NIHR | National Institute for Health Research

UNIVERSITY OF BIRMINGHAM | BCTU

Dr Dhruv Parekh & Dr Matthew Soden

Site Initiation Training

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 6.0, 22nd June 2022

Sponsor:
University of Graz, Austria

National Co-ordinating Centre:
University of Birmingham

Funder:
NIHR Health Technology Assessment (project number 17/147/33)

Agenda

Background → Objectives → Study Design → Data Management → Pharmaco-vigilance

VITDALIZE UK

- VITDALIZE is an international trial and is a collaboration between Austria, Belgium, Germany and the UK
- The target number for the international trial is 2400
- The UK arm aims to recruit is 600 patients
- Estimated recruitment end: September 2023
- Length of follow-up: main trial data collection ends at **death or at one year follow-up**, whichever occurs first

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

- 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

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

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

Primary objective

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

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

Secondary objectives

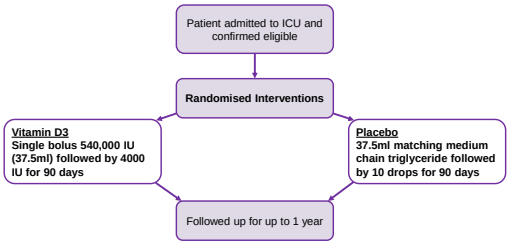
In the UK additionally:

- 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

Summary



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™ disolved in 37.5ml of medium chain tryglycerides (MCT) followed by 4000IU daily (10 drops) for 90 days

Control

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

Trial interventions

- The trial medication is provided by Fresenius Kabi Austria GmbH
- Labelling, filling, packing and distribution of the trial medication will be provided by certified pharmacy Landesapotheke, Müllner Hauptstraße 50 5020 Salzburg
- Can be stored up to 25 ˚C
- Kept out of direct sunlight
- Shelf life between 1-2 years
- Trial intervention can be given orally or through the patients feeding tube

Trial interventions

- The interventions will arrive as a pack of 28 boxes (130 x 45 x 68mm boxes) to sites
- Each box contains 5 identical bottles labelled with the annex 13 label
- When the interventions arrive the proof of receipt form should be completed to ensure the interventions have not been damaged in transit (a copy is then sent to the VITDALIZE UK Trial Office)
- Add medication to the VITDALIZE UK Accountability Log
- When a patient is randomised, the box with the identity code will be dispensed to the ICU for the patient using the accountability and dispensing log


For clinical trial use only!
Vitamin D3 or placebo 12.5ml
Please keep out of reach of children
Store below 25°C and protected from UV light
Application following the prescription of the subinvestigator
Ident.-Code: DGFTRH-???

Eligibility

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

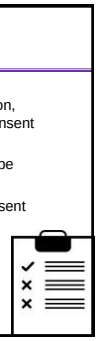
Eligibility continued

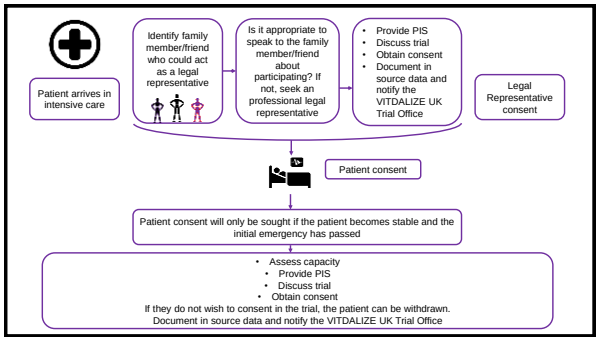
Exclusion Criteria

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 a DNAR 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 sarcoidosis within the last 12 months
7. Pregnant or who are lactating
8. Known hypersensitivity to the trial drug or excipient
9. Medical team deem it not suitable to include patient
10. Known prisoner in the custody of HM prison or probation service

Consent

- Patients will, by default be critically ill and due to the effects of sedation, infection, delirium and mechanical ventilation may lack capacity to consent for themselves
- Where patients lack capacity to consent for themselves, consent will be sought from a legal representative
- For VITDALIZE UK professional legal, personal legal and patient consent can be obtained





Consent

A copy of the **signed** informed consent form(s) will be given to the **patient or the legal representative**

The original signed form(s) will be retained at the **study site** in the **Investigator Site File** and a copy placed in the **medical notes**.

With the patients/ legal representatives **consent,** the participants **General Practitioner** (GP) should be informed on discharge – **GP letter**.

Copies of all consent forms will also be sent to the **VITDALIZE UK** Trial Office.

