

Award Number: W81XWH-12-1-0487

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

PRINCIPAL INVESTIGATOR: David Viskochil, MD, PhD

CONTRACTING ORGANIZATION: University of Utah, Salt Lake City, UT

REPORT DATE: December 2022

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE December 2022		2. REPORT TYPE Final		3. DATES COVERED 15Sep2012-01Sep2022	
4. TITLE AND SUBTITLE A Phase II Trial on the Effect of Low-Dose versus High-Dose Vitamin D Supplementation on Bone Mass in Adults with Neurofibromatosis 1 (NF1)				5a. CONTRACT NUMBER W81XWH-12-1-0487	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) David Viskochil, MD, PhD E-Mail:				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) UNIVERSITY OF UTAH, THE 201 PRESIDENTS CIR SALT LAKE CITY UT 84112-9049				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT This is a study to determine if a higher daily dose of vitamin D in adults with neurofibromatosis type 1 (NF1) who have a vitamin D insufficiency is 1) safe, and 2) decreases rate-of-loss of bone mineral density. Usually, skin exposure to ultraviolet radiation is ample for adequate levels of vitamin D. However, for those who need supplementation, the usual dose is 600 IU of vitamin D ₃ orally per day. Individuals with NF1 have lower 25-hydroxy vitamin D levels than the unaffected population, and they tend to have osteopenia (low bone mineral density), even at relatively young ages. This study aims to determine if higher daily doses of vitamin D ₃ (4,000 IU) lead to preservation of bone mineral density in both men and women between 25 and 40 years of age who have NF1 and have insufficient levels of serum 25-OH vitamin on initial screening.					
15. SUBJECT TERMS NF1, vitamin D, osteopenia, adults, double-blind randomized trial					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 1144	19a. NAME OF RESPONSIBLE PERSON USAMRDC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
1. Introduction.....	4
2. Keywords.....	4
3. Overall Project Summary.....	5
4. Key Research Accomplishments.....	11
5. Conclusion.....	12
6. Appendices.....	13

1. INTRODUCTION: Neurofibromatosis type 1 (NF1) is a multisystem disease, and many patients have skeletal manifestations that fall into three general categories: (1) characteristic focal lesions, (2) short stature, and (3) osteopenia/osteoporosis, or low BMD (bone mineral density), which occurs in almost all affected individuals by age 50. Vitamin D therapy appears to have some benefit in treating osteoporosis in the general population, and administration of vitamin D in a dose that maintains the serum 25-hydroxy vitamin D level above 30 ng/mL significantly improves BMD in individuals with NF1. These observations led to the development of a phase II clinical trial to evaluate the effectiveness of vitamin D₃ dosing in NF1 patients. This study is designed to assess the efficacy of oral vitamin D₃ and calcium therapy to prevent abnormal loss of bone mass in adults with NF1. The clinical trial is a double-blind, dose comparison of efficacy of high-dose versus low-dose vitamin D₃ on preservation of bone density as measured by DXA scanning after 2 years of treatment. It compares 2 groups of adults with NF1 between 25 and 40 years of age with insufficient levels of serum 25-hydroxy vitamin D at study entry. Participants are randomized and one group will take 600 IU and the other will take 4,000 IU on a daily basis for 2 years. Participants and investigative teams are blinded to the vitamin D₃ dose. The primary outcome measure is bone mineral density at the spine and hip. Secondary patient reported outcome (PRO) measures include a quality of life questionnaire (SF-36), fracture history survey, and activity survey.

2. KEYWORDS:

25(OH)D = 25-hydroxy vitamin D

BMD = bone mineral density

Ca = serum calcium

CCTS = Center for Clinical & Translational Science at the University of Utah

Cholecalciferol=vitamin D₃

CIN = University of Cincinnati enrollment center

CGRP = Clinical Genetics Research Program

DEXA = dual energy x-ray absorptiometry

Ddrops = formulation of cholecalciferol (vitamin D₃)

DXA = dual energy x-ray absorptiometry

FDA= Federal Drug Administration

HAM = University of Hamburg enrollment center

IRB = Institutional Review Board

NF1 = neurofibromatosis type 1

PTH = serum parathyroid hormone

PCTO = Pediatric Clinical Trials Office at the University of Utah

PO4 = serum phosphorus

PRO= Patient Reported Outcome

UBC = University of British Columbia enrollment center

UTA = University of Utah

3. OVERALL PROJECT SUMMARY (STATEMENT OF WORK)

Overall Objective: Determine best dose of cholecalciferol supplementation to optimize maintenance of bone mineral density in adults with neurofibromatosis type 1 (Funding: 9/15/2012 -09/14/2016; 48 months) – No-cost extension granted through 9/14/2017, No-cost extension granted through 9/14/2018, No-cost extension granted through 9/14/2019 and again through 9/1/2022.

