THE UNIVERSITY OF BRITISH COLUMBIA

Department of Medical Genetics

CHILDREN'S & WOMEN'S HEALTH CENTRE OF BRITISH COLUMBIA

Participant Information Form

for

A clinical study of vitamin D in adults with NF1

Full title: *A Phase II Trial on the Effect of Low-Dose versus High-Dose Vitamin D Supplementation on Bone Mass in Adults with Neurofibromatosis Type 1 (NF1)*

Overall Study Principal Investigator:

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Sponsor: US Army Department of Defense

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INVITATION
We are inviting you to take part in this research study because you are a young adult with neurofibromatosis type 1 (NF1.)

YOUR PARTICIPATION IS VOLUNTARY
Taking part in this study is voluntary. You do not have to do it. If you choose to take part, you can still quit the study at any time without it affecting your medical care.

Please take the time to understand the purpose of this study and what to expect if you choose to be in it. The information will explain the possible benefits and harm from being in the study. Please read this form. You can talk to the study nurse about anything you don't understand. You can also talk to others such as a family member, a friend, BCNF (The British Columbian Neurofibromatosis Association), or your family doctor. Please ask questions any time you like.

Taking part in a study is not the same as being cared for by your family doctor. Your family doctor's job is to care for you. In a study, the doctors want to learn things that will help other people with NF1 in the future. During the study, it is also their job to care for you about anything to do with the study. They will let you know about anything that comes up that might make you change your mind about being in this study.

WHO IS CONDUCTING THE STUDY?
In British Columbia, the study is being conducted by Dr. Jan Friedman and Dr. David Kendler. The study nurse is Patricia Birch. The overall study leader (the "principal investigator") is Dr. Dave Viskochil at the University of Utah. In addition to the British Columbia and Utah sites, the study is also taking place in Cincinnati, Ohio and in Hamburg, Germany. The study is paid for by the US Army Department of Defense through their NF1 research program.

BACKGROUND
Bone problems are common in NF1. People with NF1 have a higher risk of developing osteoporosis, which is a condition of low bone density causing fragile bones that break easily. Osteoporosis may occur in up to half of older adults with NF1. We also know that about 75 out of every 100 people with NF1 also have somewhat low levels of vitamin D in their blood compared to people without NF1. Vitamin D and calcium are building blocks of healthy bones so we think that giving extra vitamin D and calcium to adults with NF1 could improve bone health.

Vitamin D levels are measured by a blood test. But this is not a test that is usually done so most people with or without NF1 have no idea what their vitamin D level is.

Bone density is measured by a painless test called DXA (short for dual-energy x-ray absorptiometry: there is more information about this test on page 7). People usually reach their highest bone density (strongest bones) in their early to mid twenties. From then on, bone density stays the same or slowly decreases through middle age. For this reason, most people in this age group don't get their bone density tested, meaning they don't know what their bone density is. Bone density decreases in old age. For this reason, DXA is often recommended by family doctors for older adults in the general population to check for osteoporosis. There are no special recommendations yet for DXA testing in people with NF1.
If people are diagnosed with osteoporosis, there is treatment available. This is true for people with or without NF1. Treatment for osteoporosis usually includes vitamin D and calcium and may include other drugs, depending on the case. The trouble is that by the time osteoporosis has been diagnosed, it can be hard to reverse. It might be easier to stop it from happening in the first place. This is why we want to measure the effect of vitamin D and calcium supplements in younger adults with NF1. We hope that

treating people in this younger age group will prevent osteoporosis later on in life. The study will last two years. This time period is long enough to measure any effect on bone health from taking vitamin D and calcium.

Vitamins such as vitamin D are approved for use by of Health Canada. Vitamin D is a well-known compound with a lot of safety information written about it, and it is generally considered to be safe to take in the doses of this study. (There is more information about the safety of vitamin D on page 7). Health Canada has not specifically approved the use of vitamin D for young adults with NF1. However, they have allowed us to use it in this clinical study.

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to find out if vitamin D and calcium can preserve or improve bone health in young adults with NF1. We hope that this will provide a way of preventing the bone problems that older adults with NF1 often suffer from.

To test whether vitamin D and calcium can help bone health, the entire study will recruit about 220 people. In British Columbia, we expect to recruit about 36 people. These individuals will take vitamin D and calcium for two years.

