The Effect of High-Dose Vitamin D3 on 28-Day Mortality in Adult Critically Ill Patients with Severe Vitamin D Deficiency
The UK Arm of a Multi-Centre, Placebo-Controlled Double-Blind Phase III Randomised Controlled Trial

VITDALIZE UK

LEGAL REPRESENTATIVE INFORMATION SHEET

We would like to invite you to give consent on behalf of your relative/friend or a patient to take part in our research trial

This is because they are currently unable to consent for themselves and in these situations, the law allows a representative to provide consent of their behalf.

Before you decide, we would like you to understand why the research is being done and what the trial would involve. A member of our team will go through this information sheet with you and answer any questions. You can talk to others about this if you wish and please ask us if anything is not clear.

What is the purpose of the trial?

The aim of this research trial is to see if giving high dose of vitamin D in critically ill patients can improve survival, length of hospital stay and quality of life.

Vitamin D deficiency (low vitamin D levels) is common (around 70%) in patients who are unwell. This has been found to be related to an increased risk of infection and death. There are many reasons why patients are poorly and those who do survive can suffer long-term health problems in the future.

It is not known whether being vitamin D deficient is a cause or effect of being unwell, and research into whether vitamin D is useful is not clear. The reason we are doing this trial is because there are no guidelines to measure and treat patients admitted to intensive care who are critically ill and vitamin D deficient. Vitamin D is cheap, and easily available, and if using vitamin D is found to help, can be quickly put into standard practice in hospitals.

Why has your relative/friend/patient been invited? Can I say no?

You have been invited to give consent for your relative/friend/patient to be a part of this trial because they are expected to be in intensive care for more than 2 days, are critically ill and may have vitamin D deficiency.

VITDALIZE is an international trial that aims to recruit 2400 patients from across Europe. Countries that are participating include the UK, Austria, Germany and Belgium. The UK part of VITDALIZE (VITDALIZE UK) aims to recruit 600 patients into the trial.

It is up to you to decide whether to give consent on behalf of your relative/friend/patient to take part in VITDALIZE UK and if you do give consent, will be given this information sheet to keep and be asked to sign a consent form. This will stay on record in your relative/friend/patients trial file, be noted in their medical records, and be available for review by the research team, representatives of the Sponsor, regulatory authorities, or from the

NHS Trust, where relevant to their participation in this research trial. A copy will also be held at Birmingham Clinical Trials Unit, University of Birmingham and one will be made for you to keep. If you decide that you do not want them to take part, their normal treatment will not be affected in any way and they will continue to be cared for as they would normally.

Are there any benefits to taking part?

Although there may be no direct benefits to your relative/friend/patient taking part in this trial, the results of the trial will lead to the best treatment being offered to patients who are unwell and are vitamin D deficient.

What will happen to my relative/friend/patient if they take part and how do they receive the medication?

Sometimes we do not know which way of treating patients is best. To find out, we need to compare different treatments by putting patients into groups with each receiving a different treatment. To make the groups fair, each patient will be put into a group by chance (randomly). Your relative/friend/patient will receive either a high dose of vitamin D or a placebo (dummy drug); this would be given orally or by their feeding tube. They will then receive a daily dose of either vitamin D or placebo for up to 90 days, which will be taken orally (by mouth) or be given through an existing feeding tube. If they are discharged during this time, they will be given the remaining doses to take at home. Trial medication should be taken regularly as directed and your relative/friend/patient should continue to take all of their other regular medication too. The VITDALIZE UK Trial is a blinded trial; this means that no one will know what your relative/friend/patient has received. With your consent, the research team will inform you and/or your relative/friend/patient of what was received once the trial has been completed.

Screening

If you believe that your relative/friend/patient would be interested in taking part in the VITDALIZE UK Trial, they will first need to be screened to see if they are eligible to take part. This means the research team will need check if they have severe vitamin D deficiency.

If your relative/friend/patient is screened for inclusion in the VITDALIZE UK Trial the research team will:

- Review their medical history
- Take a blood sample (approximately 5-10 ml, equivalent to 2 teaspoons) to measure vitamin D level

If a blood sample has already been taken as part of your relative/friend/patients usual care today, they may not need to have another one. This will be discussed with you at the time.

Once the results of the screening tests are available, the research team will tell you whether your relative/friend/patient is able to participate in the VITDALIZE UK Trial.

What happens if the results show that my relative/friend/patient is *not able* to take part?