I. Major Goal - Assemble a cohesive multi-center team for phase II clinical trial

Task I.1 (mo 0-2): compile subcontracts between UTA and the following sites UBC (University of British Columbia, Canada), CIN (University of Cincinnati, USA), HAM (University of Hamburg, Germany).

Subcontracts were distributed by the University of Utah Office of Sponsored Projects. The University of Cincinnati has submitted invoices, and payout for October 1, 2014-September 1, 2022, was . The University of British Columbia has submitted invoices, and payout for October 1, 2014-September 1, 2022, was. The subcontract with University of Hamburg was executed, and payment was sent. The University of Hamburg returned because it was never approved as a clinical trial site.

The European Union Clinical Trials group (EurodratCT) did not approve the study. After extensive discussions between the University of Hamburg and DDrops™ of Canada, the EurodratCT group did not accept the trial supplier of cholecalciferol. Attempts by the University of Hamburg to identify a local supplier that could provide 2 doses of cholecalciferol failed. Due to this impasse, the University of Hamburg could not be initiated as a site for this study. We were unable to identify a different site to replace the site at the University of Hamburg.

We received supplemental funding from CTF Clinical Research Award Program hosted by the Children's Tumor Foundation as a mechanism to cover clinical trial costs. This application was submitted to cover unanticipated expenses to initiate the University of Hamburg site. When it became clear that the European Union Clinical Trials oversight group would not accept DDrops as the vitamin D study drug, the CTF funding was reallocated to potentially cover travel costs if our initiative to recruit from various NF registries were successful. After claiming futility due to our inability to recruit enough participants from an extensive recruitment campaign, we released of the original funding back to the Children's Tumor Foundation.

II. Major Goal - Enroll human subjects into a phase II clinical trial with vitamin D3 supplementation

Task II.1 (mo 0-24): Recruit adults with NF1 to participate in the clinical trial

A total of 27 participants were enrolled and randomized, and 26 were treated with vitamin D3/calcium supplementation. One patient was randomized and then withdrew from the study. There were 6 participants from the University of Utah, 12 participants from the University of Cincinnati, and 8 participants from the University of British Columbia. 13 patients at all sites completed 2 years on study drug.

Task II.2 (mo 1): Ensure pregnancy status prior to densitometry

Female participants of childbearing potential received a urine pregnancy test prior to densitometry. There were no pregnancies during this study or withdrawals.

Task II.3 (mo 0-12): First enrollment period for 25(OH)-vitamin D serum screening/vitamin D3 supplementation

Coordinators at each site alerted their respective adult NF1 population of the upcoming trial. Enrollment commenced at 3 sites that had achieved institutional human subjects protection approval. Twenty-seven patients were enrolled from Feb 2018 to Mar 2020.

Task II.4 (mo 12-24): Second enrollment period for 25(OH)-vitamin D serum screening/vitamin D3 supplementation

Enrollment continued through the second enrollment period; however, due to COVID-19 enrollment was halted at all sites in March 2020. UTA and CIN re-opened for enrollment in June 2020. UBC remained closed.

Recognizing that the University of Hamburg had the largest adult NF1 population, the other 3 sites pushed recruitment in their respective catchment areas. In addition, a recruitment flyer was sent to the national patient support organizations to bolster recruitment and assess interest around the country. Potential participants were given a link to the survey monkey. The link opened on Oct 8, 2020. As of Dec 8, 2020 the survey results showed:

- 43 participants opened the survey
- 35 participants had NF1 and were possibly interested in the study
- 25 of 34 respondents were eligible based on gender and age

- 20 of the 25 patients were not taking Vitamin D or a multivitamin
- 19 of 20 eligible recruits would be willing to travel

This survey demonstrated that we could not achieve study enrollment goals and led to a conference call between the 3 sites. We were in consensus agreement that achieving total enrollment for statistical significance was not feasible.

Task II.5 (mo 6-15): Maintain ongoing IRB approval

This task was achieved for the 3 recruiting sites throughout the duration of the trial.

Task II.6 (mo 18-23): Bi-annual review by safety monitor and distributed to each IRB and USAMRMC

Per IRB stipulation, safety reviews of adverse events by the study manager took place every 6 months. Data included a spreadsheet of all adverse events maintained by the clinic research coordinator serving as the study manager at the University of Utah and submitted to the safety monitoring committee for review. A process was established for the FDA to be appraised of adverse events, and a summary of the safety monitoring committee was to be provided to the FDA as part of the annual report of cholecalciferol use in adults with NF1.