This is a *phase II study*. "Phase II" studies usually involve a small number of participants – in our case, about 220 people in the whole study. Our goal is to find out what effect vitamin D has on bone health in people with NF1. Most phase II studies are also used to learn about side effects and safety. In this situation, vitamin D is a compound that is well studied and has been taken by many people with and without NF1, including in the doses used in this study. Collecting safety data is therefore not a focus of this study but we will perform a number of safety checks throughout the study. These are described in more detail on page 7.

WHO MAY BE ABLE TO PARTICIPATE IN THIS STUDY?

You may be eligible for this study if:

- you have NF1 and you are between the ages of 25 and 40 years old
- you are willing to come to one of the participating centers for monitoring three times: once at the beginning of the study, once 1 year later, and once 2 years later
- you are also willing to be contacted for safety monitoring 6 months and 18 months from the beginning of the study.

WHO CANNOT PARTICIPATE IN THIS STUDY?

You cannot participate in this study if:

- you have ever taken bisphosphonates, calcitonin or glucocorticoid medications for over 3 months
- you are taking some types of anti-seizure medications, blood thinners, thyroid treatments
- you have medical conditions that may affect bone health including; Paget's disease, hyperthyroid or hyperparathyroid problems, kidney failure, or history of a kidney stone within the last 5 years
- you are a woman who is pregnant or planning to become because pregnant women should avoid bone density testing and the unknown risk of taking vitamin D to the baby
- you have taken vitamin D supplements of 600IU or more daily for the last three months
- you have metal in your lower spine or hip (because that interferes with bone mineral density measurements)

We will take a careful history of your health and medications to check that you are not in any of the above categories and that there are no other concerns that would prevent your participation.

WHAT DOES STUDY PARTICIPATION INVOLVE?
The first part if the study involves screening. The second part is a clinical trial. Both parts are described below.

SCREENING
All potential participants will have initial screening to check their serum vitamin D level.
This screening is described below:

- You will be contacted by the study nurse to review the details of the study. If you want to participate then you will sign this consent form and we will arrange a time for your initial blood test. This arrangement can be made by telephone if you are known to have NF1. If you do not know if you have NF1 then you will be evaluated by a study doctor to verify that you have NF1, prior to screening. Dr Friedman will review your medical history to ensure that you are eligible to participate.
- Your screening blood test will be drawn by a trained technologist. If you live outside of Vancouver, then your blood draw can be arranged at a convenient local lab. The amount of blood taken is about 3 teaspoons (15ml). This blood sample is to test your serum vitamin D level. Other tests will be done on the same sample if you are eligible for the second part of the study. These are parathyroid hormone (a measure of bone health) and calcium and a second vitamin D test that will be done at the central clinical laboratory in Utah. If you are a woman we will also do a pregnancy test.
- We will tell you the result of your vitamin D testing within 1 month of the blood draw. There are 3 possible types of results, described below:
    1. **Your vitamin D level is high (also called "sufficient").** This means it is over 30 ng/ml (in metric measurements, that is over 75 mmol/L). We will thank you for participating in the screening but your level is too high for the full study.
    2. **Your vitamin D level is low (also called "deficient").** This means your vitamin D level is quite low, under 9ng/ml (in metric, that is less than 22 mmol/). If you fall into this category, we will offer to give these results to your family doctor or arrange other clinical care for you.
    3. **Your vitamin D level is a little low (also called "insufficient")**. This means your vitamin D is between 8 and 30ng/ml (in metric, that is between 22 and 75 mmol/L). If you are in this range, you will be invited to participate in the study. We expect that the majority of people screened will have insufficient vitamin D levels and therefore eligible for the full study.

If you are in the second group, with "**deficient**" vitamin D levels, you do not qualify to continue in the study because you might need more intensive vitamin D treatment than you would get in this study.

If you are in the "**deficient"** group or, if you are in the "**sufficient"** group, only your study code and vitamin D level will be sent to the USA. This is to monitor the numbers of people screened who are in each of the three screening levels.

If you are in the third group with "**insufficient"** vitamin D levels, you will be invited to continue in the clinical trial that includes daily vitamin D supplementation for two years. This is explained below

CLINICAL TRIAL

This involves about 220 people with NF1 whose vitamin D levels are **insufficient**. About 36 people will be from B.C. Participants will take extra vitamin D to see if their bone density can be maintained. It is important to study vitamins as carefully as one would study other medications, even though vitamins are generally safe. For this reason, the vitamin D supplementation will be given in carefully controlled doses and we will include safety checks on participants' health. This way, we will make sure that vitamin D supplementation is safe for study participants.

