BEST-D
Biochemical Efficacy and Safety Trial of Vitamin D

INFORMATION LEAFLET

AN INVITATION TO JOIN A HEALTH RESEARCH STUDY

BEST-D

Biochemical Efficacy and Safety Trial of Vitamin D

This is an invitation to join a research study on vitamin D.

Please spend a few minutes reading this leaflet and feel free to discuss it with friends, relatives or the research team. It is up to you to decide whether or not to take part in the study. A summary of the study is provided on the back page of this booklet.

Part 1 of this leaflet tells you the purpose of this study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

For contact details, see overleaf

British Heart Foundation

UNIVERSITY OF OXFORD

If any aspect of the study is not clear,
or if you would like more information, please contact:

Dr Harold Hin,
or one of the BEST-D study nurses at

Hightown Surgery,
Hightown Gardens,
Banbury
OX16 9DB

Telephone: 01295 270722

or the BEST-D study coordinating team at CTSU
(details below).

The study is coordinated by

Clinical Trial Service Unit (CTSU),
University of Oxford,
Richard Doll Building,
Old Road Campus,
Roosevelt Drive,
Oxford
OX3 7LF

Email: bestd@ctsu.ox.ac.uk
24-hour FREEFONE 0800 585323

Ethics committee: South-Central REC Oxford-B (reference: 12/SC/0243)
Protocol: BESTD protocol version 1.1:2012-06-11

Vitamin D and health

Vitamin D helps the body to absorb calcium and phosphorus from the diet and is important for keeping bones healthy. Vitamin D is mainly produced in the skin in response to sunlight. However, many people in Britain do not get enough sun exposure to maintain what are believed to be healthy vitamin D levels throughout the year. Only small amounts of vitamin D are found in food, mainly in liver and oily fish. Some scientists think that low blood levels of vitamin D over a long period may cause osteoporosis (thinning of the bones) and also increase the risk of heart disease and cancer, but this is not certain.

Osteoporosis is common in older people and makes bones fragile and more likely to break causing fractures. This can lead to broken hips and back pain. People in northern Europe have more fractures than people in southern Europe, possibly due to vitamin D deficiency. Vitamin D is not routinely given to prevent fractures, because there is not enough evidence that it works. The results of previous trials of vitamin D for prevention of fractures have not given clear answers. One reason for this might be that the doses of vitamin D studied in previous trials may have been too low to maintain healthy bones and to show other health benefits in older people.

This study aims to find out what daily dose of vitamin D is needed to maintain healthy blood levels of vitamin D in older people in Britain. The doses of vitamin D are 5 to 10 times higher than those used in most previous trials. We want to see if these doses are effective and safe when taken over one year. However, much higher doses than those being given in this study have been safely administered to people with vitamin D deficiency. After this study, we will know what dose is best to use in a much larger trial to find out if long-term vitamin D treatment strengthens bones making them less likely to break and improves other health conditions.

PART 1

What is the purpose of the study?

The aim of this study is to find out the daily dose of vitamin D needed in older people to maintain blood levels of vitamin D similar to those seen in healthy younger people at the end of the summer months. We will use this information to plan a much larger study of this dose of vitamin D to see whether several years of such treatment can prevent fractures and heart disease.

Why have I been invited?

You are being invited to participate in the study because you are over the age of 65 years, and live in or around Banbury where the study is taking place. Your General Practitioner has agreed to your invitation.

Do I have to take part?

No, taking part is entirely voluntary. The study nurse will go through this information leaflet with you to confirm that you understand what the study involves. If you do decide to take part, you will be asked to sign a consent form. If you do take part, you are free to withdraw from the study at any time without giving a reason and this will not affect your medical care in any way.

What will happen to me if I take part?

If you decide to join the study you will be asked to take two small capsules daily for one year. Each capsule contains either 50 micrograms (mcg) of vitamin D or plain corn oil which is used as a dummy or placebo capsule. We hope to include about 300 older people in this study with 100 people taking each dose (100 mcg or 50 mcg vitamin D or placebo).

If you choose to join the study, the dose that you would take will be decided randomly, like tossing a coin. This helps to make sure that the groups are as similar as possible except for the dose of vitamin D being taken. Neither you, nor the research nurse or doctor will know which treatment you are taking. This information will be stored securely on a computer at Oxford University and can be made available to your doctors if medically necessary. This is known as a double-blind randomized trial.

