PROTECTIVE-D: imPROving the effecTivenEss of vaccinaTion wIth positive mood and Vitamin D
Study Protocol Version v4.0 20OCT2022

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Trial title: A feasibility randomised controlled trial examining the effect of a positive mood intervention and vitamin D supplementation on the immunological responses to a boosting COVID-19 and/or influenza vaccination in healthy adults

Short title: PROTECTIVE-D: imPROving the effecTivenEss of vaccinaTion wIth positive mood and Vitamin D

EudraCT number:

REC reference:

IRAS reference: 316876

Chief Investigator: Dr Simon Royal

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Sponsor: The University of Nottingham Health Service

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Confidentiality Statement:

This document contains confidential information that must not be disclosed to anyone other than the sponsor, the investigator team, HRA, host organisation and members of the Research Ethics Committee and regulatory bodies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Dr Simon Royal.

Statement of Compliance:

This trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice, Medicine for Human Use (Clinical Trial) Regulations 2004 (as amended) and all other applicable regulatory requirements.

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Investigator agreement and notification of conflict of interest:

I approve this protocol for use in the above-named clinical trial and agree to abide by all the provisions set forth therein.

According to the Declaration of Helsinki 2018 I have read this protocol and declare no conflict of interest.

Signed: Date:

2. Contents

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3. Plain English Summary

Vaccines help us prevent diseases and keep us well. Some vaccines work better than others and there are many reasons for this. It can be to do with the vaccine itself or to do with the person having the vaccine. We have already found that people who report feeling happier on the day they are vaccinated produce more antibodies in response to the vaccination. We have also found that giving people only 15 minutes of a positive mood intervention to watch before they are vaccinated improves their mood. Recent research also suggests that the amount of vitamin D in your body at the time of vaccination can affect how well vaccines work.

In this study we will conduct a small experiment in which people who are about to receive a COVID-19 or influenza vaccination, or both, will be put in one of 4 groups at random.

- Group 1 will not be offered anything other than their vaccine (this is called usual care).
- Group 2 will receive a brief positive mood intervention, which has previously been shown to improve mood on the day they are vaccinated and for a further 6 days. They will also be advised to take a single dose of a vitamin D tablet just before they are vaccinated and once daily for the following 27 days.
- Group 3 will also receive the positive mood intervention on the day they are vaccinated and for a further 6 days, but they will not take the vitamin D tablet.
- Group 4 will be advised to take a vitamin D tablet at the time of vaccination and once daily for the following 27 days.

We will ask all participants to provide 15ml blood samples before vaccination and then at 28 days and at 6 months post vaccination. This sample will help us measure antibody responses to the vaccination and determine how well people have responded. In addition, up to 20 people across all groups will be asked to provide up to a 60ml blood sample at baseline and at day 28. These samples will allow us to understand how our interventions are changing the way the immune system works.

Finally, we will also interview a small number of participants as well as people working in vaccine clinics to gain their views on our approach to improving vaccine effectiveness. This work will help to identify if there is an easy and effective way to make vaccines work better that is acceptable to doctors and patients, doesn't have any side effects and which anyone, anywhere can try.

4. Synopsis

Study title	A feasibility randomised controlled trial examining the effect of a positive mood intervention and vitamin D supplementation on the immunological responses to a boosting COVID-19 and/or influenza vaccination in healthy adults		
IRAS reference	316876		
Short title	PROTECTIVE-D: imPROving the effecTivenEss of vaccinaTion wIth positive mood and Vitamin D		
Participants	Adults aged 65 years and over eligible for COVID-19 booster vaccination in Autumn 2022		
Sample size	~40		
Treatment	Positive mood intervention +/- vitamin D supplementation		
Treatment duration	7-28 days		
Study duration	12 months		
Planned study period	November 2022 to November 2023		
Objectives		Outcome measures	Evaluation time points
Primary	Feasibility and acceptability of study interventions for testing in future studies	Qualitative assessment of acceptability of interventions. Intervention adherence measures.	4 weeks

