TRIAL PROTOCOL

The VITDALIZE UK Trial

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

This protocol has regard for the HRA guidance

Version Number: 7.0

Version Date: 29-May-2025

Protocol Amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version number	Summary of amendment
NSA 1	**27/01/2021**	**4.0**	Minor administrative updates to the patient and legal representative information sheets (version 4.0, 13th January 2021)
SA 1	**18/01/2021**	**4.0**	Addition of sites to the VITDALIZE UK Trial
NSA 2	**19/05/2021**	**4.0**	Addition of sites to the VITDALIZE UK Trial Change of Principal Investigator at a VITDALIZE UK sites Change of name for site due to a merge between NHS sites
NSA 3	**12/08/2021**	**4.0**	Change of Principal Investigator at a VITDALIZE UK sites Removal of site from the VITDALIZE UK Trial
SA 2	**13/08/2021**	**5.0**	Grammatical updates throughout Update to the protocol amendments table (page 2) Update to TSC member (page 7) Addition of remote written consent (page 32) Addition of capturing data from non-VITDALIZE UK sites (page 34) Update to informing the GP (page 37) Addition of +4 day time window for 28-day follow-up (page 46) Update to archiving arrangements for BCTU (Page 59) Update to the data sharing agreement (page 74)
SA 3	**04/11/2021**	**5.0**	Update to the address of the company who certify the finished IMP and placebo for the trial, Section D9-2 of CTA.
NSA 4	**24/02/2022**	**5.0**	Addition of sites to the VITDALIZE UK Trial Change of Principal Investigator at a VITDALIZE UK sites Change of name for site due to a merge between NHS sites
NSA 5	**10/05/2022**	**5.0**	Change of Principal Investigator at a VITDALIZE UK sites
SA 4	**22/06/2022**	**6.0**	Update to the amendments table (page 2) Update to trial management group (TMG) (page 9) Update to co-enrolment section (page 32) Update to Cessation of Treatment/Continuation after the Trial section (page 42) Update to the Outcome Measures and Trial Procedures section (pages 48) Update to Schedule of Assessments table (Page 47) Update to Events that do not require expedited (immediate) reporting table footnotes for hypercalcemia (page 50)
NSA6	**08/12/2022**	**6.0**	Change of Principal Investigator at a VITDALIZE UK sites
NSA7	**01/12/2023**	**6.0**	Addition of sites to the VITDALIZE UK Trial
NSA8	**01/05/2024**	**6.0**	Addition of site to the VITDALIZE UK Trial Change of Principal Investigator at a VITDALIZE UK site

NSA9	**08/08/2024**	**6.0**	Minor updates to the consent forms Confirmation that the trial end date has been extended Correction of a VITDALIZE UK site name
NSA10	**10/02/2025**	**6.0**	Minor change to sample size Addition of site to the VITDALIZE UK Trial Change of Principal Investigator at a VITDALIZE UK site
SA5	**29/05/2025**	**7.0**	Correction of minor typographical errors and administrative updates (throughout) Update to UK sample size (page 16) UK-specific outcomes no longer collected and optional additional sample collection for future research no longer conducted for patients recruited post-SA5 implementation (throughout, including: • Update to trial schema (page 19) • Updates to schedule of assessment (page 48)) Removal of rapid vitamin D analyser requirement from trial setting section (page 29) Updates to consent section (page 33) Updates to enrolment and screening section (page 36) Updates to randomisation section (page 37) Correction to concomitant vitamin D supplementation section (page 41) Update to outcome measures and trial procedures section (page 44) Update to participant withdrawal section (page 49) Update to SAE administrative details (pages 52, 54) Updates to the information sheets and consent forms

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CI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

This protocol has been approved by:

Trial Name:	
Protocol Version Number:	Version: __ __
Protocol Version Date:	__ __ / __ __ / __ __ __ __
CI Name:	
Trial Role:	Chief Investigator
Signature and date:	_____ __ __ / __ __ / __ __ __ __

Sponsor statement:

By signing the IRAS form for this trial the University of Birmingham, acting as the National Co-ordinating Centre for this trial, confirm the approval and implementation of this protocol as delegated by the Sponsor.

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PI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

This protocol has been approved by:

Trial Name: Protocol Version Number:	**VITDALIZE UK** Version: __ __
Protocol Version Date:	__ __ / __ __ / __ __ __ __
PI Name: Name of Site:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

Sponsor	
Medical University of Graz	Karin Amrein
Contact Details:	Medical University of Graz, Auenbruggerplatz 2, 8036 Graz, Austria E: kk@medunigraz.at E: karin.amrein@medunigraz.at

National Co-ordinating Centre	
University of Birmingham	Birgit Whitman
Contact Details:	Head of Research Governance and Integrity, University of Birmingham Aston Webb Building Birmingham B15 2TT E: researchgovernance@contacts.bham.ac.uk

Administrative Information

Chief Investigator	
Dhruv Parekh	Associate Professor in Critical Care and Respiratory Medicine
Contact Details:	Birmingham Acute Care Research Institute of Inflammation and Ageing Queen Elizabeth Hospital Edgbaston B15 2WB T: 0121 371 7887 E: d.parekh@bham.ac.uk

Trial Steering Committee - TSC	
Chair:	
Professor Paul Dark	**Professor of Critical Care Medicine, The University of Manchester**
Independent Members:	
Professor Alistair Nicholl	**Professor of Critical Care Medicine, University College Dublin**
Dr Cassandra Brooke	**Principal Biostatistician, University of Leicester**
Dr Adam Wagner	**Associate Professor Health Economics, University of East Anglia**
Mrs Sue Boex	**PPI Representative**
Chief Investigator:	
Dhruv Parekh	See Trial Management Group for contact details

Data Monitoring and Ethics Committee - DMC	
Chair:	
Professor Peter Suter	**Professor of Anaesthesiology and Critical Care, University of Geneva**
Independent Member:	
Professor Akos Heinemann	**Professor of Pharmacology, Medical University of Graz**
Trial Statistician:	
Professor Martin Posch	**Professor of Statistics, Medical University of Vienna**

Trial Management Group - TMG	
Dhruv Parekh	**Associate Professor in Critical Care and Respiratory Medicine, University of Birmingham**
David Thickett	**Professor of Respiratory Medicine, University of Birmingham**
Karin Amrein	**Associate Professor of Endocrinology and Intensive Care Medicine, Medical University of Graz**
Daniel McAuley	**Professor of Intensive Care Medicine, Queen's University Belfast**
Gavin Perkins	**Professor of Intensive Care Medicine and Director of Warwick Clinical Trials Unit, Warwick University**
Marlies Ostermann	**Consultant in Critical Care and Nephrology, Guys and St Thomas NHS Foundation Trust**
Matthew Soden	**Deputy Trials Management Team Leader, Birmingham Clinical Trials Unit, University of Birmingham**
Trial Manager - Serena Dhir	**Trial Manager, Birmingham Clinical Trials Unit, University of Birmingham**
Samir Mehta	**Senior Medical Statistician, Birmingham Clinical Trials Unit, University of Birmingham**
Louise Jackson	**Lecturer in Health Economics, University of Birmingham**
Teresa Melody	**Critical Care Research Manager and Lead for the Clinical Research Ambassador Group, University Hospitals Birmingham NHS Foundation Trust**
Anne Devrell	**PPI Representative**
Marion Thompson	**PPI Representative**

Trial Office Contact Details	
Birmingham Clinical Trials Unit (BCTU) Institute of Applied Health Research College of Medical and Dental Sciences Public Health Building University of Birmingham Edgbaston Birmingham B15 2TT	VITDALIZE@trials.bham.ac.uk
Randomisation website/ telephone number	https://www.randomizer.at/random/login
Trial website	www.birmingham.ac.uk/VITDALIZE
Trial social media	www.twitter.com/vitdalize

ABBREVIATIONS

Abbreviation	Term
AE	Adverse Events
A&E	Accident and Emergency
ARDS	Acute Respiratory Distress Syndrome
APR	Annual Progress Report
BCTU	Birmingham Clinical Trials Unit
CACE	Complier Average Causal Effect
CEACs	Cost-effectiveness Acceptability Curves
CI	Chief Investigator
CFR	Code of Federal Regulations
CRF	Paper Case Report Forms used to capture UK-specific outcome measures
CTA	Clinical Trial Authorisation
DCF	Data Clarification Form
DMP	Data Management Plan
DMC	Data Monitoring and Ethics Committee
DNAR	Do Not Attempt Resuscitation
DoB	Date of Birth
DSA	Data Sharing Agreement
eCRF	Electronic Case Report Form (Clincase) used to capture outcome measures for the international trial
EQ-5D-5L	EuroQol Group 5 Dimensional- 5 Level Questionnaire
ESICM	The European Society of Intensive Care Medicine
EU	European Union
FDA	Food and Drug Administration
FOAMed	Free Open Access Medical Education
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
GP	General Practitioner
HES	Hospital Episode Statistics
HTA	Health Technologies Assessment

ICF	Informed Consent Form
ICS	Intensive Care Society
ICU	Intensive Care Unit
ICUsteps	Intensive Care Unit Support Teams for Ex-Patients
IMP	Investigational Medicinal Product
IOM	Institute of Medicine
ISF	Investigator Site File
ITT	Intention to Treat
LPS	Lipopolysaccharide
LV	Left Ventricular
MCT	Medium Chain Triglycerides
MHRA	Medicines and Healthcare products Regulatory Agency
NCC	National Co-ordinating Centre
NIHR	National Institute for Health Research
NHS	National Health Service
ONS	Office for National Statistics
PatRel	Critical Care Patients and Relatives Committee
PI	Principal Investigator
PIS	Participant Information Sheet
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
QoL	Quality of Life
QUALYs	Quality Adjusted Life Years
RAAS	Renin-Angiotensin-Aldosterone-System
R&D	Research and Development
RDA	Recommended Daily Allowance
REC	Research Ethics Committee
ROS	Reactive Oxygen Species
RSI	Reference Safety Information
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SOFA	Sequential Organ Function Assessment score

SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TLS	Transport Layer Security
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
UoB	University of Birmingham
UVB	Ultraviolet B-rays
VDD	Vitamin D Deficiency
VDR	Vitamin D Receptor

DEFINITIONS

Term	Abbreviation	Description
Policies	POL	Policies are developed to describe the approach of the University of Birmingham (UoB) on areas that are heavily regulated. Policies may also be developed when there is ambiguity in how regulatory requirements should be implemented in the QMS or when procedures to be captured in the QMS address areas controversial within the UoB at the time of implementation. Policies explain why the UoB has its procedures, especially when they seem to deviate from the regulatory requirements. Policies should be read in conjunction with the relevant SOP. Policies that are not part of a Quality Manual are coded up as 'POL'.
Quality Control Documents	QCD	Quality Control Documents can be instructions, forms, templates or checklists. They are developed to share best practices, promote standardisation to guarantee quality standards are maintained and reduce resources otherwise needed to develop similar documents. Unless indicated otherwise in the relevant SOP, QCDs are not mandatory and are designed to be an optional aid to UoB staff.
Quality Management System	QMS	A Quality Management System (QMS) is a system that includes procedures and policies to describe how certain tasks should be performed and that encapsulate any standards and/or regulatory requirements that may apply to those tasks. By adhering to the Quality Management System, the user and the UoB will be assured that applicable regulations are adhered to.
Standard Operating Procedures	SOP	Standard Operating Procedures are detailed written instructions to achieve uniformity in the performance of a specific function. They define tasks, allocate responsibilities, detail processes, indicate documents and templates to be used and cross-reference to other work instructions and guidance or policy documents. They are standards to which the UoB may be audited or inspected.
Adverse Event	AE	Any untoward medical occurrence in a participant or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction	AR	All untoward and unintended responses to an IMP related to any dose administered.
Serious Adverse Event	SAE	Any untoward medical occurrence or effect at any dose that: 1. Results in death

		2. Is life-threatening (life threatening in the definition of a SAE 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 that might have caused death if it were more severe) 3. Requires hospitalisation or prolongation of existing hospitalisation 4. Results in persistent or significant disability or incapacity 5. Is a congenital anomaly/birth defect 6. Or is otherwise considered medically significant by the Investigator (medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above, should be considered serious)
Serious Adverse Reaction	SAR	An Adverse Reaction which also meets the definition of a Serious Adverse Event.
Unexpected Adverse Reaction	UAR	An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction	SUSAR	A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.
Source data		All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial
Birmingham Clinical Trials Unit	BCTU	Providing trial management for the UK arm of the VITDALIZE trial.

TRIAL SUMMARY

Title: The VITDALIZE UK Trial: 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

Overall aim

The overall aim for the UK arm of VITDALIZE is to conduct a large international randomised controlled trial to determine if treatment with a high dose of vitamin D improves patient outcomes and is cost-effective, in comparison to placebo in severely vitamin D deficient (VDD) critically ill patients admitted to an intensive care unit (ICU).