The study involves a study nurse visiting you at home on three or four occasions over one year and a single visit to Hightown Surgery at the end of the year. An appointment for a study nurse to visit will be made by telephone. The first visit will take about one and a half hours, but the 6 and 12 month visits should last less than one hour.

Study visits

At the first visit, the nurse will ask about your medical history, diet and use of any prescription or over-the-counter drug treatment. This information will be entered directly onto a computer.

- If you are suitable for the study and interested in taking part, the nurse will explain what is involved and give you a chance to ask any questions. If you are willing you will be asked to sign a Consent Form and given a copy to keep.

- The nurse will measure your height, weight and hand-grip strength, blood pressure and a measure called “arterial stiffness”. Arterial stiffness is measured as part of taking your blood pressure and also by using a finger probe (a small clip-on device); both are simple and painless.

- The nurse will take a 30ml blood sample (about 2-3 tablespoonfuls) to measure blood levels of vitamin D and other markers relevant to health and disease. One of the blood samples will be

used to test genetic markers in future analyses. You are free to opt out of participation in any genetic analyses and you can indicate this on the consent form.

- The nurse will then give you two bottles of study treatment and ask you to take one capsule from each bottle every day. The capsules are small and contain either 50 mcg of vitamin D, or plain corn oil without vitamin D (ie, dummy capsules). You will be given enough capsules to last about 6 months.

At the end of the visit you will be given an appointment for the next visit. The information collected by the study nurse on the computer will be transferred to the Clinical Trial Service Unit at Oxford University where it will be stored securely in a database.

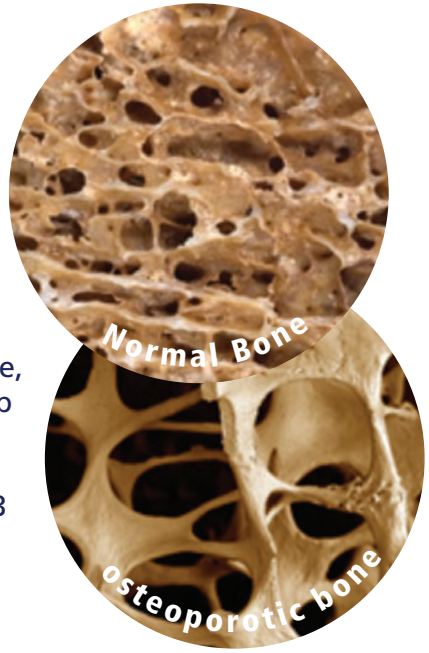
One month visit for 100 participants

Some participants will be asked to have an extra blood sample (about two tablespoonfuls) collected at one month after the first visit. This visit should only take about 15 minutes.

6 and 12 months visit

About 6 and 12 months after the first visit, the nurse will visit you at home again. You will be asked about any illnesses, falls or hospitalizations since you were last seen and a few questions about your physical activity and mood. In addition, the nurse will:

- measure your blood pressure, arterial stiffness and hand-grip strength;
- take a blood sample (about 2-3 tablespoonfuls);



- check how many of the study capsules you have taken; and
- at the 6 month visit provide a new 6-month supply of study treatment.

After the final visit, the nurse will arrange an appointment for you to attend the Hightown surgery in Banbury to have your heel and wrist bone density measured. These measurements take just a few minutes and are painless. You will be offered travel expenses to attend the surgery.

The study nurse will telephone at about 3 and 9 months after the first visit to check that you are okay and to remind you to take the capsules regularly.

What will I have to do?

Your main responsibility will be to take the capsules regularly and let the research team know if you have any problems related to the study. All your other treatments and daily activities can continue as usual.

What is the substance being tested?

The substance being tested is vitamin D, in the form of cholecalciferol (also known as vitamin D3), taken by mouth. The dose of vitamin D used in this study (either 100 mcg or 50 mcg daily) is higher than the doses used in previous studies. However, some studies have safely used a higher dose of 2500 mcg (all in one dose) of vitamin D given every few months for several years. Millions of people around the world take vitamin D supplements which can be easily bought over-the-counter and are considered safe, but the typical doses are only 10 to 20 mcg daily.

What are the side effects and risks of taking part?