Exploratory	Assessment of effectiveness of study intervention in improving immune response to COVID-19 boosting and/or influenza vaccination. Further investigate immunological response to intervention.	Anti-SARS-CoV-2 immunoglobulin levels +/- vaccine induced influenza immunoglobulin levels SARS-CoV-2/influenza neutralising antibodies and T-cell responses.	4 weeks 24 weeks 4 weeks

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5. Abbreviations

AE:	Adverse Event
AR:	Adverse Reaction
CI:	Chief Investigator
CRF:	Case Report Form
CTIMP:	Clinical Trial of Investigational Medicinal Product
DSUR:	Development Safety Update Report
EudraCT:	European Clinical Trial Database
FDA:	Food and Drug Administration
GCP:	Good Clinical Practice
GDPR:	General Data Protection Regulation
HRA:	Health Research Authority
ICF:	Informed Consent Form
ISF:	Investigator Site File
PI:	Principal Investigator
PIS:	Participant Information Sheet
PPI:	Patient and Public Involvement
REC:	Research Ethics Committee
SAE:	Serious Adverse Reaction
SAE:	Serious Adverse Event
SOP:	Standard Operating Procedure
SUSAR:	Suspected Unexpected Serious Adverse Reaction
UNHS:	University of Nottingham Health Service

6. Background and rationale

Vaccines play a critical role in reducing the burden of infectious disease in the population. However, with all vaccines there is variability in the effectiveness and durability of protection, with the greatest variability evident in older people. Previous research has shown that a range of emotional and lifestyle factors alter vaccine effectiveness including positive and negative mood[1,2] and vitamin D status[3] and that interventions which target these factors can enhance vaccine success[4]. Furthermore, there is evidence that vitamin D and negative mood may be inversely related, suggesting that an intervention which combines both adjuvants may have synergistic effects.

The proposed project would build on existing evidence which has demonstrated the benefits of positive mood and vitamin D for vaccine effectiveness. The aims would be to:

1. Adapt an existing brief single session positive mood intervention to permit delivery of multiple sessions in the seven days post-vaccination
2. Assess the feasibility and acceptability of vitamin D supplementation for 28 days and a brief positive mood intervention for 7 days in older adults.
3. Gather preliminary evidence on the effects of positive mood alone, vitamin D alone and positive mood and vitamin D in combination on the antibody response to influenza and SARS-CoV-2 virus vaccines
4. Investigate the cellular and humoral immune mechanisms mediating intervention effects

7. Methods

Patients aged 65 years or greater being targeted for COVID-19 and/or influenza vaccination will be recruited from primary care to participate in a feasibility trial. They will be randomly allocated on a 1:1:1:1 basis to receive:

- No intervention (Usual Care)
- Positive mood intervention on the day of vaccination and for the following 6 days and vitamin D supplementation on the day of vaccination and once daily for the following 27 days
- Positive mood intervention on the day of vaccination and for the following 6 days
- Single dose oral vitamin D supplementation on the day of vaccination and once daily for the following 27 days

15 ml venous blood samples will be collected to detect antibodies to the vaccine antigens. These will be measured at baseline, 4 weeks and 6 months post-vaccine to assess intervention effects on peak vaccine responses and durability of protection. Participants will also receive a daily text message reminder with a link to the positive mood intervention and/or to take their vitamin D supplement, alongside an e-diary link to complete.

A sub-sample of up to 20 patients will be invited to have blood samples collected to explore potential cellular and humoral mechanisms at day 0 and day 28. This will entail an additional maximum 60ml blood sample on each occasion.

Interviews will be conducted with patients and health care professionals involved in the pilot trial to identify barriers and facilitators to implementing the intervention in routine care.

8. Participant identification

8.1 Study participants

Adults aged 65 and over who will be receiving an invitation to a COVID-19 or COVID-19 and influenza vaccination appointment at their GP Practice and/or mass vaccination clinic as per UK government guidance in autumn 2022 or 2023 will be eligible to participate in this study.

8.2 Inclusion criteria

- Participants must be able and willing to provide written informed consent to participate in the study.
- Participants must be able and willing (in the investigator's opinion) to comply with all the study requirements.
- Participants must consent to allow investigators to discuss their medical information with their general practitioner and access medical records where relevant to the study.
- Eligible to receive a COVID-19 vaccination and/or influenza vaccination as part of usual care.