If the results show that your relative/friend/patient is not able to participate in the VITDALIZE UK Trial, the research team will let you know as soon as practically possible and explain that their care will continue as part of routine practice.

What happens if the results show that my relative/friend/patient is *able* to take part?

If the results show that your relative/friend/patient is able to take part in the VITDALIZE UK Trial, the research team will randomise them into the trial. You will be informed as soon as practically possible, after this has taken place.

How many visits are there and how long will it take?

Your relative/friend/patient will complete up to 7 visits (days 0, 5, 12, 28, 90, and 1 year), after they are randomisation into the trial. While they are in hospital, information will be gathered from their medical records.

At the beginning of the trial, your relative/friend/patient will be given either a high dose of vitamin D or placebo (day 0). They will then begin taking a daily dose of either vitamin D or placebo from day 1 to day 90.

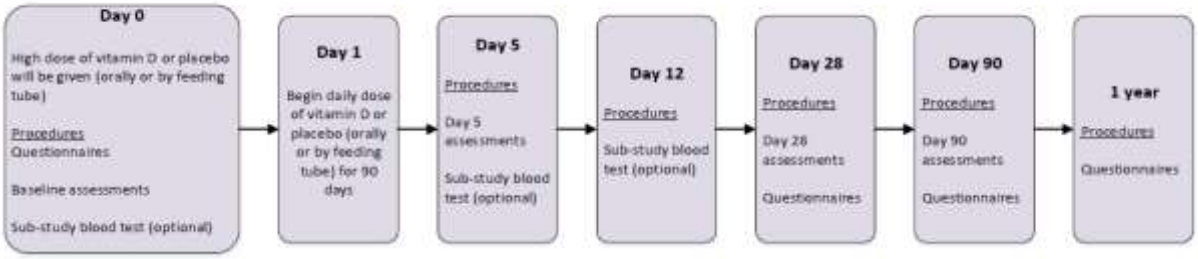
On day 5 (if your relative/friend/patient is still in hospital), the research team will take some more blood (10-20 ml, the equivalent to one tablespoon), this is to see how they are responding to treatment. Where possible, this will be taken during their standard blood tests. On rare occasions that this cannot be done, another blood test may need to be taken.

Answering some questions on your relative's/friend's behalf

Throughout the course of the trial your relative/friend may not be able to answer some of the questions that we need to ask because they are still unwell. If this happens, we would like to ask you a few questions about your relative's/friend's health. If you agree, the research team will contact you (either in person if you are visiting your relative/friend in hospital or by telephone/videocall), on days 0, 28, 90 and at 1 year. This should take no longer than 20 minutes.

As part of the VITDALIZE UK Trial, you will be asked to consent for your relative/friend/patient to provide some optional blood samples at up to 3 additional time points. This would be for future approved research assessing the effects of vitamin D treatment on vitamin D pathway and markers of immune function. This would mean providing blood samples (25-30 ml; equivalent to 2 tablespoons) on days 0, 5 and 12. The samples will be collected by the research team and initially stored at the hospital; they will then be transported to the University of Birmingham for storage and analysis by the Chief Investigator. More information relating to what happens to your samples can be found below in 'what will happen to any samples I give?' If you would prefer that your relative/friend/patient not provide these blood samples, it will not affect their participation in VITDALIZE UK.

Trial assessment flow chart



There may be some situations, during your relative/friend/patients participation in the trial where they will need to be taken to another hospital to receive specific treatment for their condition. If this happens, with your consent, we would contact the hospital where your relative/friend/patient are receiving treatment and ask them to provide some information about how they are getting on. Doing so would help us better answer the research question, but it is optional and you can say no at any time.

Are the treatments and tests safe?

High dose vitamin D can have some side effects, those reported include:

- Increased level of calcium in the blood and urine
- Digestive issues such as constipation, flatulence, nausea, stomach-ache, and diarrhoea

We will carefully monitor any side effects and there will be an independent safety committee that will oversee the trial to make sure that it is safe to continue taking the trial medication.

What happens when the research trial stops?

After the trial has finished, your relative's/friend's/patient's clinical care will revert to the current standard care for patients who have severe vitamin D deficiency. The research team will inform your relative/friend/patients GP that they had severe vitamin D deficiency and were randomised into the VITDALIZE UK Trial.

What if new information becomes available?

Sometimes we get new information about the treatments being studied. If this happens, the research doctor will tell you and/or your relative/friend/patient and discuss whether they should continue in the trial. If the trial is stopped for any other reason, we will tell you and/or your relative/friend/patient and arrange their continuing care.