III. Major Goal - Obtain laboratory, bone density, and survey data on participants in the study

Task III.1 (mo 0-48): Assemble all data collection forms, blood collection kits, and CDs at each enrollment center

A number of forms were developed for this study and are appended at the end of this report. These include:

- Protocol (section 6.1)
- Manual of Operations (section 6.2)
- ICF (Section 6.3)
 - UTA ICF (Section 6.3.1)
 - UBC ICF (Section 6.3.2)
 - CIN ICF (Section 6.3.3)
- UofU Letter of Initial Contact (Section 6.4)
- REDCap Data Collection Forms (section 6.5)

Sites were responsible for their own supplies. Samples were sent to central lab (A.R.U.P. at the University of Utah), per protocol.

Task III.2 (mo 0-24): Obtain serum 25(OH)D on 316 enrollees across 4 enrollment centers

As of Dec 2021, 34 patients had been screened. Six patients didn't qualify due to normal serum vitamin D levels. Twenty-seven participants completed day 1/randomized; 26 participants were dispensed study drug. Ten participants completed year 2. 17 participants withdrew or were lost to follow up and did not complete year 2 of the study. Two participants were unable to complete their final DXA due to the COVID-19 pandemic travel restrictions.

Task III.3 (after visits): Document processes for timely notification of serum 25(OH)D results and randomization

A system was developed to document processes with respect to 25-OH vitamin D levels and completion of randomization. Reports were sent via email to sites after completion of analysis at central lab.

Task III.4 (mo 0-24): Randomize 226 participants to either 600 IU or 4,000 IU of daily vitamin D3

As of Aug 2022, 26 participants had been dispensed study drug after randomization. Of those, 15 were randomized to low-dose Vitamin D supplementation and 11 were randomized to high-dose vitamin D supplementation; low-dose (4 at UTA, 9 at CIN, 2 at UBC) and high-dose (2 at UTA, 3 at CIN, 6 at UBC).

Task III.5 (mo 6-15; mo 18-27; mo 30-39; mo 42-47): perform initial DXA scans, brief physical exam, and perform surveys on 226 participants at 2 time-points

As of Aug 2022 – 13 participants have completed 2 DXA scans highlighted in yellow.

UTA Participants:

Participant ID	Time point Completed	Group	
1303-1	yr 2	1	low dose
1303-2	m6 - unknown	1	low dose
1303-4	M6- ET	1	low dose
1303-6	yr 2	1	low dose
1303-3	yr 2	2	high dose.
1303-7	yr 2	2	high dose

CIN Participants:

Participant ID	Time point Completed	Group	
1304-1	m6 - unknown	1	low dose
1304-2	m6 – lost to follow-up	1	low dose
1304-5	yr 2	1	low dose
1304-10	m6 - lost to follow-up	1	low dose
1304-11	yr 2	1	low dose
1304-13	yr 2	1	low dose
1304-15	yr 1 - unknown	1	low dose
1304-16	m6 - ET	1	low dose
1304-17	m6 - ET	1	low dose
1304-6	m6 – MD determined participant withdraw	2	high dose
1304-7	yr 2	2	high dose.
1304-9	m6- lost to follow-up	2	high dose

UBC Participatnts:

Participant ID	Time point Completed	Group	
1302-2	yr 2	1	low dose
1302-8	yr 2	1	low dose
1302-1	yr 2	2	high dose
1302-12	yr 2	2	high dose
1302-13	m18 – discontinued due to non-compliance	2	high dose
1302-14	yr 2	2	high dose
1302-18	yr1 - COVID restrictions	2	high dose
1302-22	yr1 - - COVID restrictions	2	high dose

IV. Major Goal – Data Analyses

Task IV.1 (mo 3-5): Collect data on all enrollees both by hard copy forms and in the study-specific database

Sites were required to enter visit information into the REDCap database. The project manager at the University of Utah verified serum samples received in lab, values for 25-OH Vitamin D, and entered in database.

Task IV.2 (monthly): Validate data collection on a monthly basis by data monitor

Project manager at the University of Utah has verified all Vitamin D samples received in lab and entered them in database. This was not performed monthly due to the lag in enrollment.

Task IV.3 (throughout study): Verify accuracy of data collection by enrollment center coordinators

Project manager at the University of Utah has verified Vitamin D samples received in lab and entered in database. Other data collection was verified by review of respective site input of all relevant data fields.

Task IV.4 (48 months): Perform comparison of low-dose vit D3 versus high-dose vit D3 on data collections

A review of the DXA results on the first 10 completed patients is pending.