8.3 Exclusion criteria

- Participants who have enrolled on a COVID-19 vaccine clinical trial of investigational medicinal product (CTIMP) in the last 12 months.
- Participants who are clinically extremely vulnerable and received a third or fourth dose in Spring 2022.
- Those aged less than 65.
- Those ineligible to receive a COVID-19 and/or influenza vaccination as part of usual care or those for whom a COVID-19 and/or influenza vaccination is contraindicated.
- Those for whom the collection of blood samples is contraindicated.
- Deemed by health care provider to be:
    - Too physically frail to participate.
    - Diagnosed with dementia or other cognitive condition which would make participation difficult.
    - Insufficient command of English language to complete surveys and provide informed consent.
- Participants who, in the past 3 months, have been prescribed oral vitamin D supplementation by a health care professional or who take over the counter supplements regularly on the advice of a health care professional.

9. Study Design

This study aims to evaluate the feasibility of large-scale testing of the intervention in future trials by evaluating its acceptability to participants and adherence markers. Samples will be taken at various timepoints during the study and Adverse Events, Severe Adverse Events and Adverse Events of Special Interest will be recorded. Figure 1 below displays the activities for the study.

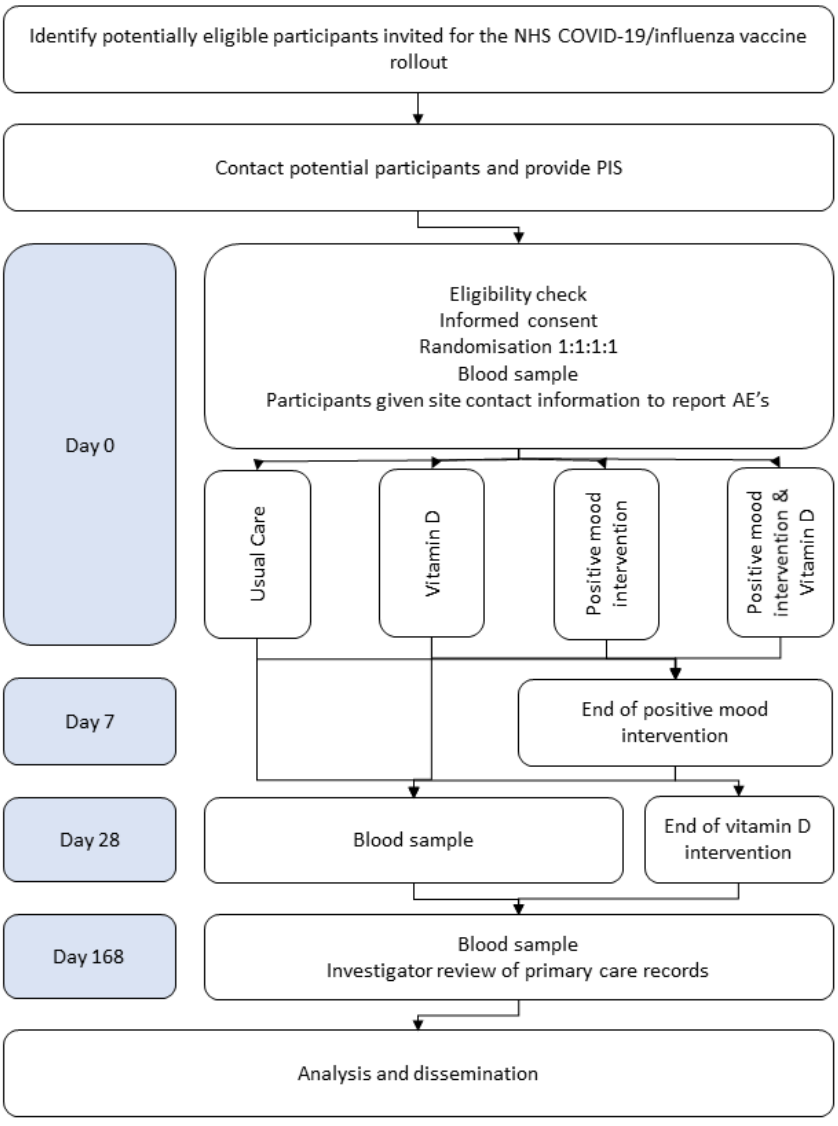

Figure 1 displays a flow chart of the proposed study design.