Very rarely, a high intake of vitamin D leads to high blood levels of calcium, which can cause people to feel unwell. Typically, they become thirsty or pass more urine than usual, feel sick or vomit, or have dizziness or headaches or become confused. However, any symptoms should disappear as soon as the vitamin D is stopped. Nevertheless, the doses of vitamin D used in this study are thought to be safe and

STUDY TIMETABLE

First visit from study nurse
Nurse checks your suitability, records clinical measurements and collects a blood sample. If you agree to take part, you will be asked to start taking two study capsules daily for one year.

Second visit for about one third of participants at one month
About 100 participants will be asked to provide a blood sample after one month of study treatment.

6-month visit from study nurse
Participants will be visited at home by a study nurse for clinical measurements, blood collection and to supply further capsules.

12-month visit from study nurse
Participants will be visited at home by a study nurse for clinical measurements and blood collection.

Visit to Hightown surgery
Participants will visit Hightown surgery for a bone density scan and to have additional measurements of physical function.

Total study duration: 12 months

Participants are selected randomly (by chance) to receive either 100mcg, or 50 mcg vitamin D or matching dummy capsules.

not expected to raise blood calcium levels above the normal range. In the unlikely event of your becoming unwell, your calcium level will be checked. If at any time you think you are having side effects from the study medication, you can contact Dr Hin, or one of the study nurses, at Hightown Surgery (01295 270722) or one of the CTSU doctors for advice (24-hour FREEFONE 0800 585323).

What are the risks of radiation in this study?

Around the time of the final visit, you will be invited to attend Hightown surgery for some additional tests, including a bone scan of your heel and wrist bones. The DEXA scan of your wrist and heel bones uses a very small dose of X-ray radiation. The dose of radiation you will receive will be approximately equivalent to the radiation you would get if you were to spend two hours in Cornwall, where background radiation is higher than elsewhere in Britain.

What are the effects of other treatments on taking part?

If you have already been diagnosed with osteoporosis and are taking treatment for it, then you will not be suitable to take part in BEST-D. If you are taking drug treatment for osteoporosis or pills containing more than 10 mcg of vitamin D daily, you will not be able to take part. If you have a history of high blood levels of calcium, overactive parathyroid gland, lymphoma, sarcoidosis, or tuberculosis, you should not take part. Also, if you had a history of a kidney or bladder stone, you should not take part.

What are the possible benefits of taking part?

It is likely that you will not feel any different from usual. It is possible you may feel better. The information gathered from this study will help guide doctors in their treatment of people with low vitamin D and help in deciding a suitable vitamin D dose for testing in a large future study.

What happens at the end of the study?

At the end of the study we will let you and your GP know the results. No further capsules will be provided. The results of the study will be published in a medical journal. You will not be identified individually in any report.

Will my details be kept confidential?

Yes. All information collected about you for the study will be kept confidential. Personal information, including your name and address, along with the information from the study visits and blood test results will be transferred to the coordinating office at the Clinical Trial Service Unit, at Oxford University, where it will be stored on secure computer servers which are protected by firewalls and in a secure building. Personal and clinical information are stored separately linked by a unique number. Access to study information is restricted to authorized study personnel on a need to know basis only, and is controlled by usernames and passwords.

The study staff may seek information from your GP about any serious illnesses that you develop. Any information received will be used in confidence, only for medical research and audit purposes. Authorised people from regulatory agencies, the Research Sponsor and NHS bodies may look at the study information to ensure that the study is being carried out correctly but will be bound by rules of confidentiality.

If the information in Part 1 has interested you, and you are thinking about taking part, then please read Part 2 of this Information Leaflet.

PART 2

What if new information becomes available relevant to the study?

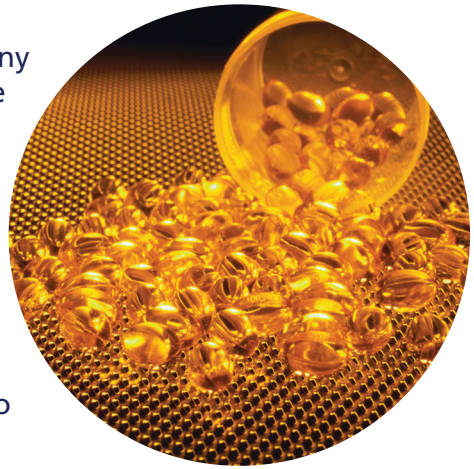
If any relevant new information becomes available about vitamin D during the course of the study, we will let you and your doctor know. You may also wish to discuss relevant information with the study team. You can then consider whether, or not, you wish to continue in the study. A study doctor is available via the 24-hour FREEFONE service if either you or your GP would like to discuss any new information.