Randomisation

To randomise a patient into the trial once eligibility has been confirmed:

1. Create a new patient using the eCRF Clincase (https://edc.medunigraz.at/clincase/app) to provide a patient trial number (this is needed to complete randomisation)
2. Use the database 'randomizer' (www.randomizer.at/random/login) using the patient trial number, sex and site ID
3. This will then provide the ident. code for the trial medication

An email confirming randomisation will be sent to the research team at site to prepare the medication ready for the patient

We also recommend the research team contact the pharmacy separately to confirm the randomisation

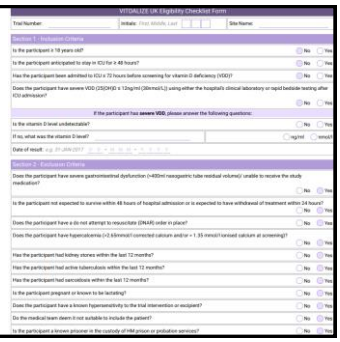
Randomisation

- Please refer to the **randomisation worksheet, flowchart and protocol** when randomising patients into VITDALIZE UK

Before randomising the patient into the trial:

- Complete the eligibility checklist CRF (send copy to the VITDALIZE UK Trial Office)
- Confirm the patient has severe VDD

VITDALIZE UK eligibility form



Things to note

- **There is no paper randomisation for VITDALIZE UK**
- If the randomisation system is not working contact the VITDALIZE UK Trial Office immediately
- At the end of the trial or expiry of trial medication, sites can dispose of the trial intervention per standard processes after approval from the VITDALIZE UK Trial Office
- If a patient misplaces their trial medication patients will not receive any further medication

Keep a log

- Keep a log of recruited patients on the VITDALIZE UK Patient and Recruitment Log (this is for your record)
- Maintain the VITDALIZE UK Screening/Enrolment Log of patients screened and enrolled (this should be available to be sent to the VITDALIZE UK Trial Office upon request)
- The VITDALIZE Screening/Enrolment Log will be used as a way to review payments for patients

Data Management

Data management

- Data for the VITDALIZE UK Trial will be entered on 2 databases
- The main trial outcomes will be collected via the eCRF, the additional UK specific outcomes will be collected on the UK database
- Data on the eCRF will be completed by the research staff at site, data for the UK database will be entered by the VITDALIZE UK Trial Office

Outcome measures - eCRF

Primary outcome

All-cause mortality at 28 days after randomisation

Outcome measures - eCRF

Secondary outcomes

- 90 day and 1-year mortality
- ICU and hospital mortality
- Hospital and ICU length of stay (starting at day 0, ending at discharge, day 90, or mortality, whichever occurs first)
- Change in organ dysfunction on day 5 (SOFA score)
- Hospital and ICU readmission until day 90
- Discharge destination (home, rehabilitation other hospital)
- Katz activity of daily life at day 90
- Self-reported infection requiring antibiotics until day 90

Outcome measures – UK Database

Secondary outcomes continued

- Health related quality of life (EQ-5D-5L) at day 0, 28, 90 and 1 year
- Disability assessment (WHODAS 2.0) at day 0, 28, 90 and 1 year
- Secondary health care utilisation in the first year (ICU and hospital length of stay, readmissions and utilisation of hospital and community care resources after hospital discharge 1 year after randomisation), from Hospital Episode Statistics, civil registry data held by NHS Digital and patient questionnaires
- Health economics analysis at day 28, 90 and 1 year
  - Cost effectiveness of screening for and treating VDD in critical illness
  - Cost per quality-adjusted life year gained 1 year after randomisation and at end of life

Outcome measure

Exploratory outcome

- Health related quality of life at randomisation (day 0)

Safety outcomes

- Hypercalcemia up to day 5 (48 hours tolerance)/ during ICU stay
- Self-reported falls, fractures until day 90
- New episodes of kidney stones until day 90

Data entry

eCRF (remote) data entry	Paper CRF data entry
• Baseline – Day 0	• Eligibility checklist form
• Day 5	• Informed consent form
• Day 28	• Contact details form
• Day 90	• Questionnaires (EQ-5D-5L; WHODAS 2.0)
• 1 Year	• Change of status form
• Discharge information	• Health economics form
• Study discontinuation	• SAE form
• Adverse event reporting	• Pregnancy form
• SAE form (international)	

Data management for eCRF

- Research staff will be provided with unique log-in usernames and passwords for the online system
- The system will include data validations that will be highlighted if there are erroneous data
- VITDALIZE UK worksheets are available to assist with data entry of data on eCRF
- If the VITDALIZE UK worksheets are used they will be classed as source data

Data management for paper CRF

- Paper CRF completion is for UK data
- Research staff be required to complete the paper CRFs and send to the VITDALIZE UK Trial Office

