis of the effect of vitamin D supplementation on the primary PANSS outcome will be conducted using linear mixed modelling (LMM). All the available follow-up data from the randomised participants will be modelled. The analysis model will include treatment arm (vitamin D or placebo), time (3 or 6 months), baseline PANSS and randomisation stratifier (ethnicity) as explanatory variables. The model will also contain a subject-varying random intercept to account for any correlation between the repeated measures. Treatment effects on the other secondary outcomes at 6 months will be assessed using similar modelling techniques, employing generalisations to non-normal data where necessary.

To address secondary research objectives, we will also estimate treatment effects for the subpopulation who were vitamin D insufficient at baseline in terms of primary and secondary outcomes except for 25OHD blood concentration levels by including relevant interaction terms between baseline vitamin D insufficiency status and treatment group in the statistical models.

We expect there to be some missing data in the post-treatment outcome variables. The LMM analyses are based on maximum likelihood and will provide valid inferences under a missing at random (MAR) missingness mechanism. We will explore predictors of missingness, if deemed suitable for adjustment we will include these as explanatory variables in the analyses. If post randomisation variables are identified, a Multiple Imputation model will be considered instead [49].

No interim analysis will be carried out. There are no formalised pre-specified stopping rules.

Data Monitoring

In accordance with ICH-GCP guidelines, the DFEND investigators will permit regular trial-related monitoring and quality assurance audits by providing direct access to source data documents. The KHP-CTO will provide monitoring throughout the study at all sites. All research staff will be advised to take care to ensure a thorough audit trail is maintained throughout the trial.

Oversight committees

Regular meetings will take place with the Data Monitoring Committee (DMC) comprising an independent chair, independent statistician and independent psychiatrist. The DMC will safeguard the interests of DFEND trial participants, periodically review and evaluate the safety of the interventions during the trial, monitor the overall conduct of the trial and make recommendations to the Trial Steering Committee (TSC) concerning the continuation, modification, or termination of the trial. The DMC will also advise the Chief Investigator and Trial Management Group (TMG) to protect the validity and credibility of the DFEND trial.

The TSC is comprised of four independent members: two independent psychiatrists (one acting as chair), two patient-and-public representatives, the DFEND Chief Investigator and a co-investigator. The TSC will provide overall supervision of the trial, reporting on behalf of the Sponsor and Funder. The TSC members ensure that the trial runs according to the rigorous standards by monitoring the safety of participants, progress of the trial, protocol adherence, patient safety and relevant information that could impact the trial aims. The TSC also advises the investigators on all aspects of the trial.

Safety Monitoring

An Adverse Event (AE) is defined as any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. Any AE that occurs between the time of consent to the study through to 28 days following the last visit will be recorded. The Principal Investigators and study doctors will assess whether the adverse event may be related to the study intervention.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR) are defined as any adverse event, adverse reaction or unexpected adverse reaction, respectively, that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity or consists of a congenital anomaly or birth defect. All SAEs will be reported for this trial except hospitalisations due to deterioration in mental state, as we anticipate a high proportion of our participants will be

hospitalised for this reason during the trial. All hospitalisations or contact with home treatment teams will be recorded (e.g.) on a Service Contact Form.

In addition, the following assessments will be used to determine subject safety during the study at 3 and 6 months:

1. Corrected serum calcium (Ca^{+2}) levels will be tested at baseline, 3 and 6 months and more frequently if nausea and/or vomiting occur.

2. At 3 and 6 months, a parathyroid hormone test (PTH) will be performed on the same sample if corrected Ca^{+2} is above normal range. If participants report nausea and vomiting between visits, they will be advised to contact their doctor for a Ca^{+2} blood test.

3. A urine dipstick pregnancy test (beta-HCG) will be performed for females at baseline. Female participants of child-bearing age refusing a pregnancy test at baseline will be excluded from participating in the trial. At each treatment visit (monthly for 6 months) a urine dipstick pregnancy test will be performed to determine pregnancy status. Pregnancy tests will not be done for female participants who are permanently sterile or who are post-menopausal (no menses for 12 months without an alternative medical cause). If the urine test is positive, the participant will be withdrawn from the trial medication but encouraged to remain in the study. In the event that it is not possible to obtain a urine sample, a blood HCG sample will be obtained and tested. No dose of IMP will be administered to female participants without first checking pregnancy status (except for patients who are permanently sterile or post-menopausal, as described above).

