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VITDALIZE UK: Effect of high-dose vitamin D3 on 28-day mortality in adult critically ill patients with severe vitamin D deficiency

Submission date	Recruitment status	[X] Prospectively registered
17/09/2020	Recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
24/09/2020	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
18/03/2025	Nutritional, Metabolic, Endocrine	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Vitamin D deficiency (low vitamin D levels) is common in patients who are unwell (around 70%). This has been found to be related to an increased risk of infection and death. There are many reasons why patients are poorly and those who do survive can suffer long-term health problems in the future. It is not known whether being vitamin D deficient is a cause or effect of being unwell, and research into whether vitamin D is useful is not clear. There are no guidelines to measure and treat patients admitted to intensive care who are critically ill and are vitamin D deficient. Vitamin D is cheap and easily available, and if using vitamin D is found to help, can be quickly put into standard practice in hospitals. VITDALIZE is an international trial that aims to recruit 2400 patients from across Europe. Countries that are participating include the UK, Austria, Germany and Belgium. The UK part of VITDALIZE aims to recruit 600 patients into the trial. The aim of this trial is to see if giving a high dose of vitamin D in critically ill patients can improve survival, length of hospital stay, and quality of life.

Who can participate?
Males and females aged 18 years and above admitted to ICU who are severely vitamin D deficient

What does the study involve?
Participants will be visited or contacted up to six times (days 0, 5, 12, 28, 90 and 1 year). At the beginning of the trial, participants will be given either a high dose of vitamin D or placebo (dummy supplement) on day 0 and a daily dose of either vitamin D or placebo from day 1 to day 90. On day 5 (if still in the hospital), the research team will take some more blood to see how participants are responding to treatment. On days 0, 28, 90 and after 1 year the research team will contact the participant (either in person if still in hospital or by telephone) to ask a few questions about their health. Participants will be asked to consent to provide some optional blood samples at up to three additional timepoints for future approved research. This would mean providing blood samples (25-30 ml; equivalent to 2 tablespoons) on days 0, 5 and 12.

What are the possible benefits and risks of participating?
There may be no direct benefits of taking part, but the results will lead to the best treatment being offered to patients who are unwell and vitamin D deficient.

Where is the study run from?
Birmingham Clinical Trials Unit at the University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
October 2019 to January 2026

Who is funding the study?
National Institute for Health Research Health Technology Assessment Programme (NIHR HTA) (UK)

Who is the main contact?
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Study website
https://www.birmingham.ac.uk/vitdalize

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2016-002460-13

IRAS number
274476

ClinicalTrials.gov number
NCT03188796

Secondary identifying numbers
IRAS 274476, CPMS 46276, DRKS00016940, HTA 17/147/33

Study information

Scientific Title
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

Acronym
VITDALIZE UK

Study objectives
1. The primary hypothesis is that in critically ill patients with severe vitamin D deficiency as defined by 25(OH)D concentration ≤ 12ng/ml (30nmol/L), a high-dose vitamin D replacement strategy, compared to placebo, leads to 28-day survival.
2. Further hypotheses are that high-dose vitamin D supplementation reduces hospital and ICU mortality, 90-day and 1-year mortality, reduces the length of stay in ICU and hospital, and improves health-related quality of life of patients and is cost-effective.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 03/11/2020, South Central – Oxford C Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8041; oxfordc.rec@hra.nhs.uk), REC ref: 20/SC/0300

Study design
Randomized; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
The participant information sheets will be available on the VITDALIZE UK website once approved by ethics and MHRA: https://www.birmingham.ac.uk/research/bctu/trials/portfolio-v/VITDALIZE/index.aspx

Health condition(s) or problem(s) studied
Vitamin D deficiency

Interventions
Once randomised into the trial, the patient will receive either:
1. Intervention: A single loading high-dose oral/enteral vitamin D3 (540,000IU cholecalciferol, Oleovit™, Fresenius Kabi, Austria, dissolved in 37.5 ml of medium-chain triglycerides – MCT) followed by 4000 IU daily (10 drops) for 90 days.
2. Control: Placebo, identical regime of loading dose of 37.5 ml MCT (Fresenius Kabi, Austria) followed by MCT (10 drops) daily for 90 days.

