NIHR | National Institute for Health Research

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VITDALIZE

VITDALIZE UK Eligibility Confirmer Training

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Effect of High-Dose Vitamin D3 on 28-Day Mortality in Adult Critically Ill Patients with Severe Vitamin D Deficiency

The UK arm of an International Multi-Centre, Placebo-Controlled, Phase III Double-Blind Trial

Protocol Version 7.0, 29th May 2025

Presentation version 2.0 28th July 2025

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Sponsor:
University of Graz, Austria

National Co-ordinating Centre:
University of Birmingham

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Agenda

Background & Objectives → Trial Intervention & Follow-Up → Eligibility → Quality Control & Assurance

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Background

- Vitamin D deficiency (VDD) is common in patients admitted to intensive care units (ICU) with prevalence between 40-70%
- It has been identified that patients who have VDD are associated with poor outcomes in critical illness
- VDD has been associated with:

• Acute respiratory failure • Duration of mechanical ventilation • Sepsis	• Nosocomial infection • Acute kidney infection • Increased mortality

- Patients who are VDD have a longer ICU stay, increased morbidity and mortality

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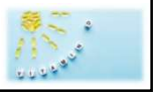
- In most cases, patients enter ICU in a deficient state due to pre-existing conditions
- However, vitamin D levels can also fall rapidly after ICU admission
- In the past decade vitamin D has been associated in the function of a wide range of tissues including the immune system
- Vitamin D has the ability to act synergistically on the immune response
- Previous research into vitamin D has been criticised due to:
  - Small number of patients recruited
  - Single centre trials
  - Vitamin D given as a single dose
  - Critically ill patients with severe VDD not included



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VITdAL-ICU pilot trial

- Recruited 475 patients
- Only phase III trial of high dose vitamin D3 supplementation (540,000IU followed by monthly 90,000IU for 5 months) in critical illness

Findings

- No difference was found in the primary endpoint of length of hospital stay between placebo and high-dose vitamin D3 treated patients
- However, a non-significant, absolute risk reduction in all-cause hospital mortality was found. The difference was large (17.5%) and significant in the predefined subgroup of patients with severe VDD (25(OH)D ≤12ng/mL)
- This was a secondary endpoint in the predefined subgroup with severe VDD and was hypothesis generating leading to the VITDALIZE Trial

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Trial rationale

- There are associations between VDD and poor outcomes in sepsis, acute kidney injury and acute respiratory failure in critical illness
- Limited number of interventional trials of vitamin D replacement in ICU
- Vitamin D testing is available in all NHS hospitals and is inexpensive

Aim

To determine if treatment with high dose vitamin D improves patient outcomes and is cost-effective when compared to placebo in severely VDD patients critically ill patients admitted to ICU

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Primary objective

- To determine whether treating severe VDD with high dose vitamin D3 replacement in adult critically ill patients decreases 28-day mortality

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Secondary objectives

To determine whether treating severe VDD with high dose vitamin D3 replacement in adult critically ill patients:

- Reduces organ dysfunction
- Reduces hospital and ICU length of stay
- Reduces mortality
- Improves long-term survival
- Reduces readmission to hospital
- Improves activities of daily living

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Secondary objectives

In the UK additionally:

- Improves health-related quality of life at 90 days and 1 year
- Reduces disability at 90 days and 1 year
- Reduces health care utilisation to 1 year
- Is cost-effective in the NHS setting

Exploratory objective

- To assess the feasibility of patient quality of life and disability at day 0

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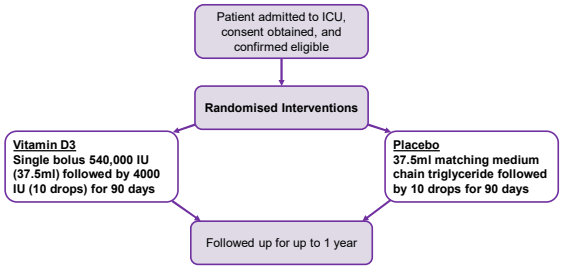
Summary



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Trial Intervention & Follow-Up

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Trial arms

- Randomisation will be done in a 1:1 ratio stratified by centre and sex

Intervention

Single loading dose (oral/enteral) vitamin D3 (540,000IU cholecalciferol, oleovit™ dissolved in 37.5ml of medium chain triglycerides (MCT) followed by 4000IU daily (10 drops) for 90 days

Control

Placebo, identical treatment regime of 37.5ml MCT followed by 10 drops MCT daily for 90 days

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Trial interventions - things to note

- Trial intervention can be given orally or through the patient's feeding tube
- Up to 800IU/day concomitant vitamin D supplementation is permitted

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Follow-Up

Length of follow-up: main trial data collection ends at **death or at one year follow-up**, whichever occurs first.

On **days 0, 28, 90 and 1 year** the research team will follow-up the patient (either in person if they are still in hospital or via telephone), who will be asked questions about their health. This should take no longer than 20 minutes.