Discontinuation of treatment will occur if a participant begins taking vitamin D doses above 400IU/day, becomes pregnant, PTH test is abnormal or at the discretion of the Principal Investigator.

Dissemination

Research findings will be disseminated via peer-reviewed journals, conferences, internal reports and user group meetings and informed by our experts by lived experience. When the project is complete, we will be able to provide all participants with a general summary of our research through a project newsletter.

Discussion

There is a growing quantity of evidence that suggests vitamin D is neuroprotective [1, 2, 10] and that vitamin D deficiency is prevalent in schizophrenia [12, 16]. Longitudinally, the severity of symptoms in psychosis has also been associated with vitamin D concentration [24]. Lack of vitamin D is also

associated with physical health problems including adverse cardiovascular outcomes [50], and so may potentially compound the poor health status associated with psychotic disorders [51, 52]. Few studies have, however, examined whether vitamin D supplementation may improve outcomes among people with psychosis. Our study is the first rigorously designed trial to investigate the impact of vitamin D supplementation in early psychosis.

Our eligibility criteria include patients that have the capacity to consent into the trial and thus with stable and minimal symptomology. We hypothesise that this will minimise the acute effect of standard treatment on our outcome measures. We have elected to not restrict eligibility to people known to be vitamin D deficient as it is not standard practice to test vitamin D levels on first presentation with psychosis; introducing testing prior to study entry would alter clinical practice and introduce a novel clinical question as to how to respond to the findings in the absence of applicable evidence. It would also limit the capacity of the study to determine whether there is benefit in supplementing all people with FEP with vitamin D. As we will be analysing baseline vitamin D levels after trial completion, we will be able to conduct a sub-analysis of this patient group.

A key strength of our study is its methodological rigour; utilising a double blind RCT will remove potential biases inherent in cross-sectional research. The study is designed to take a practical approach and recruit from local clinics. This approach will not only enhance the ecological validity of the outcomes but will also augment existing connections between clinical and academic networks.

Vitamin D supplementation in FEP is as yet an unexplored area of research and clinical equipoise exists regarding its potential for benefit [53]. This trial will evaluate whether vitamin D may improve mental health indicators in patients with FEP, with a view to informing protocols for vitamin D in patients with FEP. Vitamin D supplementation treatment is cheap, simple to access (e.g. over the counter), relatively safe, and is likely to be publicly acceptable [54]. Thus, even if vitamin D shows only small effects on clinical outcomes, vitamin D supplementation may offer a potentially effective treatment avenue for FEP patients.

Trial status

The current protocol is version 10.1 (03.05.2019). The study protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. For a list of changes to the registered protocol (ISRCTN12424842) please see Appendix 1. The study began recruiting in January 2016, and recruitment will be completed by May 2019. Follow up will continue until December 2019 and results are expected to be available in 2020.

List of Abbreviations

25OHD: 25-hydroxyvitamin D
AE: adverse event
Beta-HCG: beta- human chorionic gonadotropin
CA^{+2} : calcium
CDS: Calgary Depression Scale
CRP: c-Reactive Protein
DFEND: Vitamin D supplementation compared to placebo in people presenting with their First Episode of psychosis Neuroprotection Design
DMC: Data Monitoring Committee
eCRF: electronic case report form
ES: effect size
FEP: First Episode Psychosis
GAF: Global Assessment of Functioning
HbA1c: haemoglobin A1c
HRA: Health Research Authority
ICD-10: International Classification of Diseases 10^{th} Edition
ICH-GCP: International Council on Harmonisation – Good Clinical Practice
IU: international units
IPAQ: International Physical Activity Questionnaire
IRAS: Integrated research application system
IMP: Investigational Medicinal Product
KCTU: King's Clinical Trials Unit
KHP-CTO: King's Health Partner's Clinical Trials Office
LMM: linear mixed modelling
MAR: missing at random
MHRA: Medicines and Healthcare products Regulatory Agency
mmol/L: millimole per litre
NIHR: National Institute for Health Research
nmol/L: nanomole per litre
NHS: National Health Service
NOS: Nottingham Onset Schedule
OPCRIT: OPerational CRITeria
PANSS: Positive And Negative Syndrome Scale
PIN: Participant Identification Number
PTH: parathyroid hormone
PUMP: Physical Health and Substance Use Measures in first episode Psychosis
QP: Qualified Person
LMM: linear mixed modelling
RCT: Randomised Controlled Trial
REC: Research Ethics Committee
SAE: serious adverse event
SAR: serious adverse reaction
SIMPAQ: Simple Physical Activity Questionnaire
TMG: Trial Management Group
TMF: Trial Master File
TSC: Trial Steering Committee
UK: United Kingdom
USAR: unexpected serious adverse reaction