9.1 Recruitment

Potential participants will be contacted by the site to raise awareness of the study and offer access to study information. Contact methods include text messages, mail-outs and emails to those invited to receive their vaccination. Follow-up phone calls will be made to non-responders. Furthermore, study details will be added to the Cripps Health Centre website and promoted by Research Champions, PIC sites and other local GP practices.

9.2 Informed consent and enrolment

Patients invited for their COVID-19 booster vaccination and/or influenza vaccination as part of the national vaccine schedule that fit all other eligibility criteria will be invited to take part in the study.

The participant will have had sufficient opportunity, a minimum of 24 hours, to read and understand the contents of the PIS prior to being invited to provide informed consent, with further opportunities to ask questions and seek clarification at the consent and enrolment visit.

Each participant must give informed consent for the study and will be asked to acknowledge having read the latest approved version of the PIS and ICF before any study specific procedures are performed. Consent, randomisation, and vaccination will occur on visit 1. This will include consent, baseline blood collection, intervention administration and vaccination. The visit is not expected to take more than 60 minutes in total.

The PIS and ICF will present no less than the following information to the participant:

- The nature of and rationale for performing the study
- Implications and constraints of the protocol
- The risks and benefits involved in taking part in the trial

It will be clearly stated that there will be no provisions to supply participants with individual blood test results at any time, that the participant is free to withdraw from the study at any time, for any reason and that they are under no obligation to give the reason for withdrawal.

After giving informed consent participants will be allocated a unique study number.

9.3 Enrolment visit

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- Informed consent and eligibility will be checked by the research team (PIs, research nurse or practitioner).
- Demographics and medical history will be collected.
- Participants will be randomly allocated to one of the 4 study groups in a 1:1:1:1 ratio.
- Randomisation will be performed by an electronic randomisation system.
- Participants will provide a 15ml venous blood sample for biochemical and immunological analysis. A subgroup of participants will be invited to have a maximum 60ml blood sample taken for further immunological analysis. Venous blood samples will be collected by a phlebotomy trained Research Nurse/Practitioner using a vacutainer system or syringe and butterfly.
- Participants randomised to the positive mood intervention will receive a 15 minute positive mood intervention consisting of a combination of positive mood stimuli previously shown to enhance mood in older adults. Participants will also receive information on how to access their positive mood intervention over the next 6 days. Daily reminders to complete the intervention and e-diary will be sent via secure SMS messaging and checked by the PI and/or Research Nurse. In the event a participant is unable to work the e-diary, alternatives can be provided, such as paper copies or phone calls.
- Participants randomised to standard over the counter vitamin D supplement, will be advised to buy and take this immediately prior to vaccination and once daily for the following 27 days. Reminders will be sent to complete the intervention and e-diary as for the positive mood intervention group.
- Participants will then receive their COVID-19 booster and influenza vaccination in the standard NHS clinic which will be running at the site on that day. The vaccine will not be given as part of the study and the type of vaccine, timing or method will not be impacted by their participation in the study.

Some participants, clinicians' and other stakeholders' will then be interviewed about the intervention and trial acceptability and determine the barriers and facilitators to implementing the intervention in routine care. Interviews will be conducted by telephone, video call or face-to-face at participant preference, audio-recorded (with permission) and transcribed verbatim.

At the end of the visit, participants will be given an email address and/or phone number to report any adverse events occurring in the seven days after vaccination and will also be given an emergency 24-hour telephone number held by an investigator for advice on matters related to study participation.

9.4 Subsequent visits

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At day 28 and 168 after visit 1, participants will be asked to provide a further 15ml blood sample to measure immunological and biochemical responses.

Participants in the optional immunology subgroup cohort may be invited to have a larger blood sample (up to 60ml) collected at day 28.

A qualitative nested interview study will be used to assess participants', clinicians' and other stakeholders' views on intervention and trial acceptability and determine the barriers and facilitators to implementing the intervention in routine care. The process for obtaining participant informed consent for the study will include consent for potential inclusion in the qualitative interview nested study. The qualitative study will be reported in line with the Consolidated Criteria for Reporting Qualitative Research (COREQ: Tong et al, 2007).