Objectives

Primary objective

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

Secondary objectives

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

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

In the UK arm 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 objectives

- To assess the feasibility of patient quality of life and disability at day 0 using the proxy EQ-5D-5L and proxy WHODAS 2.0 questionnaires

Trial Design

This is the UK arm of a large international randomised double-blind placebo-controlled trial. Patients will be randomised to the intervention or control arm in a 1:1 ratio stratified by centre and sex via a web-based central randomisation system managed by the Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz.

Participant Population and Sample Size

The target population is adult critically ill patients (≥18 years) admitted to ICU with severe VDD (25(OH)D ≤12ng/ml (30nmol/L)). Total sample size of international trial n=2,400 of whom approximately 800 will be recruited in the UK.

Eligibility Criteria

Inclusion Criteria

To be eligible to participate in the VITDALIZE UK Trial, patients must meet all the following 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

Exclusion Criteria

If any of the following apply, the patient is not eligible to be randomised into the VITDALIZE UK Trial:

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 (Do Not Attempt Resuscitation) orders in place
4. Hypercalcemia (>2.65mmol/l corrected calcium and/or >1.35mmol/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 child bearing age who have tested positive for pregnancy or who are lactating[1]
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

Interventions

The intervention consists of a single loading high-dose oral/enteral vitamin D3 (540,000IU cholecalciferol, Oleovit™, Fresenius Kabi, Austria, dissolved in 37.5ml of medium chain triglycerides – MCT) followed by 4000IU daily (10 drops) for 90 days.

Control group treatment: Placebo, identical regime of loading dose of 37.5mls MCT (Fresenius Kabi, Austria) followed by 10 drops of MCT daily for 90 days.

[1] Pregnancy test taken as part of standard of care

Outcome Measures

Primary outcome:

- All-cause mortality at 28 days after randomisation

Secondary outcomes:

- 90 day and 1-year mortality
- ICU and hospital mortality
- Hospital and ICU length of stay (starting at day 0 (day of randomisation), ending at discharge from the trial site or day 90 or mortality, whichever occurs first)
- Change in organ dysfunction on day 5 as 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)
- Hospital and ICU readmission until day 90
- Discharge destination (home, rehabilitation, other hospital)
- Katz Activities of Daily Life at day 90
- Self-reported infections requiring antibiotics until day 90
- Health-related quality of life (EQ-5D-5L) at 90 days and 1 year[1]
- Disability assessment (WHODAS 2.0) at 90 days and 1 year[1]
- 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[1]
- Health economics analysis[1]
    - 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

Exploratory outcome:

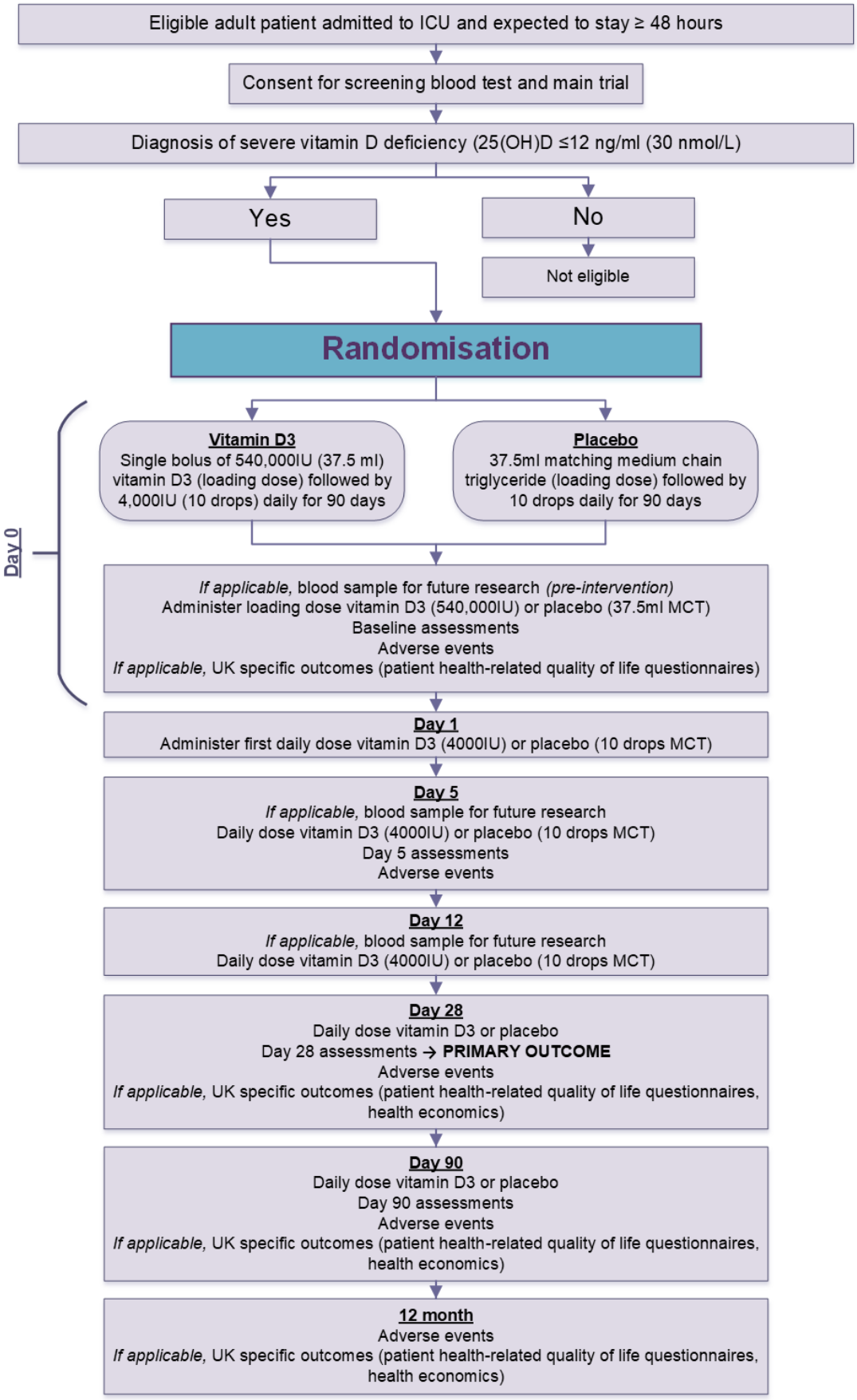
- Health related quality of life (proxy EQ-5D-5L and proxy WHODAS 2.0) at randomisation (day 0)[1]

Safety outcomes

- Hypercalcaemia 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

[1] UK-specific outcome no longer collected for patients recruited post-SA5 implementation

Trial Schema



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1. BACKGROUND AND RATIONALE

1.1. Background

In the UK, 160,000 critically ill patients are admitted annually to ICU. Mortality rates in hospital are about 20% and survivors of critical illness have increased mortality, morbidity (physical, cognitive and psychological), and social care needs in the 5 years following discharge (1, 2). Treating critically ill patients represents a substantial burden on individuals, caregivers, and society. The effect of critical illness is particularly severe in older ICU survivors who suffer a prolonged and persistent decline in both cognitive and physical function (3). With the UK population ageing, critical illness will become increasingly costly for patients, the NHS and the wider social care system in the next 10 years. Therefore, additional novel therapeutic improvements are urgently needed.

VDD is common in patients in ICU (4-6) with prevalence between 40-70% (7-10). In burn patients, the prevalence appears to be even higher (11, 12). The similarity in prevalence in diverse geographical areas with variable ultraviolet B-rays (UVB) exposure suggests that the influence of individual chronic and/or acute disease on VDD is largely independent of sun exposure (13). We and others have shown that VDD is associated with poor outcomes in critical illness (14-16). VDD has been associated with acute respiratory failure, duration of mechanical ventilation (15, 17), sepsis and nosocomial infection (18, 19), acute kidney injury (20) and increased mortality (8, 21-23) and 3 different meta-analyses confirm that patients with low vitamin D status have a longer ICU stay and increased morbidity and mortality (24-26).

Many patients enter the ICU in a deficient state due to pre-existing malnutrition and disease. However, vitamin D metabolism is dysregulated in some critically ill patients with vitamin D levels rapidly falling after ICU admission (5, 6). Recently, substantial metabolomic differences in pathways related to glutathione metabolism and glutamate metabolism were found in an observational trial in VDD compared to non-deficient ICU patients (separated by a cut-off of 15 ng/ml) (27). Hepatic, parathyroid and renal dysfunction additionally increase the risk for developing VDD. Rapid falls in circulating 25(OH)D concentrations may also be due to decreased synthesis of vitamin D binding protein due to hepatic dysfunction, interstitial extravasation caused by increased vascular permeability, renal wasting of vitamin D, decreased renal conversion to active 1,25(OH)D3 and increased tissue conversion of 25(OH)D3 to 1,25(OH)D3 (6, 28-30). Moreover, therapeutic interventions like fluid resuscitation, dialysis, surgery, extracorporeal membrane oxygenation, cardiopulmonary bypass and plasma exchange may significantly reduce vitamin D levels. There is also evidence that critically ill patients with very low 25(OH)D concentrations have blunted

responses to vitamin D replacement possibly due to conversion into alternate metabolites and epiforms (31).

1.2. **Trial Rationale**

The biological effects of vitamin D were originally focussed on the hormone's role in bone metabolism and homeostasis. In the last decade, vitamin D has been implicated in the function of a wide range of tissues including the innate and adaptive immune system (32, 33). The specific nuclear vitamin D receptor (VDR) is widely expressed in many cell types and organs relevant to critical illness (34) and is known to regulate hundreds of genes (34, 35). Therefore, vitamin D has the ability to act synergistically on the immune response to acute systemic inflammation and infection (16, 36), lung epithelial function (15), muscle function and metabolism (37) and cardiac function (38).

Sepsis and respiratory failure are 2 of the common causes for ICU admission and nosocomial infections frequently complicate and prolong ICU stay. We have previously demonstrated causation of VDD as a driver of sepsis and acute respiratory distress syndrome (ARDS). In a murine model of abdominal sepsis VDD led to increased bacterial load in the blood and peritoneum, reduced macrophage clearance of bacteria, reduced antimicrobial peptide release and increased permeability of the peritoneal and alveolar capillary (16). Experimental studies also suggest a protective effect of vitamin D in the lung. In a murine model of intra-tracheal lipopolysaccharide (LPS) challenge, dietary induced VDD resulted in exaggerated alveolar inflammation, epithelial damage and hypoxia, which were abrogated by vitamin D3 treatment (15). High dose vitamin D3 pre-treatment also protects the lung barrier in-vivo with lower changes in pulmonary vascular permeability index post oesophagectomy but this effect is more pronounced dependant on severity of VDD (39).

Cardiac impairment or suppression of function and arrhythmias are common in critical illness due to stress, surgery, infection, and inflammation. A recent trial has reported significant improvement in cardiac function (left ventricular (LV) ejection fraction and a reversal of LV modelling) after 4,000IU vitamin D3 daily supplementation for a year in patients with chronic heart failure. Although this did not result in improvement in 6-minute walk distance the trial recruited patients with less severe VDD (<20ng/ml) and demonstrates potential mechanistic rationale relevant to critical illness (40). Vitamin D may also play a role in atrial fibrillation prevention by negatively regulating the renin-angiotensin-aldosterone-system (RAAS), mediating calcium homeostasis, binding to VDR on cardiac myocytes and furthermore by having antioxidant properties that may reduce levels of reactive oxygen species (ROS) in the atria, which contribute to inflammation and proarrhythmic substrate formation (41).

Bone health has been recognized as important for ICU survivors and the limited available data suggest impaired bone health and high fracture risk (42-45). In addition to underlying disease, critical illness per se is detrimental to musculoskeletal health in various ways: immobilization, inflammation, multiple endocrine alterations, hypercatabolism including muscle wasting, malnutrition and some drugs all have the potential to disturb the delicate balance between bone formation and resorption (46, 47). Some molecular mechanism studies suggest that vitamin D impacts muscle cell differentiation, intracellular calcium handling, and genomic activity. Some animal models have confirmed that VDD and congenital aberrations in the vitamin D endocrine system may result in muscle weakness (37, 48, 49). Current treatment of VDD aims to reach levels considered necessary for optimal bone health in other populations (above 20ng/ml) (50, 51) but the optimal target in critical illness remains unclear.

Therefore vitamin D, rather than just a food supplement, is in reality a precursor to a potent steroid hormone that regulates multiple genes involved in a wide range of cellular pathways in organs that are highly relevant to the effects of critical illness upon patients and the biological rationale and mechanism of action to account for potential efficacy compelling.