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Eligibility

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Inclusion Criteria

To be eligible *to participate, patients must meet all the following inclusion criteria:*

Inclusion Criteria

1. Patients ≥ 18 years
2. Anticipated ICU stay ≥ 48 hours
3. Admission to ICU ≤ 72 hours before screening for VDD
4. Severe VDD (25(OH)D ≤ 12ng/ml (30nmol/L)) after ICU admission

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Exclusion Criteria

*If any of the following apply, the patient is **not eligible** to be randomised:*

Exclusion Criteria

1. Severe gastrointestinal dysfunction (>400ml nasogastric tube residual volume)/unable to receive trial medication
2. Not expected to survive initial 48 hours of admission or treatment withdrawal imminent (within 24 hours)
3. Patient with DNAR orders in place
4. Hypercalcemia (>2.65 mmol/l corrected calcium and/or >1.35 mmol/l ionized calcium at screening)
5. Known kidney stones within the last 12 months
6. Known active tuberculosis within the last 12 months
7. Known sarcoidosis within the last 12 months
8. Pregnant or lactating
9. Known hypersensitivity to the trial drug or excipient
10. Medical team deem it not suitable to include patient
11. Known prisoner in the custody of HM prison or probation service

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Exclusion Criteria –Reasons

Exclusion Criterion 1

- Intended to exclude patients who may not absorb the trial medication as it is a per oral or nasogastric tube dosing regimen which cannot be given parenterally.

Exclusion Criteria 2 and 3

- Intended to exclude patients unlikely to survive to day 28 primary trial endpoint.

Exclusion Criteria 4, 5, 6, 7 and 9

- Intended to exclude patients who may be at higher risk of side effects secondary to high dose vitamin D supplementation.

Exclusion Criterion 8

- To exclude patients as the potential side effects of high dose vitamin D replacement on the foetus are unknown.

Exclusion Criterion 10

- To exclude patients who may suffer severe physical or mental capacity issues and are unlikely to comply with the daily dosing of vitamin D to 90 days.

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Co-enrolment

- A list of trials VITDALIZE UK can co-enrol with can be viewed on the trial website: Co-Enrolment - University of Birmingham

If you wish to discuss additional trials, please contact the VITDALIZE UK trial team:

Email: vitdalize@trials.bham.ac.uk
Tel: +44 (0)121 414 7943

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Eligibility Continued

- **Must be confirmed by a medically qualified doctor delegated the task (task D)**
- If inclusion criteria 1-3 are met and none of the exclusion criteria are met, the patient will be considered provisionally eligible. **Written informed consent** will be gained for the trial and a screening blood sample obtained by:
  - A blood sample of approximately 5-10 ml taken from the patient (preferably from an existing line)
  - Alternatively, a vitamin D test added to a routine clinical sample already taken on the same day

Only patients who meet the threshold of 25(OH)D ≤12ng/ml (30nmol/L) will be eligible to continue in the trial.

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Eligibility Documentation

Before a patient can be randomised into the trial:

- Full eligibility must be confirmed (including confirmation that the patient has severe VDD)
- Please document eligibility confirmation in the patient's medical notes.
- Eligibility checklist form must be completed.

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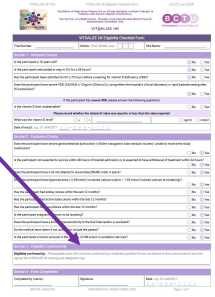
Eligibility Checklist

- A **paper CRF** that confirms all the necessary information (inclusion/exclusion) prior to randomisation.
- Can be completed by any research team member **delegated the task of CRF completion (task O)**, as only eligibility confirmer name is requested, not signature.
- If completing yourself, please ensure that you:
  - Are delegated task O.
  - Are using the current version of the form (refer to the document version control log in your ISF).
  - Enter patient initials and once randomised, trial number (do not enter any additional identifiable information on the form).
  - Initial and date any corrections.



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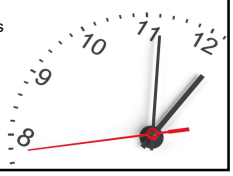
In the event of delays

Eligibility confirmation to randomisation:

If there has been a >24-hour delay since eligibility was confirmed, eligibility must be re-assessed and eligibility checklist completed prior to randomisation.

Eligibility confirmation to loading dose:

If there has been a >24-hour delay since eligibility was confirmed, eligibility must be re-assessed prior to the patient receiving the loading dose.



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Quality Control & Assurance

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Deviations and Potential Serious Breaches

- Any protocol deviations should be reported to the VITDALZE UK Trial Office

Serious Breaches:

- Sites must notify the VITDALIZE UK Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as it becomes aware of them
- Sites must provide sufficient information to report the breach and engage with undertaking any CAPA

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Delegation log

- PI has overall responsibility for study conduct at each site
  - PIs can delegate certain study-related tasks to sub-investigators, clinicians, research nurses, and any other study related staff
- Delegation log must be **signed and dated** by all staff involved in the trial and kept current throughout the trial.
- BCTU must also be in receipt of **signed and dated CVs, GCP certificates, and study training logs** for all staff listed on the delegation log

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Contact details

- Email: vitdalize@trials.bham.ac.uk
- Tel: +44 (0)121 414 7943
- Postal Address: **VITDALIZE UK** Trial Office, Birmingham Clinical Trials Unit (BCTU), College of Medical and Dental Sciences Public Health Building, University of Birmingham, Edgbaston, Birmingham, B15 2TT
- VITDALIZE UK website: VITDALIZE UK - University of Birmingham

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Questions?

If you have any questions, please discuss with your local team or contact the VITDALIZE UK Trial Office.

Training Log:

Your evidence of training can be recorded electronically here:
https://redcap.link/VITDALIZETrainingLog

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