We will conduct semi-structured interviews with a sample of patient participants and stakeholders (healthcare professionals, or other practice staff involved in explaining the trial to patients, conducting the screening and consent processes, or delivering the intervention). We aim to complete these within 4 weeks of the end of the intervention period. Interviews will be conducted by telephone, video call or face-to-face at participant preference, audio-recorded (with permission) and transcribed verbatim. Topic guides will be developed based on study aims and input from the Trial Management Group (TMG). Interview participants will be selected purposively to ensure diversity in relevant characteristics (e.g., trial group allocation, age, gender, ethnicity, deprivation index, region). Sampling will cease when we have sufficient information power relevant to the study aims (Malterud et al, 2016) although we anticipate up to 20 participants, and 10 stakeholders. Analysis of qualitative data will use appropriate methods such as inductive thematic analysis.

9.5 Sample collection and storage

Sample collection, handling and storage will be described in the laboratory analysis plan and the relevant site-specific SOPs.

9.6 Laboratory analysis

Blood Samples will be assessed for a variety of immunological parameters relevant to vaccine responses (e.g., IgG antibody levels). They may also be analysed for other immunological parameters relevant to the immune and endocrine response to vaccination (e.g., cytokines). The analyses will be conducted by the study team, overseen by Prof Lucy Fairclough. These analyses will be completed at the University of Nottingham using equipment and laboratories serviced and managed at the University of Nottingham.

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Serum vitamin D levels will be measured at each time point. This analysis will be undertaken at Nottingham University Hospital Biochemistry laboratories which is a fully accredited NHS facility.

9.7 Compliance

Compliance is defined as the proportion of participants that complete diary, receive at least one dose of the SARS-CoV-2 vaccine and provide a pre-vaccination and at least one post-vaccination blood sample.

9.8 Discontinuation/withdrawal of participants

Each participant may exercise their right to withdraw from the study at any time. In addition, the investigator may terminate the participant's involvement in the study at any time if the investigator considers it necessary for any reason including, though not exclusive to, the following:

- Ineligibility (either arising during the study or in the form of new information not declared or detected during the eligibility assessment)
- Significant protocol deviation
- Significant non-compliance with study requirements
- Any adverse event which requires discontinuation of the study procedures or results in an inability to continue to comply with study procedures
- Consent withdrawn
- Lost to follow up

The reason for withdrawal will be recorded in the study records, the withdrawn participants will not be replaced. Withdrawal from the study will not result in exclusion of the data generated by that participant from analysis unless requested by the participant.

9.9 Definition of end of study

The end of the study will be defined as the time the last blood sample is analysed.

10. Safety reporting

Safety reporting for participants in this study begins at the point of consent and ends at 168 days post-enrolment. Safety data will be collected via:

- Direct notification by the participant to the investigator via email or telephone according to the information on the study contact card given to each participant at enrolment.
- Investigator review of primary care medical records at 28 days and 168 days.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of a subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilises
- The event returns to a baseline if a baseline value is available
- The event can be attributed to agents other than to study interventions or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

10.1 Adverse event definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.

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Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect*. Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. NOTE: Pregnancy is not, in itself an SAE, but an adverse outcome of pregnancy, for example spontaneous miscarriage, may be judged to be an SAE if clinically appropriate.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question.

10.2 Assessment of causality

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Causality will be clinically assessed relative to the interventions administered during the trial by the Chief Investigator. An adverse event is considered to have a causal relationship to an intervention if the attribution is possible, probable, or very likely by the definitions listed below. An adverse event is considered to have no causal relationship to an intervention if the attribution is not related or unlikely by the definitions listed below. In the group receiving two interventions, the attribution of any adverse event to either of the individual interventions will be at the Chief Investigator's discretion.