The VITdAL-ICU (n=475) trial, the only phase III trial of high dose vitamin D3 supplementation (540,000IU followed by monthly 90,000IU for 5 months) in critical illness, did not find a difference in the primary endpoint of length of hospital stay between placebo and high-dose vitamin D3 treated patients. However, there was a non-significant, absolute risk reduction in all-cause hospital mortality. The difference was large (17.5%) and significant in the predefined subgroup of patients with severe VDD (25(OH)D ≤12ng/mL) at baseline (n=200, 28.6 vs 46.1%, p=0.01, 95% CI 0.56 (0.35-0.90), corresponding to a number needed to treat of 6 (52). As this was a secondary endpoint in the predefined subgroup with severe VDD, we regard this finding as hypothesis generating leading to this current trial application.

A recent review of vitamin D supplementation in the critically ill including 6 clinical trials from 2011 to 2016 showed no benefit of vitamin D supplementation (53). A further meta-analysis on hospital mortality in critically ill patients showed a significant association of VDD and increased hospital mortality (OR 1.76; P <0.001) (26). However, these have been criticized as most studies included only a small number of patients or were performed as single centre trials. Vitamin D was given in a single dose or over a period of a few days. None of these trials included critically ill patients with severe VDD, the only subgroup in which the VITdAL-ICU trial identified an effect of vitamin D supplementation.

7 trials are currently registered on clinicaltrials.gov examining vitamin D supplementation in the critically ill, including the VITDALIZE trial. 1 is a phase 2 trial in children (NCT02452762).

3 trials involve small numbers of selected sub-groups of critical ill patients (e.g. post liver transplantation, post-oesophagectomy). A single centre trial (n=430) is examining the effect of a single high dose (400,000IU) of vitamin D3 in critically ill patients with severe VDD (25(OH)D≤12ng/mL) with a primary outcome of hospital mortality (NCT02868827). Finally, the VIOLET trial is assessing a single 540,000IU dose in patients with pre-defined risk factors for developing ARDS with VDD of less than 20ng/mL outside of the ICU (NCT03096314). Other important differences to VITDALIZE are the lack of on-going daily replacement and inclusion of less deficient patients (<20ng/ml).

The mechanistic basis of the detrimental effects of VDD in critical illness are compelling and there are numerous observational studies which show an association between VDD and poor outcomes in sepsis, acute kidney injury and acute respiratory failure in critical illness. However to date there are a very limited number of interventional trials of vitamin D replacement in ICU. Many of these trials are small in-patient numbers, single centre, use varying dosing regimens or routes and do not specifically address the question of efficacy in a severely VDD group. Our data and the hypothesis generating sub-group analysis of the VITdAL-ICU pilot trial suggests that the treatment may only be beneficial if severe deficiency is present.

Vitamin D testing is available in all NHS hospitals, and supplementation is inexpensive. Despite the above evidence, testing for and treating VDD is currently not routinely recommended by UK national or international guidelines and is not routinely performed in patients admitted to ICU. This trial is timely: recently there has been a heightened awareness of VDD in critical illness, and increasingly some ICU physicians are testing for vitamin D levels and treating with supplementation. Currently, however, there is insufficient evidence of its effectiveness. Furthermore, there is no evidence to guide treatment thresholds or dosing strategies in critical care. At the UK Critical Care Research Forum (clinicians, researchers, allied health care professionals) in June 2018, this proposal was presented and it was unanimously felt that this was an important research question that needs answering to guide clinical management of VDD on the ICU. Importantly, if it shows no benefit, the trial will provide evidence to stop the widespread adoption of testing for VDD in this setting.

1.2.1. Justification for patient population

Data from the VITdAL-ICU pilot trial suggests that the treatment may only be beneficial if severe VDD is present. Although VDD is common in all acute admissions the prevalence of severe deficiency is higher in critically ill patients admitted to intensive care. This is also the same participant population that was recruited in the hypothesis generating VITdaL-ICU trial.

Only adults will be recruited as the dosing and effects in a paediatric population is not clear and are currently being investigated by collaborators in a paediatric trial (Clinical trials.gov, NCT03742505).

1.2.2. Choice of intervention

Currently it is not standard practice to test for VDD and correct it in the critically ill population. In the general population, it is recommended that all healthy children and adults meet a daily minimum of vitamin D - the Institute of Medicine (IOM) recommends 400 to 800IU of vitamin D3 (51). The Endocrine Society recommends 1500 to 2000IU for adult patients “at risk” for VDD (50). In critical illness however, no standard of care has been established. Typical enteral and/or parenteral nutrition formulas supply approximately 400IU per day. In healthy individuals, such doses can improve VDD, but this requires months of treatment.

In critical illness, there is evidence of rapid falls in circulating vitamin D concentrations potentially due to disrupted metabolism, fluid resuscitation, surgery, and loss of the carrier protein due to hepatic dysfunction (6, 52, 54). There is also evidence that critically ill patients with very low vitamin D concentrations have blunted responses to vitamin D3 replacement. Therefore, a bolus dose is an attractive option to rapidly improve circulating concentrations. The VITdAL-ICU trial provided an enteral 540,000 IU loading dose of vitamin D3 to critically ill adults. This dose increased 25(OH)D from 13 to 35 ng/ml until day 3 and was well tolerated (52). The daily follow-up dose of 4000 IU in our trial corresponds to the upper limit recommendation by the IOM (51).

The route chosen is per-oral because currently no high-dose mono-preparation of vitamin D3 is available. Although recently an interventional trial has tested high-dose intramuscular vitamin D3 (56), intramuscular injections may not be feasible in many ICU patients (risk of bleeding and infection).

2. AIMS AND OBJECTIVES

2.1. Aims and Objectives

Overall aim

Our aim is to conduct the UK arm of a large international randomised controlled trial to determine if treatment with high dose vitamin D improves patient outcomes and is cost-effective, in comparison to placebo in severely VDD critically ill adult patients admitted to ICU.

Primary objective

The primary objective of this trial is to determine whether treating severe VDD with high dose oral vitamin D3 replacement in adult critically ill patients decreases 28-day mortality.

Secondary objectives

The secondary objectives of the overarching trial are to determine whether treating severe VDD with high dose oral vitamin D3 replacement in adult critically ill patients:

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

3. TRIAL DESIGN AND SETTING

3.1. Trial Design

The UK arm of VITDALIZE (VITDALIZE UK) will form part of an international multi-centre double-blind randomised placebo-controlled trial. Patients who meet the eligibility criteria will be randomised in a 1:1 ratio and stratified by trial site and sex to either high-dose vitamin D or placebo.

3.2. Trial Setting

The international trial is already recruiting at participating sites across Europe, with further international sites planned. The trial is endorsed by the European Society of Intensive Care Medicine (ESICM) and the UK Intensive Care Society (ICS).

The trial will take place in ICUs in NHS hospitals in the UK with a proven record of delivering ICU research).

3.3. Additional Sample Collection for Future Research (Optional)[1]

Optional, additional blood samples (up to 30ml) will be taken and stored for analysis as part of future ethically approved research. Blood samples will be taken at the following time points, Day 0 (pre-treatment), Day 5 and Day 12(+/-2). Staff at all hospital sites will receive training and trial-specific work instructions on sample collection and processing will be provided. The samples will be processed (centrifuged and aliquoted) using established protocols, as serum, and plasma stored in -80°C freezers at sites until batch transfer at appropriate intervals to the Institute of Inflammation and Ageing, University of Birmingham (UoB) for storage.

3.4. Assessment of Risk

The assessment and management of risk is detailed in the separate VITDALIZE UK Risk Assessment.

Cholecalciferol is licensed for use within the European Union for the prevention and treatment of VDD. The first marketing authorisation was issued in 1960 and the product has a well-established safety profile. Patients randomised to VITDALIZE will have confirmed severe VDD (≤12ng/ml (30nmol/L)). Amrein *et al*. demonstrated previously that high dose vitamin D3 (loading dose of 540,000IU) could be used safely in patients with severe vitamin D deficiency in a similar clinical setting (52). The Summary of Product Characteristics (SPC)

[1] Not applicable if patient recruited post-SA5 implementation.

advises that 4,000IU is the tolerable upper intake level for adults and that doses in excess of this should be taken under medical supervision. In VITDALIZE, the loading dose (540,000IU) will be administered whilst the patient is in ICU and thus subject to close clinical monitoring. The daily maintenance dose (4000IU) is within the advised tolerable upper intake level but will continue to be taken under medical supervision.

The trial is categorised as: Type A (no higher than the risk of standard medical care)

An ongoing evaluation of risk will continue throughout the trial.

4. ELIGIBILITY

4.1. Inclusion Criteria

To be eligible to participate in the VITDALIZE UK Trial, patients must meet all the following inclusion criteria:

1. Patients ≥18 year
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))

4.2. Exclusion Criteria

If any of the following apply, the patient is not eligible to be randomised into the VITDALIZE UK Trial:

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. Patients with DNAR (Do Not Attempt Resuscitation) orders in place
4. Hypercalcemia (>2.65mmol/l corrected calcium and/or >1.35mmol/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 child bearing 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

Criterion 1 is 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. Criteria 2 and 3 are intended to exclude patients unlikely to survive to day 28 primary trial endpoint. Criteria 4, 5, 6, 7 and 9 are intended to exclude patients who may be at higher risk of side effects secondary to high dose vitamin D supplementation. Criterion 8 is to exclude patients as the potential side effects of high dose vitamin D replacement on the foetus are unknown.

Criterion 10 is 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.

4.3. **Co-enrolment**

The Trial Management Group (TMG) will consider requests for co-enrolment into other trials in accordance with best practice recommendations (54). Co-enrolment to other trials will be considered on a case-by-case basis by the VITDALIZE UK TMG and Sponsor. Prior to co-enrolment being sanctioned, the following will be reviewed: study design and statistical considerations; legal and ethical considerations; biological and scientific rationale; patient considerations and; logistical and organisational issues. Co-enrolment to CTIMPs will be restricted to Type A trials that are comparable to the risk of standard medical care, where the IMP intervention(s) would commonly be used in the treatment of the patient, and where no biological interactions or additional safety reporting will be required for concomitant administration of the IMPs.

For co-enrolment to occur, an agreement will be reached between the respective trials team prior to the patient being considered for inclusion. A log of all patients co-enrolled will be maintained by the VITDALIZE UK Trial Office.

5. 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 (see Section 5.1).

The Principal Investigator (PI) will be responsible for obtaining written informed consent for each patient and/or legal representative before performing any trial related procedure, this includes vitamin D testing when it is performed for the purpose of the trial. Consent may also be taken by other members of the site (e.g. Research Nurse) if local practice allows and this has been delegated by the PI on the Site Signature and Delegation Log.

A Participant Information Sheet (PIS) will be provided to facilitate the process of consent and will explain the aims, trial treatments, potential benefits, and hazards of the trial. In addition, that consenting to the VITDALIZE UK Trial will allow data linkage to NHS routine clinical data-sets, mortality data from Hospital Episode Statistics (HES), civil registry data by NHS Digital, other central UK NHS bodies, and other UK NHS databases that may appear in the future to allow validation of main outcomes, collect long-term health outcome and health resource usage, without further contact with trial patients. The PIS will also detail that to obtain this information the VITDALIZE UK Trial Office will require the patients date of birth (DoB), postcode, NHS number (CHI number, Scotland; H&C number, Northern Ireland), trial number and sex. It is important that this information is collected as it will link trial treatments that may become a clinical standard of care to long-term outcomes that are routinely collected in clinical data but may not be collected during the period of the trial.

If the patient and/or legal representative express an interest in the trial they will be asked to sign and date the latest version of the Informed Consent Form (ICF), giving explicit consent for the regulatory authorities, members of the research team and/or representatives of the Sponsor to be given direct access to the patient's medical records. The PI or delegate(s) will then sign and date the ICF. Copies will be provided to the patient and/or legal representative, placed in the patient's notes, sent to BCTU, and the original filed in the Investigator Site File (ISF).

If face-to-face consent is not possible, remote written consent may be undertaken. The informed consent discussions will proceed as above but by telephone, videoconference or equivalent. The research team at site will initial the boxes on the ICF in discussion with the patient and/or their legal representative and then sign and date the ICF with a witness present. The witness will also be asked to sign and date the ICF. A copy of the completed

ICF will be sent to the patient and/or legal representative and as above, a copy will also be placed in the participant's medical notes, a copy will be sent to BCTU and the original filed in the ISF.

In both instances, once the patient is entered into the trial, the patient's trial number will be entered on the ICF maintained in the ISF.

PIs or their delegate(s) will ensure that the PIS and consent procedure are adequately explained throughout the trial and follow-up visits, and that adequate time is provided to the patient and/or legal representative to review the PIS, discuss participation with others outside of the sites research team, and ask any questions. They will also inform the patient and/or legal representative that participation is voluntary and that they can refuse or withdraw at any time. If new information that may affect the patient and/or legal representatives' decision to continue, time will be given to consider continuation in the trial and dependent on the nature of the information they may be re-consented if required.