Vitamin D Supplements

We will use two different doses of vitamin D: 600 IU and 4,000 IU (IU means "International Units", which is a standard measure of the strength of the dose). The trial is "double blind". This means that neither you nor we will know which dose you get until after the trial ends. Only the medical monitor knows. In an emergency, however, we can find out.

If you agree to be in the clinical trial, you will be randomized to one or the other dose. Regardless of dose, you will be given a bottle of liquid vitamin D to take. You will take **two** measured drops every day. The vitamin D is called "D-drops" and has a dropper that automatically provides the right amount when the bottle is turned upside down. Each bottle lasts 6 months and we will give you one new sealed bottles every 6 months, all with the same dosage of vitamin D.

We believe that both the 600 IU and the 4,000 IU doses are safe for you to take. However, it is possible that the bodies of people with NF1 handle vitamin D differently. It is therefore important to make sure that you are safe during this trial. You will need to report any new medical issues or concerns throughout the 2-year period to the study nurse.

The primary measure we will use in this study to determine the effectiveness of the different vitamin D doses is bone mineral density. This is described, below, under "bone density scans".

Calcium Supplements

When we do a dietary assessment, we often find that people don't eat enough calcium. Individuals with low vitamin D are usually treated with both vitamin D and calcium supplements. We will give all participants a calcium supplement of 1,000 mg per day (400 mg of elemental calcium supplementation per day). These are the same type of calcium supplements that people can buy in a drug store – you might know them under a brand name such as "Tums."

If you choose to participate in this study, we will give you a diary to keep track of your vitamin D and calcium supplements.

Clinical Visits

We will ask you to come for a clinical visit at the beginning of the study, after one year, and at the end of the study (two years after you started). You will have a medical history and brief physical examination performed by Dr. Jan M. Friedman, paying particular attention to bone health.

Questionnaires

When you come for a clinical visit, you will also fill out a questionnaire describing how you are feeling about your quality of life. We will also ask about any history of bone fractures. In between these visits, the study nurse will speak to you to check that everything is going well for you. We will ask you to let us know about any broken bones or other bony problems that come up, or any other concerns.

Bone Density Scans

At your first clinical visit and at your last clinical visit (at year 2), you will have a bone density scan, also called a DXA scan (short for dual-energy x-ray absorptiometry). This will be in the Vancouver offices of co-investigator, Dr. David Kendler. This is a type of very low radiation x-ray that measures the density of your hip and spine. The procedure is painless and is very much like having a regular x-ray, except the radiation dosage is much lower.

If your bone density scan shows that you have osteoporosis (clinically low bone mineral density that is associated with a higher risk for bone fractures), then we will withdraw you from the study. We will give the results to you in a letter. We will also suggest that you bring the results to the attention of your family doctor and we can send a copy of the letter to your doctor if you would like. This will probably result in you receiving some clinical treatment for the osteoporosis. If you have no family doctor, and you want us to help you to find care for the osteoporosis, we will be glad to help you, outside of the study.

Blood tests

About 15ml (three teaspoons) of blood will be taken at the screening test (explained above on page 4) and at the middle and end of the study at the time of each clinical visit. The same tests will be done on each sample (vitamin D, calcium, parathyroid levels, and pregnancy tests for women).

WHAT ARE MY RESPONSIBILITIES?

You will need to come to Vancouver at the beginning, middle and end of the two year study, and be available for contact with the study nurse every six months. Most important, you must be willing to do your best to remember to take the vitamin D and calcium supplements each day for two years. If there is anything about your health or the study that you are worried about, you will need to let us know as soon as you can.

An important responsibility is to store the vitamin D and calcium safely away from children. Although these are very safe drugs, the amount of either vitamin D or calcium in a full bottle could harm a child and require hospitalization.

WHAT POSSIBLE HARM OR DISCOMFORT CAN COME FROM PARTICIPATING?

Vitamin D and calcium supplements

The risk of vitamin D toxicity with the doses of supplementation in this study is very low. However, the risk of vitamin D toxicity is greater for those randomized to the higher 4,000 IU dose. You will be checked for this through phone calls with the study nurse when you begin the study, with safety monitoring every six months and at your clinical visits. You are also asked to take note of any worrisome symptoms and contact us or your own doctor if you are concerned. Vitamin D overdose causes “hypercalcemia” (high levels of calcium in the blood and/or urine). The early symptoms of this include nausea and vomiting, weakness, headache, sleepiness, dry mouth, constipation, metallic taste, muscle and bone pain, and itching. Later symptoms include excessive drinking and urinating, weight loss and calcium deposits in the soft tissue in the kidney and liver. Contact us if you are at all worried at any time during the study. If you think you are seriously ill, contact your own doctor or the emergency department immediately.