Task IV.5 (48 Months): Perform all analyses according to specifications, share output and finding with all investigators

The de-identified, unblinded data have been provided to the statistician at the University of British Columbia and is presently under review.

Task IV.6 (48 Months): Work with data core and dissemination of findings (abstracts, presentation, publications, DOD)

The enrollment is too small to reach statistical significance; however, reflections of anticipated issues and limitations for additional vitamin D supplementation trials in adults with NF1 will be consolidated from all sites and submitted to a journal for publication. In this way, pitfalls in recruitment/enrollment can be recognized prior to initiating other similar trials.

Task IV.7 (48 Months): Milestone Achieved: Report results from data analyses

There were no results to report at 48 months, which was the anticipated end of study. The inability to have the University of Hamburg join the multicenter study delayed the initiation of recruitment and enrollment. Data are now being analyzed even though the cohort sizes are too small to reach statistical significance.

Subcontracts between U of Utah (UTA) and CIN, UBC, and HAM

Organization name: Cincinnati Children's Hospital Medical Center (CIN)
Organization address:

Tana Housh
Manager, Sponsored Projects 3333 Burnet Ave-MLC 7030
Cincinnati, OH 45229-3039
Investigators: Elizabeth Schorry, MD Collaborators: Heidi Kalkwarf, PhD

Organization name: University of British Columbia (UBC)
Organization address:
Dr. Martin Kirk
Director, Research Services 102-6190 Agronomy Rd. Vancouver, BC V6T 1Z3
Investigators: Jan M. Friedman, MD, PhD Collaborators: David Kendler, MD

4. KEY RESEARCH ACCOMPLISHMENTS:

As of August 2022, 27 participants have been enrolled; 26 have treated; 10 participants have completed 2 years on the study and data are under review by the statistical team at UBC.

5. CONCLUSION:

Only 3 of the 4 anticipated sites became active and enrolled participants. Due to logistical issues HAM could not enroll as a site. Funds designated for HAM site were distributed to other sites for participant recruitment and additional participant visits needed.

Vitamin D was received from DDrops in Aug 2017. Vitamin D has been randomized and shipped. In mid-Nov 2017, DDrops notified us that one of the 2 lots had been determined to have declined in potency at a greater than anticipated rate. DDrops monitors all lots on a monthly basis. All sites sent all DDrops back to the University of Utah at the end of Nov 2017. DDrops resent a new batch. New labels and drug assignment was completed and shipped to sites in Feb/Mar 2018. Screening and enrollment began in Feb/Mar 2018 at UTA and CIN, and in Sept 2018 at UBC.

We needed to recruit at least 163 participants, which was determined to require a recruitment effort throughout North America for 2 of the 3 sites to make up for lost enrollment from the MAN site, which was anticipated to enroll the highest number of participants. Flyers were made available to NF1 patients nationwide who were identified through the CTF (Children's

Tumor Foundation) and NF Network. Of those who contacted Utah, we compiled a list to determine if we could recruit 163 participants. The survey was left open for 2 months. There were 43 responses and 20 participants eligible for enrollment. A request to the statistician on our DSMB was sent to review the DXA results of the 10 completed patients to determine the observed mean difference in BMD loss between the groups to determine a revised enrollment goal, and if such enrollment could be achieved.

In May 2021 DEXA data from 10 patients was reviewed. The last 2 participants were unable to travel to UBC for their final DEXA due to the COVID-19 pandemic travel restrictions in Canada. A decision was made to end the study based on futile enrollment determined from survey results and travel restrictions on travel to open sites.

The year 2021 was spent trying to obtain approval of our No-Cost Extension, which was needed to close out the study. Our NCE was approved on Mar 4, 2022. The CIN site PI, Elizabeth Schorry, MD, retired in 2021, and a replacement has not been identified to close out the study at the CIN site.

6. APPENDIX:

- Protocol (section 6.1)
- Manual of Operations (section 6.2)
- ICF (Section 6.3)
 - UTA ICF (Section 6.3.1)
 - UBC ICF (Section 6.3.2)
 - CIN ICF (Section 6.3.3)
- UofU Letter of Initial Contact (Section 6.4)
- REDCap Data Collection Forms (section 6.5)

Protocol

Appendix 6.1

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)

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)

Protocol Number: NF1 Vitamin D

Amendment V2: 29 Feb 2016

Amendment V1: 5Nov2015

Original Protocol: 2014

IND: 119135

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)

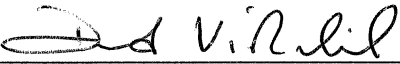
Signature Page

Protocol V: 10Feb2016 Amendment 3

The signature below constitutes that I agree to the following:

I have reviewed the protocol and the attachments.