Intervention Type
Supplement

Primary outcome measure
All-cause mortality, measured face-to-face (if an inpatient), by telephone, medical records, NHS digital/ONS data, at 28 days after randomisation

Secondary outcome measures
1. Mortality measured using telephone call, medical records, NHS digital/ONS data at 90 days and 1 year
2. ICU and hospital mortality measured face-to-face (if an inpatient), by telephone, medical records, NHS digital/ONS data at day 5, 28, 90 and 1 year
3. Hospital and ICU length of stay measured face-to-face (if an inpatient), by telephone, medical records, NHS digital/ONS data, starting at day 0, ending at discharge from the trial site or day 90 or mortality, whichever occurs first
4. Organ dysfunction measured by Sequential Organ Function Assessment score (SOFA), number of organ failures (0-6; defined as > 2 SOFA points in each of the 6 categories) on day 5
5. Hospital and ICU readmission measured using telephone call, medical records, NHS digital/ONS data until day 90
6. Discharge destination (home, rehabilitation, other hospital) measured using telephone,

medical records, NHS digital/ONS data at discharge
7. Assessment of psychosocial functions measured using Katz Activities of Daily Life at day 90
8. Self-reported infections requiring antibiotics measured face-to-face (if an inpatient), by telephone, medical records, NHS digital/ONS data until day 90
9. Health-related quality of life measured using EQ-5D-5L at 90 days and 1 year
10. Disability assessment measured using WHODAS 2.0 at 90 days and 1 year
11. Secondary healthcare utilisation (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 in the first year after randomisation
12. Health economics analysis measured face-to-face (if an inpatient), by telephone, medical records, NHS digital/ONS data at day 28, 90 and 1 year
13. Cost-effectiveness of screening for and treating VDD in critical illness measured using telephone call, medical records, NHS digital/ONS data at day 28, 90 and 1 year
14. Cost per quality-adjusted life-year gained measured using telephone call, medical records, NHS digital/ONS data at 1 year after randomisation and at end of life

Exploratory outcome:
Health-related quality of life measured using proxy EQ-5D-5L and proxy WHODAS 2.0 at randomisation (day 0)

Safety outcomes:
1. Hypercalcaemia measured using medical records on day 5
2. Self-reported falls, fractures measured face-to-face (if an inpatient), by telephone, medical records, NHS digital/ONS data until day 90
3. New episodes of kidney stones measured using medical records until day 90

Overall study start date
01/10/2019

Completion date
31/01/2026

Eligibility

Key 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 ≤12 ng/ml [30 nmol/l]) using either the hospital's clinical laboratory or rapid bedside testing after ICU admission

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 2400; UK Sample Size: 600

Key exclusion criteria
1. Severe gastrointestinal dysfunction (>400 ml 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 (Do Not Attempt Resuscitation) 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. Women of childbearing age who have tested positive for pregnancy or who are lactating
9. Known hypersensitivity to the trial drug or excipient
10. Medical team deem it not suitable to include patient
11. Known prisoners in the custody of HM Prison and Probation services

Date of first enrolment
12/04/2021

Date of final enrolment
31/01/2026

Locations

Countries of recruitment
England

Northern Ireland

United Kingdom

Wales

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Trust HQ, PO Box 9551
Queen Elizabeth Medical Centre
Edgbaston
Birmingham
United Kingdom
B15 2TH

Study participating centre
South Tees Hospitals NHS Foundation Trust
James Cook University Hospital
Marton Road
Middlesbrough
Cleveland
United Kingdom
TS4 3BW

Study participating centre
Bolton NHS Foundation Trust
The Royal Bolton Hospital
Minerva Road
Farnworth
Bolton
United Kingdom
BL4 0JR

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
St Thomas' Hospital
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
Belfast Health & Social Care Trust
Knockbracken Healthcare Park
Saintfield Road
Belfast
United Kingdom
BT8 8BH