What will happen if I want to stop participating in the study?

You are free to stop taking the study capsules at any time. If you wish to stop, then please call one of the study team. However, even if you do stop taking the capsules we would like, if possible, to keep in contact with you at least by telephone until the study is completed to find out how you are getting on. We would also like to be able to use any information about you already collected.

What if there is a problem?

If you want to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Dr Hin by telephone (01295-270722), or by email (haroldhin@hotmail.com). Alternatively, you may wish to call the coordinating team at CTSU using the 24-hour FREEFONE service (0800-585323). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure at your surgery or the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865-572224 or the head of CTRG, email heather.house@admin.ox.ac.uk.



The University has arrangements in place to provide insurance against harm arising from participation in the study for which the University is the Research Sponsor. NHS indemnity operates in respect of the clinical treatment with which you are provided. You would retain the same rights of care as any other patient treated in the National Health Service.

What will happen to any samples that I give?

Blood samples taken will be used to check blood levels of vitamin D and other substances that are related to the action of vitamin D and for central storage. Blood samples are identified by a unique number linked in the computer to other study information. You will be asked if you are willing to allow storage of blood samples for future analyses related to the study (including genetic markers). No genetic analyses will have any identifiable information. The results of genetic tests will not be made available on any individual participants.

Will any genetic tests be done?

Genetic tests will be done to look for genetic markers associated with vitamin D and immunity. You will be asked to indicate your explicit agreement for genetic tests on the Consent Form. In the genetic analyses, you will not be identifiable. The results of genetic tests will not be made available on any individual participants.

What will happen to the results of the research study?

The results of this study will be published in a scientific journal. No individual participant would be identified in any publication.

Who is organising and funding the research?

This study has been designed and coordinated by Oxford University's Clinical Trial Service Unit (CTSU) and will be supervised by Dr Harold Hin, General Practitioner (GP), Hightown Surgery in Banbury. Dr Hin

will oversee recruitment of study participants from Hightown Surgery (and, if necessary, from other nearby GP practices). Your GP will be aware of your participation. You should also tell any other doctors treating you about taking part in the study. The vitamin D and placebo treatment is provided free of charge by Tishcon Corporation, New York, USA. The study is being funded by the University of Oxford and the British Heart Foundation.