Details of the informed consent discussions, including at follow-up visits and regarding re-consent (if required), will be recorded in the patient's medical notes. This will include the date of discussion, the name of the trial and a summary of the conversation, version number of the PIS given to the patient and/or legal representative, the version number of ICF and date consent was received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes of the time the consent was obtained and what time the procedures started.

Electronic copies of the PIS and ICF will be available from the VITDALIZE UK Trial Office. Details of all patients approached about the trial will be recorded on the Participant Screening/Enrolment Log.

5.1. Patients who lack capacity to consent for themselves

Where potential eligible patients lack capacity to consent for themselves the research team at site will initially seek to identify a personal legal representative as defined below:

A personal legal representative is a person independent of the trial, who by virtue of their relationship with the trial participant is suitable to act as their legal representative for the purposes of the trial and who is available and willing to so act for those purposes.

The personal legal representative will be approached and will be provided with the REC-approved Legal Representative PIS explaining the trial and the options for the patient's involvement, including the need for them to give consent on behalf of the patient. The

personal legal representative will then have time to consider the information provided, after which a member of the research team at site will ask when the personal legal representative would like them to come back and discuss participation further and if appropriate, receive consent.

If a personal legal representative cannot be identified, the research team at site will seek to identify a professional legal representative as defined below:

A person independent of the trial, who is the doctor primarily responsible for the medical treatment provided to that adult. Or a person nominated by the relevant healthcare provider.

Informed consent given by a professional legal representative shall represent the patient's presumed will. Where a professional legal representative gives consent, should a personal legal representative be identified they will be informed at the earliest opportunity and consent for the patient to continue in the trial will be sought from them.

If the patient does regain capacity during the follow-up period, they will be asked to give consent for themselves using the process outlined previously in Section 5. The patient's wishes (consent or refusal) will supersede the consent obtained from the personal or professional legal representative. If the patient does not wish to consent to continue, they will be withdrawn from the trial, but the data collected to that point will be retained. In the event that the patient never regains capacity or dies, then they will remain in the trial and their data will be included in the analysis.

5.2. Patients transferred to non-VITDALIZE UK sites

There may be some situations where patients recruited to the VITDALIZE UK Trial have to be transferred to other hospitals for specialist care. In most cases this would be a short term arrangement but there may be some instances where patients remain in specialist care for a longer period of time.

In these circumstances with the patients and/ or legal representatives' consent, the CI, VITDALIZE UK Trial Office and/or the research team at site shall engage with the non-VITDALIZE UK hospital to request a minimal dataset for the patient. The dataset requested will comprise of both patient safety and compliance data.

6. RECRUITMENT, ENROLMENT AND RANDOMISATION

6.1. Recruitment

In the VITDALIZE UK Trial a medically qualified Doctor who is delegated the task on the VITDALIZE UK Trial Delegation Log will confirm eligibility prior to randomisation.

6.2. Enrolment and Screening

All patients admitted to ICU will be screened daily for eligibility. Eligible patients will need written informed consent to have the screening blood test for vitamin D measurement (as this is currently not standard practice in UK ICUs) and only those that are found to have a 25(OH)D concentration ≤12ng/ml (30nmol/L) will be eligible for randomisation into the trial. The research team at site will maintain a Participant Screening/Enrolment Log, which will include data on the numbers of patients meeting the inclusion criteria for the trial but were not entered into the trial along with the reasons for non-enrolment.

If inclusion criteria 1-3 are met and none of the exclusion criteria are met, the patient will be considered provisionally eligible. At this point, written informed consent, as detailed in section 5, will be gained for a screening blood sample, this will be obtained by:

- A blood sample of approximately 5-10 ml will be taken from the patient (preferably from an existing line)
- Alternatively, the site can request that a vitamin D test be 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 and proceed to randomisation.

Following confirmation that the patient is severely VDD (according to the definition in the protocol), randomisation should occur as soon as practically possible (recommended within 24 hours of receiving screening result). Patients who are not found to be severely VDD (according to the definition in the protocol) will be informed of their result and will continue with their ongoing standard medical care. For all patients screened, the research team at site will provide the patient and/or legal representative with the outcome of the screening result at the earliest opportunity.

6.3. **Randomisation**

Randomisation will be provided by a secure online randomisation system 'Randomizer' developed by the Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Austria (available at https://www.randomizer.at/random/login). Patients will be randomised at the level of the individual in a 1:1 ratio to either high dose vitamin D3 or placebo and stratified by trial site and sex ensuring allocation concealment. An independent statistician at the Medical University of Graz will set up the trial and have access to the trial allocations in the 'Randomizer'.

Data obtained during randomisation for the VITDALIZE Trial will be stored electronically by the Sponsor. The randomisation set-up, including all patient randomisations, will be downloaded prior to database lock for storage in the VITDALIZE Trial data file at the Medical University of Graz. Randomisations performed at UK specific sites will be requested by BCTU for storage in the UK Trial Master File (TMF) prior to database lock.

Following randomisation, a confirmatory e-mail will be sent to the randomising user, , VITDALIZE UK Trials Team, UK and international CI, all of whom will have been assigned permissions on the randomisation database. The randomising user should forward the confirmatory e-mail to any other appropriate site staff, including pharmacy staff. Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising patients into the trial as detailed on the VITDALIZE UK Trial Signature and Delegation Log. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. There will be no paper randomisation available for the VITDALIZE UK Trial.

After eligibility has been confirmed and informed consent has been received, the patient will be randomised into the trial. For a patient to be randomised into VITDALIZE UK, the research team at site will complete the following:

- The Eligibility Checklist Form: Sites should complete this form prior to randomisation to confirm that all the necessary information (inclusion/exclusion) prior to randomisation is captured. ***If there has been a >24-hour delay since eligibility was confirmed, eligibility must be re-assessed and eligibility checklist completed prior to randomisation.***
- The research team at site will 'create a new patient' using Clincase (https://edc.medunigraz.at/clincase/app) which will provide a patient trial number (a patient trial number is required to complete randomisation)

- Using ‘Randomizer’ (www.randomizer.at/random/login) the research team at site can then randomise the patient. This will require the patient’s trial number (created using Clincase), sex and site ID

The research team at site will keep their own trial file log which links patients with their allocated trial number in the VITDALIZE UK Patient Recruitment and Identification Log. The research team at site must maintain this document, which is **not** for submission to the VITDALIZE UK Trial Office. The research team at site will also keep and maintain the VITDALIZE UK Screening/Enrolment Log, which will be kept in the ISF and should be available to be sent to the Trials Office upon request. The VITDALIZE UK Patient Recruitment and Identification Log and VITDALIZE UK patient Screening/Enrolment log should be held in strict confidence.

6.4. Informing the patient’s General Practitioner (GP)

With the patient’s (or their legal representative’s) consent, their GP should be notified that they were randomised into the VITDALIZE UK Trial using the VITDALIZE UK GP Letter. The GP Letter will be sent after the patient has been discharged from hospital. The letter will include the patient’s vitamin D level at inclusion in the trial and trial-related follow-up procedures. For those patients that have been randomised into the trial, a request will be made that no additional vitamin D testing occur or vitamin D supplementation provided above the RDA (400-800IU) until the intervention period (days 0 – 90) has ended as there are currently no guidelines that higher doses are beneficial to patients. It will be at the discretion of the GP to decide whether to retest and treat the patient after the intervention period based on the results communicated.

For patients who were screened for VITDALIZE UK and found to be ineligible, the GP will be informed of the patient’s vitamin D level as part of standard clinical practice by the research site.

6.5. Blinding

Patients, the research team at site, other attending clinicians and the trial statisticians will remain blind to the trial drug allocation throughout the duration of the trial.

Should any Serious Adverse Event (SAE) occur, the management and care of the patient will be initiated as though the patient is on high dose vitamin D. Where events are considered serious, unexpected and possibly, probably or definitely related (please refer to Section 9.3) the research team at site can perform an emergency unblind of the patient using the ‘randomizer’ database (www.randomizer.at/random/login). The research team at

site will have 24/7 access to the database and it can be accessed anywhere there is an internet connection. Following an emergency unblind, the research team at site should notify the VITDALIZE UK Trial Office, in writing. A trial-specific work instruction will be in place to detail the process.

In all other circumstances, the research team at site will remain blind to treatment allocation whilst the patient remains in the trial. However, if a patient is withdrawn from the treatment and the treatment allocation is required for the continued medical management of the withdrawn patient, clinicians should contact the VITDALIZE UK Trial Office. Requests for non-emergency unblinding should be made in writing to the VITDALIZE UK Trial Office.

The VITDALIZE UK Trial Office will be provided the un-blinding treatment code table by the Sponsor at the end of the trial once the database has been locked. The VITDALIZE UK Trial Office will then disseminate the treatment information to patients (high dose vitamin D or placebo) using an ethically approved document.

7. TRIAL TREATMENT / INTERVENTION

7.1. Treatment(s) and Dosing Schedule

The intervention is a therapeutic dose of Cholecalciferol (Oleovit D3 or vitamin D3) versus placebo in an otherwise identical oily solution of MCT, either given by nasogastric or jejunal feeding tube or swallowed. We will use the preparation that is commercially available in Europe (Cholecalciferol, 12.5ml per bottle, 400IU per drop, total dose of 180,000IU per bottle):

- Vitamin D: oral/enteral pharmacological dose of cholecalciferol (vitamin D3)
    - Loading dose of 540,000IU (dissolved in 37.5ml of MCT) followed by 4000IU daily (10 drops) for the entire active trial period (90 days) – total dose 900,000IU
- Placebo: identical regime
    - Loading dose of 37.5ml MCT followed by 10 drops daily

7.1.1. Justification of dosing

In critical illness, there is evidence of rapid falls in circulating vitamin D concentrations potentially due to disrupted metabolism, fluid resuscitation, surgery, and loss of the carrier protein due to hepatic dysfunction (6, 52, 55). There is also evidence that critically ill patients with very low vitamin D concentrations have blunted responses to vitamin D3 replacement. Therefore, a bolus dose is an attractive option to rapidly improve circulating concentrations. The VITdAL-ICU Trial provided an enteral 540,000IU loading dose of vitamin D3 to critically ill adults. This dose increased 25(OH)D from 13 to 35 ng/ml until day 3 and was well tolerated (52). The daily follow-up dose of 4000IU in our trial corresponds to the upper limit recommendation by the IOM (51).

The route chosen is per-oral because currently no high-dose mono-preparation of vitamin D3 is available. Although recently an interventional trial has tested high-dose intramuscular vitamin D3 (56), intramuscular injections may not be feasible in many ICU patients (risk of bleeding and infection).

7.2. Drug Interaction or Contraindications

Inducers of CYP450 metabolic enzymes such as rifampicin, carbamazepine, phenytoin, barbiturates (e.g. phenobarbital, primidone) and glucocorticoids may reduce the efficacy of vitamin D due to increased inactivation. Concomitant use of these medicinal products can increase the vitamin D requirement. Isoniazid may reduce the effectiveness of vitamin D3

due to inhibition of the metabolic activation of vitamin D. Medicinal products leading to fat malabsorption, e.g. orlistat and cholestyramine, may impair the absorption of vitamin D. Increased parathyroid hormone levels can increase the vitamin D metabolism and thus increase the vitamin D requirement.

Concomitant treatment with cardiac glycosides can increase their toxicity due to hypercalcaemia (risk of arrhythmias). Strict medical supervision is needed and, if necessary, monitoring of ECG and serum calcium levels.

Concomitant use of thiazide-type diuretics increases the risk of hypercalcaemia as they reduce the urinary elimination of calcium. In this case, serum calcium levels should be regularly monitored.

Magnesium-containing medicines (e.g. antacids) should not be used during therapy as this may lead to hypermagnesaemia.

Vitamin D3 might increase the intestinal absorption of aluminium.

7.3. **Accountability Procedures**

At randomisation, the trial treatment number will be provided, and this reference will correspond to a trial treatment pack available in the participating site's pharmacy. The pharmacist will receive notification of the name and trial number of the patient and will prepare the trial treatment for dispensing.

The local pharmacist should keep accurate records of trial drugs dispensed using an Accountability Log provided by the VITDALIZE UK Trial Office. Trial drugs must be kept in the packaging supplied and under no circumstances used for other patients or non-patients.

7.4. **Concomitant Vitamin D Supplementation**

Routine low-dose vitamin D supplementation (≤800IU/day) is allowed during the trial period and will be documented. This is the current recommended daily allowance (RDA) by the Institute of Medicine. Patients will be advised not to take more than this and the GP will be sent a letter on recruitment advising them of their patient's inclusion in the trial and advice to not prescribe more than the RDA until completion of the trial medication at 90 days. Furthermore, patients will be asked if they took additional supplementation during telephone assessment at day 90.