Study participating centre
Mid Yorkshire Hospitals NHS Trust
Pinderfields Hospital
Aberford Road
Wakefield
United Kingdom
WF1 4DG

Study participating centre
East Lancashire Hospitals NHS Trust
Royal Blackburn Hospital
Haslingden Road
Blackburn
United Kingdom
BB2 3HH

Study participating centre
Great Western Hospitals NHS Foundation Trust
Great Western Hospital
Marlborough Road
Swindon
United Kingdom
SN3 6BB

Study participating centre
Diana, Princess of Wales Hospital
Scartho Road
Grimsby
United Kingdom
DN33 2BA

Study participating centre
Derriford Hospital
Derriford Road
Derriford
Plymouth
United Kingdom
PL6 8DH

Study participating centre
Royal Bournemouth Hospital Bcsc
Royal Bournemouth Hospital
Castle Lane East
Bournemouth
United Kingdom
BH7 7DW

Study participating centre

Sandwell and West Birmingham Hospitals NHS Trust
City Hospital
Dudley Road
Birmingham
United Kingdom
B18 7QH

Study participating centre
Musgrove Park Hospital
Musgrove Park
Taunton
United Kingdom
TA1 5DA

Study participating centre
Scunthorpe General Hospital
Cliff Gardens
Scunthorpe
United Kingdom
DN15 7BH

Study participating centre
The Royal Oldham Hospital
Rochdale Road
Oldham
United Kingdom
OL1 2JH

Study participating centre
Nottingham University Hospitals NHS Trust - Queen's Medical Centre Campus
Nottingham University Hospital
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Royal Liverpool University Hospital NHS Trust
Royal Liverpool University Hospital
Prescot Street
Liverpool

United Kingdom
L7 8XP

Study participating centre
Barnsley Hospital NHS Foundation Trust
Gawber Road
Barnsley
United Kingdom
S75 2EP

Study participating centre
Hampshire Hospitals NHS Foundation Trust
Basingstoke and North Hampshire Hos
Aldermaston Road
Basingstoke
United Kingdom
RG24 9NA

Study participating centre
Kings College Hospital
Denmark Hill
London
United Kingdom
SE5 8AB

Study participating centre
Kingston Hospital
Galsworthy Road
Kingston upon Thames
United Kingdom
KT2 7QB

Study participating centre
Leeds Teaching Hospitals NHS Trust
St. James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
Northampton General Hospital NHS Trust
Cliftonville
Northampton
United Kingdom
NN1 5BD

Study participating centre
The Dudley Group NHS Foundation Trust
Russells Hall Hospital
Pensnett Road
Dudley
United Kingdom
DY1 2HQ

Study participating centre
Mersey and West Lancashire Teaching Hospitals NHS Trust
Whiston Hospital
Warrington Road
Prescot
United Kingdom
L35 5DR

Study participating centre
East Suffolk and North Essex NHS Foundation Trust
Colchester Dist General Hospital
Turner Road
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CO4 5JL

Sponsor information

Organisation
Medical University of Graz

Sponsor details
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+43 (0)31638582383
karin.amrein@medunigraz.at

Sponsor type
University/education

Website
http://www.medunigraz.at/en/

ROR
https://ror.org/02n0bts35

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme; Grant Codes: 17/147/33

Alternative Name(s)
NIHR Health Technology Assessment Programme, HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. The international protocol has been published: https://pubmed.ncbi.nlm.nih.gov/31722941/
2. The UK protocol has some minor changes, this will be made available on the VITDALIZE UK website once approved by ethics and MHRA: https://www.birmingham.ac.uk/research/bctu/trials/portfolio-v/VITDALIZE/index.aspx
3. Planned publication will be in a high-impact peer-reviewed journal approximately 1 year after the overall trial end date

Intention to publish date
01/10/2026

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

(Updated 20/11/2020, previously: The datasets generated and/or analysed during the current study will be included in the subsequent results publication)

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol article		12/11/2019	15/01/2025	Yes	No