Paper CRFs

- Complete CRFs should posted to the VITDALIZE UK Trial Office

VITDALIZE UK Trial Office
Birmingham Clinical Trials Unit
Institute of Applied Health Research
College of Medical and Dental Sciences
Public Health Building
University of Birmingham
Edgbaston
Birmingham
B15 2TT

- Please retain a copy at site and file in your site file

VITDALIZE UK CRF Form Completion Timeline

Pre-randomisation	Baseline (Day 0)	Day 5	Day 28	Day 90	1 year
Eligibility Checklist Form	Visit 1 (day 0) eCRF/ worksheet	Visit 2 (day 5) eCRF/ Worksheet	Visit 3 (day 28) eCRF/ Worksheet	Visit 4 (day 90) eCRF/ Worksheet	Visit 5 (1 year) eCRF/ Worksheet
Informed Consent	WHODAS 2.0		WHODAS 2.0	WHODAS 2.0	WHODAS 2.0
Contact Details Form	EQ-5D-5L		EQ-5D-5L	EQ-5D-5L	EQ-5D-5L
			Health economics CRF	Health economics CRF	Health economics CRF
					Study discontinuation eCRF/ worksheet

Other forms that require completion without specific time point

Discharge information eCRF/ Worksheet	Requires completion for the following: • Once the patient has been discharged from primary ICU **If patient was discharged to a ward,** • The form will require updating again once the patient is discharged from there.
Study discontinuation eCRF/ Worksheet	Requires completion for the following: • Death of patient • Lost to follow-up • Withdrawal • Completion of study
Change of status CRF (UK; paper)	Requires completion for the following: • Death of patient • Lost to follow-up • Withdrawal **Once completed, send to the VITDALIZE UK Trial Office**
Adverse events eCRF/ Worksheet	Requires completion if the patient has suffered an adverse event as defined in the protocol
SAE form eCRF	Requires completion if the patient meets the criteria as defined in the protocol within 24 hours of being made aware of the event. **The adverse events form needs to be completed with the SAE question answered yes**
SAE form (UK; paper)	Requires completion if the patient meets the criteria as defined in the protocol. **Once completed, send to the VITDALIZE UK Trial Office within 24 hours of being made aware of event**
Pregnancy form (UK; paper)	Requires completion if a patient becomes pregnant within the specified time defined in the protocol.

Trial discontinuation

The study discontinuation form will need to be completed for the following reasons:

- Death
- Lost to follow-up
- Withdrawal
- Completion of trial

In addition, the ***paper change of status form*** will require completion if the patient has:

- Died
- Withdrawn

Send a copy to the VITDALIZE UK Trial Office

Patient withdrawal

The patient would like to withdraw from trial treatment, but is willing to be followed up in accordance with the schedule of assessments and via any central UK NHS bodies for long-term outcomes (i.e. the patient has agreed that data can be collected and used in the trial analysis)

The patient would like to withdraw from trial treatment and does not wish to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and via any central UK NHS bodies for long-term outcomes (i.e. the patient has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes)

The patient would like to withdraw from trial treatment and is not willing to be followed up in any way for the purposes of the trial and for no further data to be collected (i.e. only data collected prior to the withdrawal can be used in the trial analysis)

Details of the reason(s) for withdrawal should be documented on the Case Report Forms (CRFs)

Data entry

When completing data entry we recommend that the worksheets are completed to assist with data entry

We also recommend that you use the VITDALIZE UK work instructions to assist with data entry regarding the eCRF

Data queries

VITDALIZE UK uses a Data Clarification Form (DCF) process:

Paper CRF data queries	eCRF data queries
• The VITDALIZE UK Trial Office at BCTU will to generate data queries to sites in batches • DCFs should be completed by members of the site staff who are on the delegation log and have been assigned the roles of CRF completion and correction • Sites will continue to receive reminders about outstanding DCFs approximately every 2 weeks until resolution	• The Sponsor will review data held on the eCRF and produce data queries • Data queries will be sent to the VITDALIZE UK Trial Office every 6 months • The VITDALIZE UK Trial Office will distribute these to sites to action

Quality control

BCTU will perform central data monitoring and will regularly assess data quality and timeliness

The Sponsor may also perform monitoring (ad hoc or triggered) as part of ongoing oversight

Any missing, late or unusual data will be queried by the VITDALIZE UK Data Manager at BCTU

Monitoring and audit

Central in-house Monitoring

Including consent verification, checking balance of allocations and data checks

On-site Monitoring

Including source data verification

Monitoring and audit

Trial Steering Committee

Independent supervision of the trial, including recruitment rates, compliance with trial drug, withdrawal, follow-up etc.

Data Monitoring Committee

Is the trial safe? Has a clear result been reached?