7.5. **Cessation of Treatment / Continuation after the Trial**

Patients may discontinue trial treatment at any point if they choose to or if their clinical team feel that continued treatment within the trial is inappropriate. Those who do discontinue trial medication will be asked if they are still willing to be followed-up as part of the trial. Discontinuation of the trial treatment will be documented on the Electronic Case Report Form (eCRF) and Change of Status Form.

Any patients who decide to discontinue trial treatment, withdraw, or complete follow-up (1 year) will continue their ongoing standard of care pathway.

In instances where the trial treatment has not been administered for 14 days due to misplacement or an adverse reaction, the trial treatment should be withdrawn on the 15th day. A discontinuation of the trial treatment will be documented on the eCRF and Change of Status Form. In addition a file note should be sent to the VITDALIZE Trial Team at BCTU to outline why the trial treatment has been withdrawn.

7.6. **Treatment Supply and Storage**

Unlabelled Cholecalciferol (Oleovit D3 or vitamin D3) bottles, unfilled identical bottles, and the placebo MCT solution will be provided by Fresenius Kabi Austria GmbH (the marketing authorisation holder for Cholecalciferol).

7.6.1. Treatment Supplies

Distribution of the trial medication to participating centres in the UK will be performed at a certified pharmacy Landesapotheke, Müllner Hauptstraße 50 5020 Salzburg. Prior to site activation, the VITDALIZE UK Trial Office will arrange for the supply of high dose vitamin D and placebo to be delivered to the pharmacist of each participating site. Local pharmacists will check the amount and condition of the supply and confirm these details in a Proof of Receipt Form, a copy of which should be provided to the VITDALIZE UK Trial Office.

7.6.2. Packaging and Labelling

A certified pharmacy Landesapotheke, Müllner Hauptstraße 50 5020 Salzburg is responsible for labelling and packaging of both the high dose vitamin D preparation and the placebo and for final QP release for clinical trial use (according to Annex 13 guidelines). The labelled and QP released medication will be shipped to trial sites prior to site activation and before the regulatory green light being issued.

7.6.3. Drug Storage

The high dose vitamin D preparation and placebo preparation should not be stored above 25˚C and should be kept out of direct sunlight. Temperature monitoring at site will be done according to local standard practice.

At the end of trial or upon expiry of the drug and/or placebo, participating sites can dispose of the trial intervention as per their standard processes following approval from the VITDALIZE UK Trial Office.

In situations where a patient misplaces their trial medication, the patient will be followed up per protocol and be included in the analysis on an intention to treat basis. Patients will not receive any further medication.

8. OUTCOME MEASURES AND TRIAL PROCEDURES

Screening – Day -3 to 0

- Vitamin D analysis
- Eligibility
- Informed consent

Please note, details of the screening assessment have been described earlier in Section 6.2.

Baseline – Day 0

The patient receives the loading dose of the allocated intervention (vitamin D or placebo) and the following is recorded.

- Age
- Sex
- ICU admission diagnosis
- ICU type (medical, surgical, neurological, cardiac)
- Charlson comorbidity index (based on co-morbidities on ICU admission)
- Simplified Acute Physiology Score (SAPS III)
- Therapeutic Intervention Scoring System (TISS 28)
- SOFA score (on admission to ICU)
- Number of organ failures
- Katz Activities of Daily Life (prior to ICU admission)
- Serum calcium
- If applicable[1], patient health-related quality of life questionnaire (EQ-5D-5L and WHODAS 2.0, proxy if patient does not have capacity)
- If applicable[2], blood sample for future research (pre-intervention)

Please note, 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.

Please note, the day of the study medication loading dose is the start for the calculation of the time dependent outcome data.

The SOFA and SAPS III scores will also capture data on the presence of sepsis and renal dysfunction (our 2 predefined sub-groups).

Day 1

The patient begins daily dose treatment with allocated intervention for 90 days.

Day 5

- Survival status
- Serum calcium
- Treatment with allocated trial medication
- Trial medication compliance
- SOFA score and type(s) of organ support
- Presence of sepsis/infection
- Targeted adverse events (refer to Section 9.3.2)
- If applicable[2], blood sample for future research

Day 12

- If applicable[2], blood sample for future research

Day 28

- Survival status (primary endpoint 28-day mortality)
- Serum calcium (if still in hospital)
- Targeted adverse events (refer to Section 9.3.2)
- Treatment with allocated trial medication
- Trial medication compliance
- If applicable[1], patient health-related quality of life questionnaire (EQ-5D-5L and WHODAS 2.0, proxy if patient does not have capacity)
- If applicable[1], health economics questionnaire

Day 90

- Survival status
- Katz Activities of Daily Living
- Targeted adverse events (including self-reported infections requiring antibiotics, self-reported falls and fracture, hospital, and ICU admissions)
- Discharge destination
- Trial medication compliance
- If applicable[1], patient health related quality of life (EQ-5D-5L and WHODAS 2.0, proxy if patient does not have capacity)
- If applicable[1], health economics questionnaire

Day 90 marks the end of the trial intervention.

1 year

- Survival status
- If applicable[1], patient health related quality of life (EQ-5D-5L and WHODAS 2.0, proxy if patient does not have capacity)
- If applicable[1], health economics questionnaire

Information obtained at day 28, 90 and 1 year (see above) can be obtained from the hospital's data management systems or via telephone interview with the trial patient or delegated family member. Additional information will be obtained from reviewing hospital clinical records and via NHS Digital and if applicable[1], patient Health economics questionnaire.

The following questionnaires will not be collected for patients recruited post substantial amendment 5 (SA5) implementation:

- *EQ-5D-5L*
- *WHODAS 2.0*
- *Health economics questionnaire*

[1] Only applicable if patient recruited pre-SA5 implementation

[2] Only applicable if patient recruited pre-SA5 implementation and consents to the sub-study

8.1. Primary Outcome

- All-cause mortality at 28 days after randomisation

8.2. 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 from the trial site or day 90 or mortality, whichever occurs first)
- Change in organ dysfunction on day 5 as 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)
- Hospital and ICU readmission until day 90
- Discharge destination (home, rehabilitation, other hospital)
- Katz Activities of Daily Life at day 90
- Self-reported infections requiring antibiotics until day 90
- Health-related quality of life (EQ-5D-5L) at 90 days and 1 year[1]
- Disability assessment (WHODAS 2.0) at 90 days and 1 year[1]
- 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[1]
- Health economics analysis[1]
    - 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

8.3. Exploratory outcome

- Health related quality of life (proxy EQ-5D-5L and proxy WHODAS 2.0) at randomisation (day 0)[1]

8.4. Safety outcomes

- Hypercalcaemia at day 5
- Self-reported falls, fractures until day 90
- New episodes of kidney stones

[1] UK-specific outcome no longer collected for patients recruited post-SA5 implementation

8.5. Schedule of Assessment

ASSESSMENT	Screening	Enrolment Baseline	Begin Daily Dose	Follow-Up	Follow-Up	Follow-Up	Follow-Up	Follow-Up
	Day -3 to Day 0	Day 0	Day 1	Day 5	Day 12	Day 28	Day 90	Month 12
Time window (days)				±2	±2	+4	±14	±30
25(OH)D	X							
Eligibility assessment	X	X						
Informed consent	X	X						
Randomisation		X						
Baseline demographics		X						
SAPS III		X						
TISS 28		X						
Charlson comorbidity index		X						
Adverse events								
Mortality[1]				X		X[2]	X	X
Serum calcium	X	X		X		X[3]		
Falls							X	
Fractures							X	
New episodes of nephrolithiasis							X	
Number of organ failures[1]		X		X				
Infections requiring antibiotics[1]							X	
Hospital and ICU readmission[1]							X	
Intervention								
Loading dose 540,000 IU or matched placebo		X						
Daily dose 4,000 IU or matched placebo			X	X	X	X	X	
Outcome measures								
SOFA		X		X				
qSOFA		X						
Discharge destination							X	
Katz Activity of Daily Living		X					X	
NHS digital, ONS/HES data								X
(vitamin D metabolic profiling (optional research)		X[4]		X[4]	X[4]			
UK specific outcomes								
Health related quality of life (proxy EQ-5D-5L)		X[5,6]				X[5,6]	X[5,6]	X[5,6]
Health related quality of life (EQ-5D-5L)		X[5]				X[5]	X[5]	X[5]
Disability assessment (proxy WHODAS 2.0)		X[5,6]				X[5,6]	X[5,6]	X[5,6]
Disability assessment (WHODAS 2.0)		X[5]				X[5]	X[5]	X[5]
Health economics questionnaire						X[5]	X[5]	X[5]

[1] Outcome measure
[2] Primary outcome
[3] If still an inpatient
[4] If patient recruited pre-SA5 implementation and consents to the sub-study
[5] If patient recruited pre-SA5 implementation
[6] To be used if the patient does not have capacity

8.6. **Participant Withdrawal**

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether to participate. It is a continuous and dynamic process and patients should be asked about their ongoing willingness to continue participation.

Patients should be aware at the beginning that they can freely withdraw (discontinue participation) from the trial (or part of) at any time.

Types of withdrawal as defined are:

- 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)

The details of withdrawal (date, reason, and type of withdrawal) should be clearly documented in the source data.

If a patient decides to withdraw from the VITDALIZE UK Trial, the site should complete the Change of Status Form. The Change of Status Form is required to capture withdrawal relating to the UK specific outcomes.

A Study Discontinuation Form should be completed in ClinCase for the following reasons:

- Completed study alive
    - Final visit at 12 months done
    - This also includes patients whose study medication was lost or who did not want to proceed taking the medication

- Death
    - Documented death before/at final visit (12 months +-30 days)
- Lost to follow-up
    - No further information can be obtained at final visit (12 months +-30 days)
- Withdrawn consent
    - Full withdrawal of consent, no further data will be collected
    - Data are used until withdrawal is documented
- Other reason
    - Other individual circumstances may apply

9. ADVERSE EVENT REPORTING

9.1. Reporting Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. The Investigator will assess the seriousness and causality (relatedness) of all AEs experienced by the patient. This should be documented in the source data with reference to the approved reference safety information (refer to Section 9.6).

9.2. Adverse Events

Patients randomised to VITDALIZE UK will, by nature of their condition, be critically ill and most of the resulting AEs (whether serious or not) will be anticipated in the sense that they are recognised and accepted complications of critical illness. Additionally the safety profile of the trial intervention is well established so although the severity and causality of all AEs should be recorded in the patient's medical notes, a strategy of targeted reporting (to the Sponsor) of AEs will not compromise the safety of patients. Refer to Section 9.3 for guidance on SAE reporting procedures.

9.3. Serious Adverse Events (SAE)

9.3.1. Events that are excluded from reporting

At whatever time they occur during an individual's participation (from randomisation until 15 days post last IMP administration), 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.

9.3.2. Events that do not require expedited (immediate) reporting

The below events are regarded as expected SAEs for the purpose of the trial and recorded on the follow-up Case Report Forms (CRF). If mortality is related to a pre-existing condition, it should be documented on the Study Discontinuation Form and Change of Status Form. If mortality is deemed to have causal relationship with the intervention it should be reported in an expedited manner as outlined in Section 9.3.3.

Table 1: Non-expedited events

Event	CRF
Mortality[1]	Study Discontinuation Form, Change of Status Form and SAE Form[4] (if applicable)
Change in organ dysfunction (number of organ failures)	Day 0; Day 5 Form; Adverse Events Form[5]
Hypercalcaemia[2]	Adverse Events Form[5]
New episodes of nephrolithiasis[3]	Adverse Events Form[5]
Falls and fractures	Adverse Events Form[5]
Infections requiring antibiotics treatment	Day 90 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] Where persistent hypercalcemia is present, it is a clinical recommendation for a parathyroid hormone (PTH) test to be performed before continuing with the trial medication
[3] Decrease/increase in kidney function, specifically CKD 4 (eGFR <30mL/min/1.73m^2)
[4] SAE form to be completed if there is a causal relationship to intervention
[5] Please note that the Adverse Events Form is **not** a SAE Form

9.3.3. Events that require expedited (immediate) reporting

The research team at site will report all SAEs that are not defined in Sections 9.3.1 and 9.3.2 in an expedited manner. The research team at site are required to report expedited SAEs using both the:

- eCRF (minimum dataset)
- Paper SAE Form

The additional paper SAE form has been included to ensure that appropriate key data points (from a UK-regulatory perspective) are captured. Please refer to Section 9.5.2 for more detail on reporting expedited SAEs.

9.3.4. Monitoring pregnancies for potential Serious Adverse Events

There is an identified risk of congenital anomalies or birth defects in the offspring of patients that may occur as a result of their participation in the trial. The outcome of pregnancies of patients will therefore be monitored in order to provide SAE data on congenital anomalies or birth defects.