What will happen if I do not want my relative/friend/patient to carry on?

You can request that your relative/friend/patient is withdrawn from the trial at any time without giving a reason. If they are withdrawn, the information collected up until their withdrawal may still be used as part of the trial analysis.

What if there is a problem?

If you have a concern about any aspect of this trial, you should ask to speak to the researchers who will do their best to answer your questions **(see contact details on the last page)**. If you remain unhappy and wish to complain formally, in England and Wales you can do this by contacting the Patient Advice and Liaison Services (PALS), in Scotland you

contact the Patient Advice and Support Service (PASS) and Northern Ireland Patient and Client Council.

Contact details are: << INSERT LOCAL DETAILS HERE>>.

Insurance and indemnity arrangements for VITDALIZE UK

On behalf of the Sponsor, The Medical University of Graz, The University of Birmingham will act as the National Coordinating Centre (NCC) and will oversee the management of the VITDALIZE Trial in the UK. In the unlikely event that something does go wrong and your relative/friend/patient is harmed during the research due to someone's negligence, then you and/or and your relative/friend/patient may have grounds for legal action and compensation against The University of Birmingham but you and/or and your relative/friend/patient may have to pay your legal costs. The normal NHS complaints mechanisms will still be available to you and your relative/friend/patient if appropriate.

The University of Birmingham has taken out clinical trial insurance for participants in the UK for the duration of the trial. The insurance will cover legal liability or no fault insurance to assist your relative/friend/patient if a claim is made.

The Sponsor is responsible for obtaining general liability insurance cover for any claims against them.

Will my details be kept confidential?

Health and care research should serve the public interest which means that we have to demonstrate that the research serves the benefits of society as a whole. We do this by adhering to the regulations that govern clinical trials in the UK.

All information collected about your relative/friend/patient for this trial will be subject to the General Data Protection Regulation (GDPR) and Data Protection Act 2018 for health and care research and will be kept strictly confidential. Data collected in the UK for the VITDALIZE UK Trial by the NCC or UK hospitals is the exclusive property of the NCC. The NCC will be using information from your relative/friend/patient medical records in order to undertake this trial and will act as the data processor and data controller. This means that the NCC are responsible for looking after your relative's/friend's/patient's information and using it properly. The NCC and the NHS will keep identifiable information about your relative/friend/patient for at least 25 years after the trial has finished to allow the results of the trial to be verified if needed.

All information collected by the NCC will be securely stored in the VITDALIZE UK Trial Office at the University of Birmingham on paper and electronically, and will only be accessible by authorised personnel. The only people in the University of Birmingham who will have access to information that identifies your relative/friend/patient will be people who manage the trial or audit the data collection process. There is an open-access VITDALIZE UK Trial website www.birmingham.ac.uk/vitdalizeuk that contains information about the trial. No identifiable information about your relative/friend/patient will be available on this website.

The NHS will use your relative's/friend's/patient's name and contact details to contact you and/ or your relative/friend/patient about the research trial and make sure that relevant information about the trial is recorded for your friend's/relative's/patient's care, and to oversee the quality of the trial. With your permission, a copy of your signed consent form will also be sent to the University of Birmingham as the NCC in the UK for this trial.

At the VITDALIZE UK Trial Office, a unique trial number will identify your relative/friend/patient. In routine communication between your friend's/relative's/patient's hospital and the VITDALIZE UK Trial Office, your relative/friend/patient will be identified by trial number, initials and date of birth. Data may be provided to the VITDALIZE UK Trial Office on paper or electronically.

By taking part in the trial, you will be agreeing to allow research staff from the VITDALIZE UK Trial Office to look at your relative's/friend's/patient's trial records, including your relative's/friend's/patient's medical records. It may be necessary to allow authorised personnel from government regulatory agencies (e.g. Medicines and Healthcare Products Regulatory Agency (MHRA), the Sponsor, the NCC and/or NHS bodies to have access to your friend's/relative's/patient's medical and research records. This is to ensure that the trial is being conducted to the highest possible standards.

The data collected for all participants in the VITDALIZE UK Trial will be used by the Sponsor (Medical University of Graz) and international collaborators in the European Union (EU) in compliance with the current data transfer regulations. The data transferred will be pseudo-anonymised and comprise your relative's/friend's/patient's trial number, age and sex.