Causality term	Assessment criteria
0 No relationship	No temporal relationship to study product **and** Alternate aetiology (clinical state, environmental or other interventions); **and** Does not follow known pattern of response to study product
1 Unlikely	Unlikely temporal relationship to study product **and** Alternate aetiology likely (clinical state, environmental or other interventions) **and** Does not follow known typical or plausible pattern of response to study product.
2 Possible	Reasonable temporal relationship to study product; **or** Event not readily produced by clinical state, environmental or other interventions; **or** Similar pattern of response to that seen with other vaccines
3 Probable	Reasonable temporal relationship to study product; **and** Event not readily produced by clinical state, environment, or other interventions **or** Known pattern of response seen with other vaccines
4 Definite	Reasonable temporal relationship to study product; **and** Event not readily produced by clinical state, environment, or other interventions; **and** Known pattern of response seen with other vaccines

10.3 Assessment of severity

The severity of adverse events will be assessed according to scales based on FDA toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials, listed in the table below.

Severity grade	Assessment criteria

Grade 1	Mild: Transient or mild discomfort (< 48 hours); No interference with activity; No medical intervention/therapy required
Grade 2	Moderate: Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required
Grade 3	Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required.
Grade 4	Potentially Life-threatening: requires assessment in A&E or hospitalisation

10.4 Safety reporting procedures

SAEs and AESIs will be reported to the CI as soon as possible after being reported to a member of the team. The CI will be responsible for deciding whether the participant is able to continue the study; whether the study can continue; and whether the sponsor should be informed.

Assignments of causality will only be made in relation to the administration of Vitamin D and/or positive mood intervention during the study. Any SAEs which occur following externally administered vaccines or medicines e.g., those given as part of the patient's usual care, will be judged to be unrelated to the study vaccine and should additionally be reported through national pharmacovigilance mechanisms as applicable.

Hospitalisation (including inpatient or outpatient hospitalisation for an elective procedure) for a pre-existing (existing prior to administration of Vitamin D during the study) condition that has not worsened unexpectedly does not constitute an SAE. Emergency department attendances should not routinely be reported as SAEs unless they meet the SAE definition described above.

The procedure for reporting of Serious Adverse Events is to complete an SAE report form for all reportable SAEs. The CI or delegate will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor. The safety profile will be continuously assessed by the Investigators. The CI and relevant investigators (according to the study delegation record) will also review safety and SAE issues as they arise.

11. Statistics

Evaluation of the findings will be conducted by the study team using SPSS and overseen by the study statistician Dr Kieran Ayling.

The main statistical analysis will be to identify a statistically significant difference in the four groups and identify any additional immune effect of vitamin D supplementation given at the time of vaccination. We will use a range of advanced techniques, such as multivariate statistical methods and advanced clustering and classification approaches to assess the independent and combined contribution of psycho-behavioural factors to immunological responses to the vaccination.

All validated measures employed will be summarised according to published guidelines.

11.1 Sample Size Determination

We do not specify *a priori* sample size since we will be assessing recruitment, study procedures and retention in order to inform the planning of a larger trial at a future date. We will pause recruitment when we have a minimum of 10 participants in each arm (about 40 participants in total).

At that point we will perform an interim analysis of both the quantitative and qualitative data obtained and determine whether we have enough outcome measures to meet the primary objective. This decision will be taken by the study steering group which will comprise all of the investigators and the study co-ordinator. The decision will be based on whether the data obtained is sufficient to fully inform the design of the larger trial to follow, specifically whether the methodology is acceptable to participants and study staff and whether the intervention adherence measures are capturing data as intended. We have expertise in qualitative methodology in the study steering group.

If the group feel that we have sufficient data to achieve the primary objective, the study will be stopped and the exploratory outcome data will be analysed. If the group feel further data is needed, we will not analyse exploratory outcome data at this point and recruitment will resume until a minimum of 20 patients per arm have been recruited (about 80 participants in total). When data collection is complete, we will perform a final analysis of all primary and exploratory outcome data.

11.2 Procedure for Accounting for Missing, Unused, and Spurious Data

Reasons for missing data (including withdrawal of consent or inability to obtain any laboratory results) will be indicated, but missing data will not be imputed.

11.3 Inclusion in analysis

Analysis will be conducted of a full data set for all participants who are deemed to have no major protocol violations that could interfere with the objectives of the study. Such a set will comprise all participants, who complete the e-diary (and consent form) and for whom post-baseline assessment of the primary outcome measure is available.