Pregnant or women who are lactating are excluded from the trial. However, in the event that a patient becomes pregnant during the SAE reporting period a Pregnancy Notification Form will be completed and returned to the VITDALIZE UK Trials Office. If a female patient is found to be pregnant whilst in the trial, they will be advised to stop taking their trial medication and with their permission, they will continue to be followed up per the trial protocol and included in the analysis per intention to treat. Details of the outcome of the

pregnancy should be captured on a Pregnancy Notification Form. A congenital anomaly, birth defect, foetal death or stillborn will be reported as an SAE and in compliance with the section on SAEs.

There is no risk identified from male patients who take vitamin D3 whose partner subsequently becomes pregnant.

9.4. Reporting period

Details of the targeted AEs will be documented and reported from the date of randomisation until 15 days post last IMP administration. If the patient has suffered an AE within the 15 days post last IMP administration then the information should be documented on the relevant forms and patients medical notes.

9.5. Reporting procedure – at site

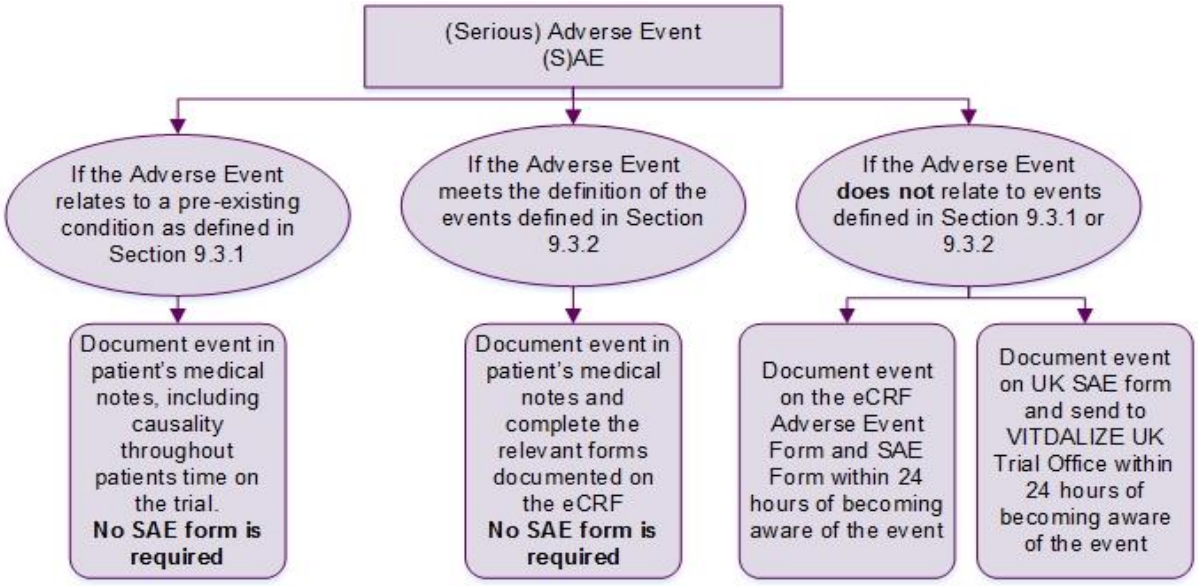
9.5.1. Adverse Events

The safety profile of the IMP used in this trial is well characterised, therefore only the expected AEs described in Section 9.3.2 should be reported to the VITDALIZE UK Trial Office. However, all AEs should be documented in the source data.

9.5.2. Serious Adverse Events

Sites should report SAEs which are NOT classed as 'protocol exempt' or those that can be reported in non-expedited manner (as defined in Sections 9.3.1 and 9.3.2), to the VITDALIZE UK Trial Office within 24 hours of site being made aware of event.

Table 2: Reporting SAEs



On becoming aware that a patient has experienced a SAE, the PI or delegate should report the SAE to their own Trust in accordance with local policies and to the VITDALIZE UK Trial Office in accordance with the VITDALIZE UK Protocol. In addition, the research team at site will be required to respond to any related queries raised by the VITDALIZE UK Trial Office as soon as possible.

The PI (or medically qualified delegate) will assess relatedness and severity of the SAE. The following categories will be used to define the relatedness (causality) of the SAE:

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely	
Possibly	There is some evidence to suggest a causal relationship, however, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship; there is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant events or medication)	Unrelated
Not related	There is no evidence of any causal relationship	

To report an expedited SAE to the VITDALIZE UK Trial Office, the PI or delegate must complete, date, and sign the trial specific VITDALIZE UK SAE forms. The completed form should be uploaded on the eCRF and sent to the VITDALIZE UK Trial Office using the contact details listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

Completed SAE Forms can be sent to the VITDALIZE Trial Office on:

Via email: vitdalize@trials.bham.ac.uk

On receipt of a SAE Form, the VITDALIZE UK Trial Office will assign the SAE a unique reference number and return this via email to the site as proof of receipt. If the site has not received confirmation of receipt of the SAE from VITDALIZE UK Trial Office or if the SAE has not been assigned a unique SAE identification within 1 working day, the site should contact the VITDALIZE UK Trial Office. The site and the VITDALIZE UK Trial Office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the Site File.

Following reporting of a SAE, the patient should be followed up until resolution or stabilisation of the event. Follow-up information should have the SAE reference number provided by the VITDALIZE UK Trial Office and be recorded as follows:

- Updating the information via the eCRF
- Completing a new paper SAE form with the follow-up information

Once the SAE has been resolved, all follow-up information has been received and the paperwork is complete, the **original paper SAE form** that was completed at site must be returned to the VITDALIZE UK Trial Office and a copy kept in the Site File.

9.6. Reporting Procedure – BCTU Trials Office

Proof of receipt will be provided to the site within 1 working day. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the actual SAE in the TMF.

On receipt of an SAE Form, the CI or delegate will determine the seriousness and causality of the SAE. An SAE judged by the CI or delegate(s) to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The causality assessment given by the PI will not be downgraded by the CI or delegate(s). If the CI or delegate(s) disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

The CI or delegate(s) will also assess all expedited SAEs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the approved version of the Reference Safety Information (RSI): Section 4.8 Undesirable Effects - Summary of Product Characteristics (SPC) Cholecalciferol – Oleovit D3 14,400 IU/ml oral drops, solution, December 2015 it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

9.7. Reporting to the Competent Authority and Research Ethics Committee

9.7.1. Suspected Unexpected Serious Adverse Reactions

BCTU will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA), REC and Sponsor within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as non-life threatening SUSARs will be reported within 15 days.

9.7.2. Serious Adverse Reactions

The Sponsor will prepare report details of all SAEs (including SUSARs) for the MHRA and REC annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR). The reports will be sent to the MHRA and REC by the National Co-ordinating Centre (NCC) on behalf on the Sponsor.

9.7.3. Adverse Events

Details of all AEs will be reported to the MHRA on request.

9.7.4. Other safety issues identified during the course of the trial

The MHRA, REC and Sponsor will be notified immediately if a significant safety issue is identified during the course of the trial.

9.8. **Investigators**

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to PIs. A copy of any such correspondence should be filed in the Site File.

9.9. **Data Monitoring Committee**

The independent Data Monitoring Committee (DMC) will review all SAEs.

9.10. **Reporting to Third Parties**

All SAEs will be reported to the Sponsor, who will be responsible for reporting SAEs and trial related progress to the manufacturer of the Investigational Medicinal Product (Fresenius Kabi) in line with their contractual requirements.

10. DATA HANDLING AND RECORD KEEPING

10.1. Source Data

Source data is defined as all information in original records and certified copies of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. To allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

For the eCRF, sites will be provided worksheets which can be used to capture source data. In situations where sites do not use worksheets, source data should be kept as part of the patients' medical notes generated and maintained at site (Please refer to Tables 3 and 4).

Table 3: Source Data

Data	Source
Patient Reported Data (EQ-5D-5L; WHODAS 2.0)	The completed paper form is the source and a copy will be forwarded directly to the VITDALIZE Trial Office.
Laboratory results	The original lab report, which may be electronic, is the source data and will be kept and maintained, in line with normal local practice. Worksheets will be provided that can be used to document lab results. In situations where these are used, will be source data.
Clinical event data	The original clinical annotation is the source data. This may be found on clinical correspondence, or electronic or paper patient records. Clinical events reported by the patient, either in or out of clinic (e.g. phone calls), must be documented in the source data. Worksheets will be provided that can be used to document lab results. In situations where these are used, will be source data.
Health economics (resource use) data	This will be completed on the Health Economics (resource use) CRFs via interview or telephone with the patient and/or legal representative. The completed paper form is the source and a copy will be forwarded directly to the VITDALIZE Trial Office.
Recruitment	The original record of the randomisation is the source. It is held on the Medical University of Graz eCRF servers as part of the randomisation and data entry system.
Withdrawal	Where a participant expresses a wish to withdraw, the conversation must be recorded in in the source data.

11. CASE REPORT FORM COMPLETION

Staff delegated to complete the data entry will be trained to adhere to:

- CRF completion and corrections
- Date format
- Time format and unknown times
- Rounding conventions
- Trial-specific interpretation of data fields
- Entry requirements for concomitant medications (generic or brand names)
- Which forms to complete and when
- What to do in certain scenarios, for example when a patient withdraws from the trial
- Missing/incomplete data
- Reporting SAEs
- Repeat laboratory tests
- Protocol and GCP non-compliances

11.1.1. Electronic data entry at site

Data reported on the eCRF will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous electronic data entry will be queried. Paper worksheets replicating the data to be entered on the eCRF will be provided to sites and may be used to capture data variables.

11.1.2. UK specific CRFs

For the UK specific outcomes, data reported on the CRF and eCRF will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried.

In all cases, it remains the responsibility of the site's PI to ensure that the CRFs and patient questionnaires are completed correctly, and that the data are accurate. This will be evidenced by the signature of the site's PI, or delegate(s), on the CRF and eCRF.

11.2. Patient Completed Questionnaires

For the UK specific outcomes, the EQ-5D-5L and WHODAS 2.0 questionnaire will be completed and forms part of the secondary outcomes. Patients randomised into the VITDALIZE UK Trial will be critically ill therefore there will be situations where the patient will be unable to complete the questionnaires. In those scenarios, the patients legal representative will complete them as 'proxy'. If the patient is unable to complete the questionnaires alone, the research staff can provide physical assistance where appropriate. In such circumstances, questions are to be read to the patient verbatim and research staff must not lead responses.

Patients or their legal representative should be encouraged to respond to all questions but can refuse to answer any or all of the questions should they wish.

Patient completed questionnaires will be completed either in clinic/bedside or via telephone dependent on the location of the patient at that visit. If the questionnaires are completed in clinic/bedside, the patient or legal representative should complete the questionnaires. The research staff delegated the task should oversee their completion. Where a questionnaire is returned to the research staff, in person, with some questions unanswered, research staff should clarify with the patient that they have chosen not to respond specifically to the unanswered questions and that they have not simply missed them in error.

Where a questionnaire is completed via telephone, the research team at site are required to read questions from the questionnaire to the patient or legal representative verbatim and must not lead responses. In situations where the patient or legal representative do not answer or refuse to answer a question, the research team at site will move on to the following question.

11.3. Health Economics Analysis

The health economics (resource use) questionnaire will be completed via telephone. The research team at site are required to read questions from the questionnaire to the patient or legal representative verbatim and must not lead responses. In situations where the patient or legal representative do not answer or refuse to answer a question, the research team at site will move on to the following question. NHS digital, ONS/HES data will be collected at the end of trial follow-up to collect long term outcomes (survival status).

11.4. 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 entered on the eCRF will be completed by the research staff at site whereas data items for the UK database will be entered by the VITDALIZE UK Trial Office.

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the VITDALIZE UK Data Management Plan (DMP). For the UK specific database, coding and validation will be agreed between the Trial Manager, Statistician and Analyst Programmer and the trial database will be signed off once the implementation of these has been assured.

Missing and ambiguous data for VITDALIZE UK will be queried using a data clarification system in line with the VITDALIZE UK DMP and will focus on data required for trial outcome analysis and safety reporting. Data entry for VITDALIZE UK will consist of electronic and paper data entry. Data entry for the main trial will consist of remote data capture and entry by the research staff at site; UK specific outcomes will be entered centrally by the VITDALIZE UK Trials team (See Table 4).

11.4.1. Data management for electronic data entry at site

Research staff at site who are delegated the role of CRF completion will enter and submit data on the eCRF. They will be provided with unique log-in usernames and passwords to use the online system. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access the trial database using another person's login details. The VITDALIZE UK Trial Office will be unable to edit data forms entered by site staff on the eCRF. The system will include data validations to improve data quality (e.g. to prevent nonsensical dates or numerical values). Changes to the data on the system will be documented and attributable, with a reason for the change documented and will be made by the research staff at site.