Inspections from MHRA and/or audits from Trust R&D Department

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
- BCTU must also be in receipt of **signed and dated CVs and GCP certificates** for all staff listed on the delegation log

Site file

- BCTU will provide each site with an 'Investigator Site File' containing the essential document set
- Essential documents:
  - Help you understand the project's purpose and methodology and record relevant approvals
  - Provide evidence that trial staff are qualified and authorised to work on the trial
  - Record approvals and substantial amendments
  - Document SAEs
  - Record the trial's findings, dissemination and archiving arrangements

Site approval

- Signed agreement (contract)
  - signed by NCC, PI and local signatory
- SoECAT
- Localised documents
- Signed and dated CVs
- Current GCP certificates
- Honorary contracts (if applicable)
- Signed delegation log

Pharmacovigilance

Definitions

Adverse event

Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product which does not necessarily have a causal relationship with this treatment

Adverse reaction

Any untoward response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

Relatedness must be determined by medically qualified personnel.

Definitions - serious

Any adverse event or adverse reaction that:

- Is life-threatening
- Results in death
- Requires hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect

Definitions - unexpected

An adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product set out in the SmPC or IB for that product.

For the VITDALIZE UK Trial, the SmPC will be provided for vitamin D3 and will be used to assess expectedness.

Reporting

- The reporting period is from randomisation until 15 days after the last IMP administration
- The Investigator will assess the seriousness and causality (relatedness) of all AEs experienced by the patient.
- All AEs should be assessed during follow-up and recorded in the patient's medical notes
  - Data on AEs are collected on the eCRF

Reporting

SAEs that are excluded from reporting

- At whatever time they occur during an individual's participation the following are 'protocol exempt' SAEs:
  - Events related to the patient's pre-existing condition(s)
- All events which meet the definition of 'serious' must be recorded in the patient's medical notes, including causality, throughout the patient's time on the trial.

Reporting

SAEs that do not require expedited (immediate) reporting

Event	CRF
Mortality[1]	Study Discontinuation Form, Change of Status Form and SAE Form[3] (if applicable)
Change in organ dysfunction (number of organ failures)	Visit 1; Visit 2 Form; Adverse Events Form[4]
Hypercalcaemia	Adverse Events Form[4]
New episodes of nephrolithiasis[2]	Adverse Events Form[4]
Falls and fractures	Adverse Events Form[4]
Infections requiring antibiotics treatment	Visit 4 Form

[1] Mortality due to a pre-existing condition requires documenting on the Study Discontinuation Form located on the eCRF and Change of Status Form
[2] Decrease/increase in kidney function, specifically CKD 4 (eGFR <30mL/min/1.73m^2)
[3] SAE form to be completed if there is a causal relationship to intervention and reported in an expiated manner

Reporting

Events that require expedited (immediate) reporting

- The research team will report all other SAEs that are not previously defined in an expedited manner.
- The research team are required to report expedited SAEs using both the:
  - eCRF (minimum dataset)
  - Paper SAE Form
- If mortality is deemed to have a causal relationship with the intervention it should be reported in an expedited manner.

Reporting SAEs

To report SAEs the following is required:

1. Complete the UK SAE paper form and send to the VITDALIZE UK Trial Office
2. Complete the adverse events form on the eCRF
3. Complete the paper SAE form for the eCRF and send to the VITDALIZE UK Trial Office

Report both SAE forms to the VITDALIZE UK Trial Office by:

- Email (vitdalize@trials.bham.ac.uk)
- Fax (0121 415 8871 or 0121 415 9135)
- UoB secure electronic depository (https://beardatashare.bham.ac.uk/login)
- In all cases, please either call the VITDALIZE UK Trial Office (0121 415 8445) or email to inform that a SAE is expected

We recommend that the SAE work instruction is used to assist with the reporting procedure

What needs to be urgently reported?

All SUSARs and SAEs must be reported to BCTU within 24 hours of the site being made aware of the event

Associate PI scheme

- VITDALIZE UK is registered to the NIHR associate PI scheme and is aimed at:
  - Healthcare professional who want to gain knowledge of what it means to deliver an NIHR portfolio trial.
  - Able to commit to six months of working on a study registered on the Scheme at their local site.
  - Do not currently work in research and would like the opportunity to gain experience and mentorship from a local study PI.
- Further details on how to register as an associate PI can be found on the NIHR website:
  - https://www.nihr.ac.uk/health-and-care-professionals/career-development/associate-principal-investigator-scheme.htm

Contact details

- Email: vitdalize@trials.bham.ac.uk
- Tel: +44 (0)121 415 8445
- Fax: +44 (0)121 415 9135
- 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
- Trial website (data entry): https://edc.medunigraz.at/clincase/app
- Randomisation website: https://www.randomizer.at/random/login
- Confirm training: https://redcap.link/VITDALIZETrainingLog

Questions?