Calcium overdose will not occur if taken at the dose in this study. If you are worried that you may have accidentally taken many calcium pills at one time, you should contact the emergency department of your local hospital. Most likely, you would receive supportive treatment. Again, contact us if you are worried about this.

Clinical examinations

Some people find clinical examinations to be embarrassing. We will do our best to be professional and respectful at all times and we will not ask you to undress more than is necessary to confirm your diagnosis and check your bone health.

Questionnaires

The questionnaire on quality of life asks some personal questions such as whether you have felt full of life, happy, "down" or depressed in the last month. Occasionally, questions like these can make people feel badly about themselves. You can leave out these questions if you want to.

Bone Density Scans

All medical procedures try to minimize the amount of radiation people are exposed to, particularly for research studies. The radiation for a bone mineral density scan is about 6 mrem (mrem is a measure of radiation exposure). For comparison, the annual background radiation exposure from the earth and atmosphere in an average person is roughly 300 mrem.

Blood tests

You may experience brief pain or possible bruising from the blood test. Infection is uncommon but can occur. The procedure will be performed by a trained technician or nurse to minimize these risks.

Pregnancy

All women must have pregnancy testing before study participation and before having a bone density scan. In addition, we recommend that women use birth control during the study and for one month afterwards. This is for three reasons:

(1) Women who are pregnant will not be eligible for the clinical trial because of the small risk of radiation from the bone density scan to cause birth defects.

(2) Although there is no evidence of any risk of taking 4000 IU of vitamin D during pregnancy, we can't be certain of its safety. This is because there are few studies on vitamin D in pregnancy. However, in one situation, no birth defects occurred when pregnant women accidentally took between 10 and 60 times the maximum amount you might receive in this study.

(3) Hormone changes in pregnancy could alter your bone mineral density, and we would not be able to judge if any change was due to the pregnancy or the study vitamin D and calcium

If you become pregnant while enrolled in this study you will need to contact the study team immediately. We would ask you to stop taking the vitamin D and calcium and would withdraw you the bone scan part of the study as well. Pregnancy would limit your participation to the study questionnaires and the blood tests.

There are no known risks from taking vitamin D and calcium while breast feeding or fathering a child.

WHAT ARE THE POSSIBLE BENEFITS OF PARTICIPATING IN THIS STUDY?

Nobody knows whether or not you will benefit directly from participating in this study, and benefit cannot be guaranteed.

Everyone will receive a copy of all the results of their individual testing at the end of the study.

After the initial screening, people will be told their vitamin D status:

It is likely that some of the participants in this study (the "**deficient**" group) will be diagnosed with low bone mineral density and osteoporosis. This may be of benefit to them because this is a treatable condition. Other people may receive reassurance about their vitamin D levels (the "**sufficient**" group).

The individuals in the **"insufficient"** group, who participate in the clinical trial may benefit from taking vitamin D and calcium, which we hope may be able to prevent or slow the development of osteoporosis. We do not know if this is the case, which is why we are doing this study.

We hope that the information learned from this study can be used in the future to benefit other people with NF1.

WHAT ARE THE ALTERNATIVES TO STUDY TREATMENT

Vitamin D testing and bone mineral density assessments are not usually performed in people of your age, so it is unlikely that you would know these results if you are not in the study.

If you choose not to participate in the study, you can do your best to exercise and maintain a healthy diet to give your bones the best chance of remaining healthy.

WHAT IF NEW INFORMATION BECOMES AVAILABLE THAT MAY AFFECT MY DECISION TO PARTICIPATE?

If you choose to enter this study and at a later date a better treatment becomes available, we will tell you about it. We will also tell you about any new information that may affect your willingness to remain in this study.

WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE?

You may withdraw from this study at any time without giving reasons.

If you choose to enter the study and then decide to withdraw at a later time, all data collected about you during your enrollment in the study will be kept for analysis. By law, these data cannot be destroyed.

CAN I BE ASKED TO LEAVE THE STUDY?

If you are unable to follow the study procedures, you may be asked to leave the study. If this was the case, we would explain this to you and give you the chance to ask questions about this decision.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of The US Army Department of Defense (the funding organization), Health Canada, the U.S. Food and Drug Administration, the external medical safety monitor, and the UBC Research Ethics Board for the purpose of monitoring the research.