11.4.2. Data management for paper data entry (UK-specific outcomes only)

UK specific outcomes will be captured using paper CRFs and entered centrally by the VITDALIZE UK Trials Office. The research staff at site will be responsible for sending the paper CRFs to the VITDALIZE UK Trial Office for data entry. Sites will be sent Data Clarification Forms (DCF) requesting missing data or clarification of inconsistencies or discrepancies per the DMP.

VITDALIZE UK is a CTIMP which has been formally risk assessed by BCTU as 'Type A' on the basis that the intervention has a well-established safety profile. Therefore, on-site monitoring will, for the most part, be triggered by poor recruitment or poor data returns. CRFs may be checked against the source data where on-site monitoring is conducted and must be available for verification.

Table 4: Data Entry

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

11.5. Data Security

Every international centre working on the VITDALIZE Trial will have access to the eCRF Clincase (Quadratek, Data Solutions Ltd., Berlin, Germany). Clincase is a validated electronic data capture and clinical data management system which complies fully with the European Union (EU) and Good Manufacturing Practice (GMP) Annex 11 regulations.

Data security for the eCRF is the responsibility of the Medical University of Graz, Austria. The access to the eCRF is secured by a rights and role system with password aging. Internet communication with the eCRF uses to the Transport Layer Security (TLS) and includes data back-up and data mirroring.

The security of the UK database system is governed by the policies of the University of Birmingham. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at the University of Birmingham have to be registered with Data Protection Officer and data held in accordance with the Data Protection Act. The University will designate a Data Protection Officer upon registration of the trial. BCTU have arrangements in place for the secure storage and processing of the trial data, which comply with the University of Birmingham policies.

The System incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.

- Logical measures for access control and privilege management: including restricted accessibility, access-controlled servers, separate storage of non-identifiable data etc.
- Network security measures: including site firewalls, antivirus software, and separate secure network protected hosting etc.
- System Management: the System shall be developed by the BCTU Programming Team and will be implemented and maintained by the BCTU Programming Team.
- System Design: the system shall comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- Operational Processes: the data will be processed and stored within the trial centre (University of Birmingham).
- Data processing: Statisticians will only have access to anonymised data.
- System Audit: The System shall benefit from the following internal/external audit arrangements:
    - Internal audit of the system
    - An annual IT risk assessment
- Data Protection Registration: The University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

11.6. Archiving

All records created by following trial procedures, and all documents listed in guidance relating to the conduct of the trial, must be retained and archived including electronic documents, where used. No documents should be destroyed without prior approval from the VITDALIZE UK Trial Office.

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, ISFs, Pharmacy Files, patients' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years.

The TMF will be stored at BCTU for at least 3 years after the end of the trial. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored securely and confidentially for at least 25 years. BCTU has standard processes for both hard copy and computer database legacy archiving.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Site Set-up and Initiation

The CI is required to sign a Clinical Trials Task Delegation Log, which documents the agreements between the CI, BCTU and the NCC. In addition, all local PIs will be asked to sign the necessary agreements including a Site Signature and Delegation Log and supply a current signed CV and GCP certificate to BCTU. All members of the site research team are required to sign the Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a meeting or a teleconference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF and a Pharmacy File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The VITDALIZE UK Trial Office must be informed immediately of any change in the site research team.

12.2. Monitoring

The monitoring requirements for this trial have been developed following trial specific risk assessment by BCTU.

12.3. Central Monitoring

The VITDALIZE UK Trial Office will be in regular contact with the site research team to check on progress and address any queries that they may have. The VITDALIZE UK Trial Office will check incoming ICFs, CRFs and the eCRF for compliance with the protocol, data consistency, missing data, and timing. In addition, the Sponsor will review the data held on the eCRF and produce data queries approximately every 6 months. These queries will be sent to the VITDALIZE UK Trial Office who will in turn, distribute them to the applicable participating sites. Sites will be requested to send in copies of signed ICFs and other documentation for in-house review for all patients who have provided explicit consent for this to take place. This will be detailed in the Monitoring Plan.

12.4. Onsite Monitoring

Onsite monitoring will be carried out as required following a trial-specific risk assessment and as documented in the Monitoring Plan. Any monitoring activities will be reported to the research team at site and any issues noted will be followed up to resolution. Additional onsite monitoring visits may be triggered, for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required, the VITDALIZE UK Trial Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. The research team at site will allow designated BCTU staff access to source documents as requested. Appropriate staff at BCTU and the Sponsor will conduct any onsite monitoring in the UK.

12.5. Audit and Inspection

The PI will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The PI will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections.

12.6. Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the VITDALIZE UK Trial Office will notify the UK licensing authority on behalf of the Sponsor in writing of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a “serious breach” is a breach that is likely to affect:

- The safety or physical or mental integrity of the subjects of the trial
- The scientific value of the trial

Sites are therefore requested to notify the VITDALIZE UK Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the VITDALIZE UK Trial Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the VITDALIZE UK Trial Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action. Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the CI, Sponsor, Trial Management Group (TMG), Trial Steering Committee (TSC), the REC and the relevant

regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA. A copy is sent to the University of Birmingham Clinical Research Compliance Team and Medical University of Graz Governance Team at the time of reporting to the REC and/or relevant regulatory bodies.

13. END OF TRIAL DEFINITION

The end of trial will be 6 months after the last data capture[1]. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The VITDALIZE UK Trial Office will notify the MHRA and REC that the trial has ended within 90 days of the end of trial. Where the trial has terminated early, the VITDALIZE UK Trial Office will inform the MHRA and REC within 15 days of the end of trial. The VITDALIZE UK Trial Office will provide them with a summary of the clinical trial report within 12 months of the end of trial.

A copy of the end of trial notification as well as the summary report will also be sent to the Sponsor.

[1] 'Last data capture' is defined as being the last data capture for the whole trial (all participating countries).

14. STATISTICAL CONSIDERATIONS

14.1. Sample Size

The sample size for the multinational trial is based on the primary endpoint 28-day mortality. In the VITdAL-ICU trial, in the pre-defined subgroup with severe VDD, 28-day mortality rates of 36% (37/102) in the placebo group and 20% (20/98) in the vitamin D group were observed (51). The VITDALIZE trial has been designed to be powered to detect a smaller, but clinically relevant absolute mortality difference of 5% with a power of 80% or a 6% difference with 90% power with an assumed baseline mortality rate of 25% (close to the lower limit of the 95% CI of the 36% mortality observed in VITdAL-ICU). This corresponds to a clinically important relative risk reduction of between 20% and 24%. Using a fixed sample size design and a 2-sided log-rank test for equality of survival curves with a 2-sided alpha level of 5%, a sample size of over 1000 patients per group will be needed (total sample size of approximately 2200). The table below shows this, and varies the baseline event rate from 25% to 30% to illustrate that our assumptions are robust to modest variations in our assumptions.

Placebo 28-day all-cause mortality	**25%**		**30%**	
	80% power	**90% power**	**80% power**	**90% power**
VitD 28-day all-cause mortality	20%	19%	25%	24%
Hazard ratio	0.78	0.73	0.81	0.77
N = (per group)	1093	1002	1248	1149
Total number of events required	486	434	686	620
N = (total)	2186	2004	2496	2298

Accounting for a drop-out rate of approximately 10% yields a total sample size of N=2400 patients with the UK contributing 25% of the sample size with 600 patients. Loss to follow up in critical care trials for 28-day mortality is low and is approximately 3% in previously published critical care trials (51, 56, 57) so this 10% estimate of loss to follow up is also conservative.

14.2. Analysis of Outcome Measures

A separate Statistical Analysis Plan (SAP) will be produced by the Sponsor outlining the analysis of VITDALIZE, the UK specific outcomes will be appended to the SAP completed by the UK Statistician in collaboration with the UK CI. The SAP will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below. The primary comparison groups will be composed of those treated with vitamin D3 versus those treated with placebo.

Intention-to-treat (ITT) population: The primary analysis will be performed on the ITT population. The ITT population will include all patients who receive at least the loading dose of the trial medication. All patients included here will be analysed according to the treatment assignment during randomisation.

Per protocol population: The per protocol population will include all patients who received the loading dose and have a compliance >80%. Compliance is defined as self-reported percentage of doses ingested until day 90. Other protocol violations may also lead to exclusion of patients from the per protocol population. This will be discussed on an individual basis within the international trial's teams working on VITDALIZE.

Safety population: The safety analyses will be based on the treated set, which is defined as all randomised patients who receive at least 1 dose of trial medication. All patients will be analysed according to the treatment they received.

All available data will be used in the analyses and data summaries. There will be no imputation of any missing data. All outcomes will be adjusted for the baseline values (where available) and the stratification parameters (gender and centre). If covariate adjustment is not practical, then unadjusted estimates will be produced and it will be made clear in the output why this occurred, e.g. due to lack of model convergence.

14.3. Data analysis

14.3.1. General Aspects

All clinical and safety data collected for the VITDALIZE trial will be analysed with SAS v9.4 procedures. Data will be presented as summary tables and, where appropriate, as plots. Continuous data will be described by means, standard deviations, medians and upper and lower quartiles unless otherwise stated. The number of observations and minimum and maximum values will also be included. All descriptive summaries will be displayed to 1 more decimal place than actually measured. Categorical data will be summarized using frequencies and percentages.

14.3.2. Demographic and Baseline Characteristics

A summary of demographic, baseline and diagnostic characteristics, including relevant medical history will be presented by treatment groups using appropriate descriptive and inferential statistics.

14.3.3. Primary Outcome Measure

The primary outcome, 28-day mortality will be displayed using Kaplan Meier estimates of survival curves in each treatment. A mixed effects Cox Proportional Hazard model including

centre as a random effect will be fitted to obtain an adjusted hazard ratio and 95% confidence interval. For the UK arm only, a complier average causal effect (CACE) analysis will also be performed for the primary outcome. Details of the primary outcome analysis will be defined in the SAP approved by the Sponsor and approved by the international DMC prior to any interim analysis. The UK specific outcomes will be defined in a separate SAP that will describe all of the statistical analysis that will be undertaken for the UK arm only and appended to the Sponsor approved SAP.

14.3.4. Secondary Outcome Measures

ICU, hospital mortality, 90-day mortality and 1-year mortality will be analysed using the same methods as described for the primary outcome. For any other secondary outcomes that are continuous, these will be analysed using mixed effects linear regression model. The safety outcomes, (hypercalcemia on day 5, new kidney stones, self-reported falls, and fractures until day 90) will be analysed as binary variables and compared using a mixed effects binomial model.

14.3.5. Subgroup Analyses

The effect of high dose vitamin D versus placebo will be evaluated in the following *a priori* subgroups: i) patients with sepsis (admission diagnosis) vs non-sepsis (based on the evidence that vitamin D has antimicrobial properties that may benefit this population in particular (16); ii) kidney function, CKD 4 (eGFR<30mL/min/1.73m2) or lower vs higher (based on the possible effect of pre-existing CKD and VDD on increased mortality and alternate metabolism of vitamin D3 (cholecalciferol); iv) COVID-19 or Non-COVID-19 patients.

14.3.6. Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all trial patients; it is thus anticipated that missing data will be minimal. There will be no imputation of missing data for the purpose of the trial.

14.4. Additional Analysis in the UK Arm (Health Economic Evaluation)

The economic analysis will determine the costs and outcomes associated with treatment with high dose vitamin D, in comparison to placebo, in severely VDD critically ill adult patients admitted to ICU. If treatment with high dose vitamin D in severely VDD critically ill adult patients is effective in reducing mortality and improving morbidity, there are likely to be important cost implications for the healthcare sector, both in the short and longer term. The

primary base case analysis will therefore adopt a NHS / Personal Social Services (PSS) perspective in line with National Institute for Health and Care Excellence (NICE) guidelines (60).

14.5. Data Collection

Resource use data will be collected prospectively to estimate the costs associated with each of the trial arms (for the intervention and placebo). This will include: (1) the cost of screening critically ill patients for VDD. For example, the cost of the analyser (machine) to test for VDD, the costs of consumables associated with testing, the cost of the dose and other resource use; (2) costs experienced during the inpatient period, for example, ICU and hospital length of stay and other acute care costs; (3) costs associated with readmissions, Accident & Emergency (A&E) attendances, GP attendances and other NHS care; (4) social care costs. Information on unit costs or prices will be sourced to attach to each resource use item, to enable an overall cost per patient to be calculated (e.g. Unit Costs of Health and Social Care (60) and NHS Reference Costs (61).