Laboratory data, such as blood samples, from all participants who enrol in the study will be included in the analysis.

12. Data management

The Chief Investigator will be responsible for all data that accrues from the study.
All protocol-required information will be collected and into the CRF. CRF entries will be therefore considered source data. All other information will be entered onto their medical record and/or ISF. Source documents are original documents, data, and records from which the participant CRF data are obtained. For this study, these will include, but are not limited to, volunteer consent form, laboratory records, medical records, and correspondence. As part of the informed consent process, permission will be sought to access the participant's data from pertaining to basic demographic information and contact details.

All source data and participant files will be stored securely.

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorised third party, without prior written approval of the sponsor

Each study participant will retain the unique participant number first assigned at randomisation. Samples sent to laboratories for processing will be identified by participant number. All documents will be stored safely and securely in confidential conditions. Direct access will be granted to authorised representatives from the Sponsor and the UNHS and the regulatory authorities to permit study-related monitoring, audits and inspections. Participant name and any other identifying detail will NOT be included in any trial data electronic file.

The Investigators will maintain appropriate medical and research records for this trial, in compliance with GCP and regulatory and institutional requirements for the protection of confidentiality of volunteers. The Chief Investigator, co-Investigators and clinical research nurses will have access to records. The Investigators will permit authorised representatives of the Sponsor(s) and Host institution, as well as ethical and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. Identifiable information such as contact details will be stored for a minimum of 5 years from the end of the study. Participants shall be approached should there be any unexpected safety signals emerging post-licensing surveillance. This includes storage of consent forms. Storage of these data will be reviewed every 5 years and files will be confidentially destroyed if storage is no

longer required. Considerations at the time of this review will include the value of retaining this information for participant safety, as a resource for the participants (e.g., if they wish to check which vaccines they have received in the study) and any regulatory requirements. De-identified research data maybe be stored indefinitely. If volunteers consent to be contacted for future research, a record of this consent will be recorded, retained and stored securely and separately from the research data. If volunteers consent to have their samples stored and used in future research, information about their consent form will be retained and stored securely as per Biobanking procedures and SOP.

Data collection tools will undergo appropriate validation to ensure that data are collected accurately and completely. Datasets provided for analysis will be subject to quality control processes to ensure analysed data is a true reflection of the source data. Trial data will be managed in compliance with local data management SOPs.

13. Quality assurance procedures

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. Approved and relevant Standard Operating Procedures (SOPs) and Laboratory plans will be used at the laboratory site.

14. Protocol deviations and Serious breaches

Any deviations will be documented in a protocol deviation form and filed in the ISF. Each deviation will be assessed as to its impact on participant safety and study conduct. Significant protocol deviations will be listed in the end of study report.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –
(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial.”

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the relevant NHS host organisation within seven calendar days.

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15. Ethical and regulatory considerations

15.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the current version of the Declaration of Helsinki.

15.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and principles of Good Clinical Practice (GCP). All members of the study team on the delegation log will have valid GCP training certification.

15.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC) for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

15.4 Other Ethical Considerations

As with all qualitative research, there is potential for distress in focus groups and/or interviews. This would be managed by pausing or stopping the interview if necessary. Furthermore, mental health appointments can be made for the participant with their usual GP or health and wellbeing team as part of routine care.

There is no other ethical consideration in relation to this study protocol.

15.5 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the REC, host organisation and Sponsor.

15.6 Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database. Results will be uploaded to the European Clinical Trial (EudraCT) Database within 12 months of the end of trial declaration by the CI or their delegate. Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

15.7 Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018 in the UK which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16. Finance and insurance

16.1 Funding

Partial funding of the study is provided by NIHR CRN East Midlands. Funding is also provided by Cripps Health Centre to build Research Capacity.

16.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

16.3 Contract arrangements

Appropriate contractual arrangements will be put in place with all third parties.

17. Publication policy

The Chief Investigator will co-ordinate dissemination of data from this study. All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study will be reviewed by each sub-investigator and by the Sponsor prior to submission.

18. Development of a new product/process or the generation of intellectual property

Not applicable

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19. References

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20. Appendices

20.1 Vitamin D Supplementation

Vitamin D - NHS (www.nhs.uk)