From time to time, we may be asked to share the trial information (data) we have collected with researchers running other studies in this organisation and in other organisations so that they can perform analysis on the data to answer other important questions about critical illness and vitamin D deficiency. These organisations may be universities, NHS organisations or companies involved in health research and may be in this country or abroad. Any such request is carefully considered by the trial researchers and will only be granted if the necessary procedures and approvals are in place. This information will not identify your relative/friend/patient and will not be combined with other information in a way that could identify them. The information will only be used for the purpose of health research and cannot be used to contact you or your relative/friend/patient or to affect their care. It will not be used to make decisions about future services available to your relative/friend/patient, such as insurance. Under no circumstances will your relative/friend/patient be identified in any way in any report, presentation or publication arising from this or any other trial.

To allow accurate follow up of all participants it will be necessary for the VITDALIZE UK Trial Office to contact other UK NHS bodies to provide information about your relative's/friend's/patient's health. This would mean that the VITDALIZE UK Trial Office would use some of your friend's/relative's/patient's personal identifiers (date of birth, NHS number (CHI number for patients in Scotland, H&C numbers for patients in Northern Ireland), trial number, age and sex. Your relative's/friend's/patient's information will be held and maintained by central UK NHS bodies such as NHS digital.

All individuals who have access to your relative's/friend's/patient's information have a duty of confidentiality to you and your relative/friend/patient.

Your rights to access change or move their information is limited, as we need to manage their information in specific ways in order for the research to be reliable and accurate. To safeguard your friend's/relative's/patient's rights, we will use the minimum personally identifiable information possible. Under the provisions of GDPR 2018, you have the right to know what information the VITDALIZE UK Trial Office has recorded about your relative/friend/patient. If you wish to view this information or find more about how we use this information, please contact Legal Services at the address below. Please note that a small fee may be payable to retrieve this information.

Legal Services University of Birmingham Edgbaston Birmingham, B15 2TT

Involvement of your relatives/friends/the patient's family doctor?

Your friend's/relative's/patient's GP will be informed of their participation in the trial. By consenting on behalf of your relative/friend/patient to take part, you agree to us sharing their progress in the trial with their GP, as needed for their clinical care.

What will happen to any samples my relative/friend/patient provides?

If you consent for your relative/friend/patient to take part in the trial, we will take a blood sample to see if your relative/friend/patient has vitamin D deficiency (hospitals do not currently screen for this in the UK). These samples will be used and tested at the hospital and once the test is complete, the sample will be disposed of.

If you agree for your relative/friend/patient to having additional blood tests taken, the research team will take up to 3 further blood samples. These will firstly be stored at the hospital where your relative/friend/patient is being treated and will then be transferred to the University of Birmingham for analysis and storage by the Chief Investigator of the VITDALIZE UK Trial. The samples will be pseudo-anonymised labelled using your friend's/relative's/patient's trial number, date and time point (e.g. visit 1) upon arrival at the University of Birmingham. The results may be shared with collaborators involved in the VITDALIZE UK Trial at the end of the trial in a pseudo-anonymised way (trial number, date and time point). Once the samples have been analysed the samples will be disposed of.

What will happen to the results of the research?

At the end of the trial, we will report results to the funder of the research and publish them in appropriate academic and professional journals and at conferences. We will contact you and/or your relative/friend/patient with the results of the trial once it is finished. The publications are made available to the general public on websites such as the NIHR, ClinicalTrials.gov, ICU networks, INVOLVE Clinical Research Ambassador Group, PubMed, open access Medical Education (FOAMed), charities such as the Intensive Care Unit Support Teams for Ex-Patients (ICUsteps) and the Critical Care Patients and Relatives Committee (PatRel), should you and/or your relative/friend/patient be interested. There will also a Patient and Public Involvement (PPI) dissemination event to discuss the findings. Your relative/friend/patient will not be identified in any publication.

Who is organising and funding the research?

VITDALIZE UK is funded by the National Institute for Health Research Health Technology Assessment Programme (Project Number: 17/147/33). It is sponsored by the Medical University of Graz, Austria and is being organised and run on their behalf by the Birmingham Clinical Trials Unit, located at the University of Birmingham in the UK.

No member of the research team are being paid for including your relative/friend/patient in this trial.

Who has reviewed the trial?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This trial has been reviewed and given favourable opinion by South Central – Oxford C Research Ethics Committee.

Key points about this research:

Thank you for taking the time to read this information leaflet and for considering taking part in this research trial.

If you have any questions, please contact the trial research nurse on

<INSERT CONTACT DETAILS HERE>

Alternatively, you can contact the Chief Investigator for the research trial:

<INSERT CONTACT DETAILS HERE>