Resource use data will be captured via a variety of mechanisms. Firstly, within the trial, the resource use and costs associated with screening and treating patients with high dose vitamin D, hospital and ICU length of stay will be captured via trial reporting mechanisms. The main focus will be on the differences in resource use between the 2 trial arms. NHS and social care costs will be captured via a questionnaire for trial patients at 28 days, 90 days and 12 months; this will include A&E visits, community nurse visits, readmissions, GP visits, social care costs and other NHS resource use. We will also undertake an analysis of Hospital Episode Statistics (HES) data at 12 months to analyse secondary care resource use in detail.

Alongside the clinical outcomes collected in the trial and in line with recommendations from NICE, data will also be captured that will allow quality-adjusted life years (QALYs) to be used as an outcome measure in the cost-effectiveness analysis(59). It is recommended that QALYs are calculated so that cost-effectiveness can be compared across disease areas. This will require changes in health-related quality of life (HRQL) to be captured for both trial arms. NICE recommends the use of EQ-5D-5L to measure HRQL. These questionnaires will be administered to compare changes in health-related quality of life for the 2 trial arms at baseline, 28 days, 90 days and 1 year. The outcomes of the survival analysis using Office for National Statistics (ONS) data will be incorporated as part of the health economic analysis.

14.6. Economic Analysis

In order to assess the costs and benefits of treatment with high dose vitamin D in comparison to placebo in severely VDD critically ill adult patients admitted to ICU, both a within trial analysis and a model-based economic analysis will be undertaken.

14.6.1. Within trial analysis

The within trial analysis will use the data collected within the trial, and so estimates of costs and benefits will relate to the initial period of 28 days, to reflect the primary outcome for the trial. Further analyses of costs and outcomes will be undertaken at 90 days and 12 months, based on the secondary outcomes associated with the trial. The data used for this analysis will primarily be the trial-specific resource use data and costs. The initial economic analysis will assess cost-effectiveness based on incremental cost per life gained at 28 days and 90 days reflecting the primary outcome of the trial. A secondary analysis of incremental cost per QALY gained over a 12-month period will also be undertaken in line with NICE recommendations. Initially, the base case analysis will be framed in terms of a cost-consequences analysis for the trial arms, and data will be reported in a disaggregated manner on the incremental cost and important consequences assessed in the trial.

14.6.2. Model-based analysis

If the trial shows that treatment with high dose vitamin D is effective in reducing mortality and improving HRQL, in comparison to placebo, it will be necessary to assess the cost-effectiveness of the intervention in the longer term. Therefore, if deemed necessary, based on the results of the trial, a decision-analytic model will be used to extrapolate costs and outcomes beyond the end of the trial and synthesise data on costs and outcomes from a range of sources (63). The model development process will use, as a starting point, other models developed for interventions to improve VDD in older people (e.g. (64, 65)). Assuming that a Markov model is found to be appropriate, it will be constructed using TreeAge Pro software. This is a widely-used software package ideally suited to the construction and analysis of Markov models. The evidence used in the model will be drawn from the trial and a comprehensive review of the literature. The literature review will include evidence on rates of hospital readmissions, residential care admissions and social care costs, and other longer term outcomes. The final model will compare the incremental benefits gained and costs treatment with high dose vitamin D, in comparison to placebo, in severely VDD critically ill adult patients admitted to ICU, over the lifetime of the patients where possible.

14.6.1. Presentation of results and sensitivity analyses

The economic evaluation will be conducted and reported in accordance with relevant guidelines (66, 67). Results will be presented using cost-effectiveness acceptability curves

(CEACs) to show the uncertainty surrounding the cost-effectiveness of the intervention, for a range of thresholds for cost-effectiveness (68). We shall use both deterministic and probabilistic sensitivity analyses (PSA) to explore the inherent uncertainty around the estimates employed in the evaluation. The choice of distributions for the PSA will be based upon current best practice in modelling. (69). For the longer-term analyses, discounting will be undertaken to reflect recommendations by NICE and the Treasury.

14.7. Planned Interim Analysis

1 interim analysis will be performed at inclusion of 50% (N=1200) of patients having their day 28 assessment completed or discontinuing the trial. This interim analysis is intended to test for efficacy on the primary outcome i.e. the trial will be terminated after the interim analysis, if the main question can already be answered at this interim analysis. Given the risks of false positive results with early stopping for benefit, statistical significance will be declared using small p-values established by O'Brien-Fleming boundaries on the primary outcome (if the p-value of the log rank test is smaller than 0.003, then the trial can be stopped early).

14.8. Planned Final Analyses

The final analysis of the main VITDALIZE trial shall be undertaken 6 months after all patient data capture (UK and International).

The analysis for VITDALIZE will occur once all patients have completed the 1-year follow-up and corresponding outcome data has been entered onto the trial database and validated as being ready for analysis. This will be specified in the SAP produced by the Sponsor (the UK specific outcomes appended to the SAP; see Section 14.2).

15. TRIAL ORGANISATIONAL STRUCTURE

15.1. Sponsor

The Medical University of Graz is the Sponsor for the VITDALIZE UK Trial.

15.2. Coordinating Centre (UK)

The Birmingham Clinical Trials Unit within the University of Birmingham will be the National Co-ordinating Centre for VITDALIZE UK.

15.3. Trial Management Group

The TMG will comprise the CI, other lead investigators (clinical and non-clinical) and members of BCTU. The TMG will be responsible for the day-to-day running and management of VITDALIZE UK and will convene at regular intervals.

15.4. International Trial Management Group

The membership of the International TMG will comprise the CI of each participating country, other co-applicants (clinical and non-clinical), and other country-specific Trial Management Group members as required. The International TMG will be responsible for disseminating key information of the VITDALIZE trial locally and will convene at regular intervals.

15.5. Trial Steering Committee

The role of the TSC is to provide overall supervision of the trial. The TSC will meet at least annually and will monitor trial progress and conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC). Further details of the remit and role of the TSC are available in the TSC Charter.

15.6. Data Monitoring Committee

Data analyses will be supplied in confidence to the international, independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further patients. The development and finalisation of the DMC charter is the responsibility of the Sponsor. The DMC will meet at least annually unless there is a specific reason to amend the schedule.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is

identified. The DMC will report directly to the international TMG and TSC as applicable who will convey the findings of the DMC report as appropriate e.g. TMG, MHRA, funders, and/or Sponsor. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise patient safety. The trial will stop early if the interim analyses shows differences between treatments that are deemed to be convincing to the clinical community.

15.7. Finance

The National Institute for Health Research (NIHR) Health Technologies Assessment (HTA) Programme is funding the UK arm of this trial (project number: 17/147/33).

16. ETHICAL CONSIDERATIONS

The VITDALIZE UK Trial forms part of an international trial collaborating with teams across Europe. The VITDALIZE UK Trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the United Kingdom (UK) Policy Framework for Health and Social Care Research 2017, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the General Data Protection Regulation (GDPR) 2018, and the EU Clinical Trials directive.

This trial will be carried out under a Clinical Trial Authorisation (CTA) in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the REC prior to circulation and the start of the trial. All correspondence with the MHRA and/or REC will be retained in the Trial Master File/Investigator Site File,

Before any patients are enrolled into the trial, the PI at each site is required to obtain Confirmation of Capacity and Capability. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the BCTU trials team.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

17. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with GDPR, 2018 and/or UK Data Protection Act 2018.

Patients will always be identified using their unique trial identification number and initials on the CRF and any correspondence with the VITDALIZE UK Trial Office. Patients will give their explicit consent for the movement of their consent form, giving permission for BCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process.

The research team at site must maintain documents not for submission to BCTU (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

BCTU will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer (the competent authority and Sponsor). Representatives of the VITDALIZE UK Trial Office and Sponsor may be required to have access to patient notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

18. FINANCIAL AND OTHER COMPETING INTERESTS

Fresenius Kabi will be providing the drug and intervention for VITDALIZE. However, they will have no involvement in the trial design and will not influence the management, analysis and dissemination.

19. INSURANCE AND INDEMNITY

The Medical University of Graz as Sponsor has agreed with the NCC, UoB, that the NCC take out and maintain, throughout the duration of the trial in the UK, clinical trial insurance solely for participants in the UK for the UK arm of the trial. The insurance provided by the NCC does not extend to any part of the study outside of the UK and does not cover the Sponsor. The NCC will obtain appropriate insurance, as required by applicable legal and regulatory requirements for claims that arise against the NCC. In addition, the NCC will remain liable for any negligent harm, claims, actions, or expenses resulting from or connected with negligence, breach, omission, or fault of the NCC and for the UK specific protocol.

The Sponsor is responsible for obtaining general liability insurance cover, as required by applicable legal and regulatory requirements for claims against the Sponsor. The Sponsor shall remain liable for any negligent harm, claims, actions, or expenses resulting from or connected with the negligence, breach, omission, or fault on the part of the Sponsor.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

20. AMENDMENTS

All amendments will be tracked in the VITDALIZE UK protocol. The decision to amend the protocol and associated trial documentation will be initiated by the TMG. The NCC will discuss and agree any amendments with the Sponsor. This includes deciding whether an amendment is substantial or non-substantial. The NCC will authorise any amendment for the UK as delegated by the Sponsor. Substantive changes will be submitted to REC, HRA and if required, the MHRA for approval. Once this has been received, R&D departments will be notified of the amendment and requested to provide local approval.

21. POST-TRIAL CARE

When the patient has completed follow-up or if they withdraw fully from the VITDALIZE UK Trial they will follow their normal standard of care pathway.

22. ACCESS TO THE FINAL TRIAL DATASET

The VITDALIZE UK Protocol will be made publicly available via both the VITDALIZE UK webpage, hosted by BCTU and subsequently published in an appropriate journal, in advance of the final data set. The overarching protocol has already been published in BMJ open (71).

The final data set itself will only be available to the direct UK VITDALIZE Trial Team, including the TSC, in the first instance. Requests for data generated during the VITDALIZE UK Trial will be considered by BCTU and Sponsor.

Only scientifically sound proposals from appropriately qualified research groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in absence of the CI) any of the following: the Trial Sponsor, the TMG, and TSC.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully anonymised unless the DSA covers transfer of patient identifiable information. Any data transfer will use a secure and encrypted method.

23. PUBLICATION POLICY

Our dissemination plan will ensure the findings from this trial influence health services policy to deliver public benefit. The trial is registered on the ClinicalTrials.gov website (Identifier: NCT03188796). The overarching trial protocol has been published (71) to ensure transparency in our methodology. An on-going update of the trial will be provided on a trial website. Trial progress in the UK will be communicated through NIHR and ICU networks. The VITDALIZE Trial primary and secondary outcomes will be published as part of the international collaboration, the additional UK specific outcomes will be published separately.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The success of the trial depends on the collaboration of doctors, nurses and researchers from across the trial sites, therefore the results of the trial will be reported first to trial collaborators/research teams. Our broad co-applicant group will ensure rapid comprehensive dissemination. The trial findings will be presented at national and international meetings with abstracts on-line. Presentation at these meetings will ensure that the results and implications quickly reach all of the UK intensive care community. This will be

facilitated by our investigator group, which includes individuals in executive positions in the UK Intensive Care Society. In accordance with the open access policies proposed by the NIHR we aim to publish the clinical findings of the trial as well as a paper describing the cost-effectiveness in the NHS setting in high quality peer-reviewed open access (via Pubmed) journals. This will secure a searchable compendium of these publications and make the results readily accessible to the public, health care professionals and scientists. A final report will also be published in the NIHR HTA journal. We will actively promote the findings of the trial to journal editors and critical care opinion leaders to ensure the findings are widely disseminated (e.g. through editorials and conference presentations) and are included in future guidelines. In addition, we will use Free Open Access Medical Education (FOAMed) resources to ensure as wide an audience is reached.

With the help of our PPI representative, a lay person's summary will be sent to local and national patient support and liaison groups notably the Critical Care Patients and Relatives Committee (PatRel) and the Intensive Care Unit Support Teams for Ex-Patients (ICUsteps). We will also create a short video and info graphic for the trial website. A report of the trial findings will be sent to the INVOLVE registry (an open access database which registers research health care projects involving members of the public as partners in the research process). Following peer reviewed publication, appropriate key findings will also be posted on institutional websites available to the public. In addition, the most significant results will be communicated through press releases to ensure dissemination to research patients and the broader public. Through its media teams, the ICS and UoB have achieved recent successes in combining trial publication of MRC, British Lung Foundation and NIHR supported studies with simultaneous and extensive national "prime time" radio, TV, and social media coverage.

Any secondary publications and presentations based on UK specific outcomes will be prepared by Investigators must be reviewed and approved by the TMG. If secondary publications and presentations are based on the primary and secondary outcomes of the VITDALIZE Trial, these will be reviewed and approved by the international TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham, BCTU, the Medical University of Graz and Fresenius Kabi. Intellectual property rights will be addressed in the Clinical Trials Agreement between Sponsor and site.

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25. APPENDICES