Declarations

Ethics approval and consent to participate

This protocol and related documents have been approved centrally by the National Research Ethics Committee – London Dulwich (REC reference number 14/LO/1588), and by the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation (reference 14523/0261/001-004). It has also been approved by the Health Research Authority (reference IRAS 147978). Substantial amendments will be sent to the REC and HRA, and MHRA if applicable. Non-substantial amendments will be communicated to the HRA, and REC and/or MHRA if applicable. Local approvals will be obtained at study sites prior to starting recruitment. Participants will be notified of any amendments that may affect their decision to continue in the study and will be asked to re-consent to an updated informed consent form.

An ICH-GCP trained clinician (research nurse, doctor or allied health professional) will be responsible for obtaining written informed consent from all trial participants prior to baseline assessment.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

FG has received honoraria for advisory work and lectures or CME activity support in the last 3 years from Lundbeck, Otsaka and Sunovion, is a collaborator on an NHS Innovations project co-funded by Janssen and has a family member with professional links to Lilly and GSK, including shares. RM has received honoraria for lectures from Lundbeck, Janssen, and Sunovion. SR has received honoraria for lectures from Lundbeck. All other authors declare no competing interests.

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Authors' contributions

FG, JJMcG, MB, SS, conceived the study. FG, JJMcG, MB, SS, DT, PMcG, SL, and RM further developed the study design and are grant holders. SL and DS provided statistical expertise in clinical trial design and developed the primary statistical analysis strategy. PL and MA provided service user and carer expertise throughout. PGS, JC, GW, LA and FG drafted and edited the manuscript, and the trial-registered protocol document on which it is based. SR, AB and MF are Principal Investigators at sites. SC, AK, HJ, BS collected primary data. All authors contributed to refinement of the study protocol and approved the final manuscript.

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Appendix 1

Changes to registered protocol

Protocol version	Description
2	Addition of new questionnaires including level of sun exposure, vitamin D in food frequency, Key Service contacts, Fitzpatrick Skin Type, levels of physical activity (IPAQ) and duration of untreated psychosis.
3	Addition of second questionnaire assessing physical activity (SIMPAQ). Addition of PANSS assessment at month three.
4	Changes to all study documents for clarification and to include site specific information/logos.
5	The definition of first episode psychosis was changed from “six months post-first presentation to services” to “3 years post-first presentation to services”.
6	Change in inclusion criteria to allow patients to take up to 400IU/daily of vitamin D in view of new Public Health England recommendations.
7	Change to inclusion criteria to allow patients aged up to 65 years to participate. Removal of anticonvulsants as an exclusion criterion. Change in SAE definition which will not include hospitalisations due to deterioration in mental health. Blood-HCG test was included if urine test is not possible. Clarification for permitted dosing windows. Total study duration was reduced from 12 to 6 months.
8	Removal of exclusion criteria regarding anaemia, sickle cell anaemia and thalassemia.
9.1*	Clarification of outcome measures. Time between doses to be minimum 24 days. Clarification of window for collection of final assessment. Pregnancy test not required if medically sterile or post-menopause. Vitamin D levels will be sent to GP at the end of the study. Phase II designation (not Phase IV).
9.2	Change in study end date to December 2019.
10.1*	Discontinuation of RNA sample collection. Increase in participant reimbursement. Clarifications to existing procedures regarding safety iPTH test, service contact form use, AE collection and attempts to contact

	participants in follow-up.

Note: Protocols version 9 and 10 were resubmitted as version 9.1 and 10.1 respectively addressing the committee's comments for documentation purposes.