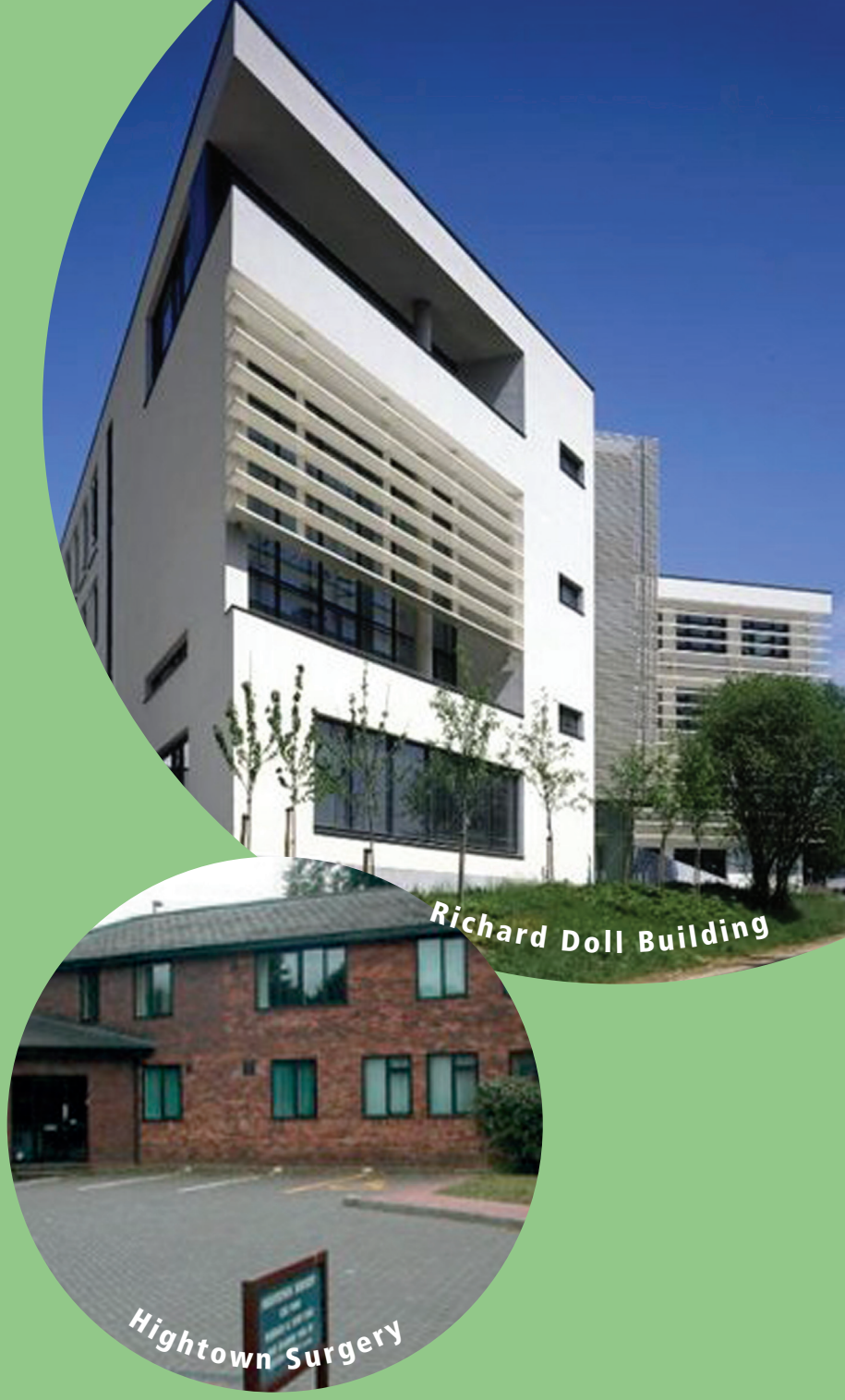
Who has reviewed the study?

The study protocol has been designed by researchers and doctors based at the CTSU, University of Oxford, in collaboration with Dr Hin at Hightown surgery. The study protocol has been reviewed and approved by an independent Research Ethics Committee which includes people from outside the medical profession. The study has been given a favourable opinion for conduct by the South-Central Research Ethics Committee-Oxford B (ref:12/SC/0243).

I am interested in participating; what should I do?

We are delighted you would like to consider participating in the study. Please indicate your interest on the enclosed reply form and return it to Hightown Surgery using the freepost envelope. You will then be contacted by someone from the GP practice to guide you through the next steps.

THANK YOU FOR TAKING THE TIME TO READ THIS LEAFLET.
Please keep this information leaflet for your own records.



Summary of invitation

Vitamin D: A Comparison of 100 mcg daily, 50 mcg daily, and placebo

- Vitamin D helps the body to absorb calcium and phosphorous and is important for keeping bones healthy. It may also have other health benefits.

- Low blood levels of vitamin D are common in older people especially in the winter.

- It is not clear whether vitamin D supplements should be used routinely to increase vitamin D levels. The purpose of this study is to find out what daily dose of vitamin D is needed by older people to keep vitamin D levels at the peak summer levels seen in younger adults.

- One third of those taking part will be given 100 mcg vitamin D daily; one third will be given 50 mcg vitamin D daily, and one third will have dummy capsules which look the same. Neither you, nor the study nurse or your doctors, will know which treatment you are on, this will be decided randomly (like tossing a coin).

- You will be asked to take two capsules of study treatment daily for one year and see the study nurse on at least three occasions over this period.

- The results of BEST-D will help with planning of a large study to test whether long-term vitamin D treatment protects against osteoporosis and other chronic health conditions.

If you have any questions about the study, please call:
Dr Harold Hin or the study nurses at Hightown Surgery
on 01295 270722 or 24-hour FREEFONE
0800 585323 (BEST-D coordinating team at CTSU)
bestd@ctsu.ox.ac.uk

THANK YOU FOR YOUR HELP