No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

You will be assigned a unique study number as a participant in this study. This number will not include any personal information that could identify you (e.g., it will not include your Personal Health Number, SIN, or your initials, etc.). Only this number will be used on any research-related information collected about you during the course of this study, so that your identity will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to insure that your privacy is respected.. Further details about these laws are available on request to your study doctor.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Any study related data or blood samples that are sent outside of Canadian borders may increase the risk of disclosure of information because the laws in those countries dealing with protection of information may not be as strict as in Canada. However, all study related data and samples, that might be transferred outside of Canada will be coded (this means it will not contain your name or personal identifying information) before leaving the study site. By signing this consent form, you are consenting to the transfer of your information and samples to Dr. David Viskochil at the University of Utah Health Sciences Center.

Studies involving humans now routinely collect information on race and ethnic origin as well as other characteristics of individuals because these characteristics may influence how people respond to different medications. Providing information on your race or ethnic origin is voluntary.

WHAT HAPPENS IF SOMETHING GOES WRONG?

By signing this form, you do not give up any of your legal rights and you do not release the study doctor, participating institutions, or anyone else from their legal and professional duties. If you become ill or physically injured as a result of participation in this study, medical treatment will be provided at no additional cost to you. The costs of your medical treatment will be paid by your provincial medical plan.

In case of a serious medical event, please report to an emergency room and inform them that you are participating in a clinical study and that the following person can then be contacted for further information: Dr. Jan M. Friedman at telephone number: 604-875-2157.

WHAT WILL THE STUDY COST ME?

The vitamin D and calcium supplements will be given to participants at no cost to them.

All participants will receive $25 to partially compensate them for their time, parking expenses, and gas for the screening study.

In addition to the screening honorarium, people in the clinical trial will receive $50 for the initial examination, $50 for the 12 month visit and $75 for the second year visit.

Participants in the clinical trial from outside the lower mainland will receive higher partial compensation for travel for each of the three clinical visits. For example, people coming from the Okanagan will be offered reimbursement of $70 per visit. People from others locations will be compensated in a similar manner. We will discuss this with you in advance of your appointment and will let you know in writing what the travel compensation will be. Payment will be mailed to you after you participate in each of the three assessments.

WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY

If you have any questions or desire further information about this study before, during, or after participation, you can contact the Principal Investigator, Dr. Jan M. Friedman, or Patricia Birch (research nurse) at 604-875-2000 ext 5622, or you may email Patricia Birch at: Patricia.Birch@ubc.ca

WHO DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY RIGHTS AS A PARTICIPANT DURING THE STUDY?

If you have any concerns or complaints about your rights as a research participant and/or your experiences while participating in this study, contact the Research Participant Complaint Line in the University of British Columbia Office of Research Ethics by e-mail at RSIL@ors.ubc.ca or by phone at 604-822-8598 (Toll Free: 1-877-822-8598).

AFTER THE STUDY IS FINISHED

Your identifying information will be removed from the blood and urine samples but the samples will be kept in the lab for one year in case it is necessary to check the findings. Should you wish to obtain general results about the study as a whole, they will be available in summarized form from the Principal Investigator approximately two years from the end of the study. As mentioned above, specific results relating to you will be given to you upon study completion.

STUDY SUMMARY

Below is a table that may give you a useful overview of the whole two-year study.

Procedure	**Screening**	**Day 1 (study begins)**	**Month 6**	**Year 1**	**Month 18**	**Year 2 (study ends)**
Consent to study	X					
Blood collection	X			X		X
Urine Pregnancy	X	X		X		X
DXA Scan		X				X
Physical Exam		X		X		X
Questionnaires		X		X		X
Dispense vitamin D ("D-drops")		X	X	X	X	
Study Diary (dispense and collect)		Dispense only	X	X	X	Collect only
On-going monitoring of your health		X	X	X	X	X

PARTICIPANT'S CONSENT

My signature on this consent form means:

- I have read and understood the information in this consent form.
- I have been able to ask questions and have had satisfactory responses to my questions.
- I understand that my participation in this study is voluntary.
- I understand that I am completely free at any time to refuse to participate or to withdraw from this study at any time, and that this will not change the quality of care that I receive.
- I authorize access to my health records and blood samples as described in this consent form.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I understand that there is no guarantee that this study will provide any benefit to me.

I will receive a signed copy of this consent form for my own records.

I consent to participate in this study.

_____	_____	_____
Participant's Signature	Printed name	Date

_____	_____	_____	_____
Signature of Person Obtaining Consent	Printed name	Study Role	Date