- This trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable local and federal regulations and International Conference on Harmonisation (ICH) guidelines.

	<u>29 Feb 2016</u>
Investigator's Signature	Date
<u>David Viskochil</u>	
Investigator's Printed Name	

Accepted for the Sponsor:

_____	_____
Signature	Date

Printed Name	

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)

This is a two-year prospective, double-blind trial of two different doses of vitamin D supplementation in adults with neurofibromatosis type 1 (NF1) and low serum 25-(OH) vitamin D [25(OH)D].

OBJECTIVE

Osteoporosis and vitamin D insufficiency are common manifestations of NF1 (Illes et al., 2001; Stevenson et al., 2007; Seitz et al., 2010), but there are no proven preventative or treatment strategies in NF1 patients. This study is designed to assess the efficacy of oral vitamin D therapy to prevent abnormal loss of bone mass in young adults with NF1.

HYPOTHESIS

We hypothesize that bone mineral density (BMD) in patients with NF1 and vitamin D insufficiency can be preserved by oral vitamin D and calcium supplementation.

SPECIFIC AIM

This is a randomized clinical trial of oral vitamin D therapy in adults with NF1 and vitamin D insufficiency to compare the effects of a 600 IU daily supplement of cholecalciferol with a therapeutic dose of cholecalciferol (4,000 IU/day) on maintenance of BMD. All participants will also take an oral calcium supplement (400 mg elemental calcium) daily.

BACKGROUND/INTRODUCTION

Neurofibromatosis 1 (NF1)

NF1 is a genetic condition, affecting 1 in 3000 people worldwide, caused by a constitutional heterozygous “loss of function” mutation in the *NF1* gene on chromosome 17q11.2. NF1 is a multisystem disease, and almost all affected individuals develop osteopenia or osteoporosis by the time they are 50 years old.

Bone Mineral Density (BMD) and Osteoporosis

Bone mass is accumulated in childhood and adolescence, and peak bone mass is normally reached by approximately age 25 years (Compston, 1995). Once peak bone mass is achieved, bone is continually remodeled by a balance of absorption and deposition to maintain bone homeostasis (Rizzoli et al 2001, Gilsanz and Wren 2007). The maintenance of normal BMD in younger adults reduces the risk of osteoporosis later in life (IOM 2011). After menopause in women and with aging in men, bone mass is lost, mainly due to sex hormone deficiency (Slemenda et al 1996).

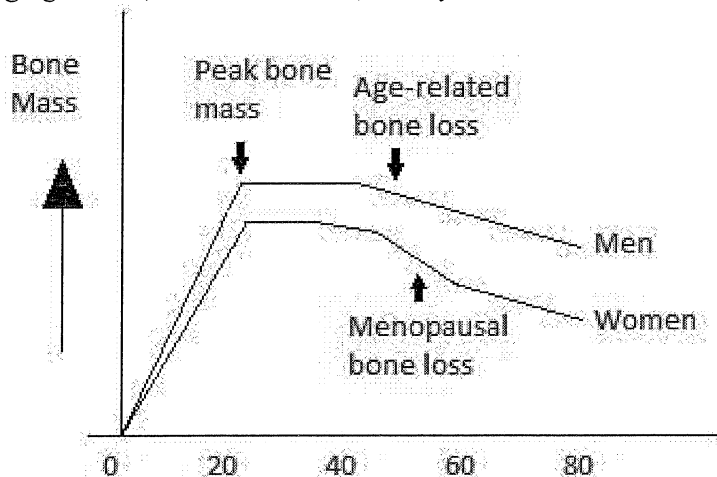


Figure 1. Diagrammatic representation of life-time changes in bone mass (Figure reproduced from Compston JE: *Osteoporosis, corticosteroids and inflammatory bowel disease. Aliment Pharmacol Ther* 1995;9:237-50)

DXA is commonly used to measure BMD at the hip, lumbar spine and wrist. BMD is measured in gm/cm², and this value is usually converted to a “Z-score” or “T-score” for each site. The Z-score is based on comparison of the measured BMD to an age-, sex- and sometimes race-matched reference group. The T-score is based on comparison to a reference group of young adults, whose bone mass is at its lifetime peak. The Z-score or T-score is the number of standard deviations above or below the mean for this reference group. In older adults, a T-score from 2.5 SD above the mean to 1.0 SD below the

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)

mean ($T = -1.0$ to $T = 2.5$) is considered to be normal. Low BMD (also called osteopenia) is defined as between $T = -1.0$ and $T = -2.5$. Osteoporosis is defined as a T score lower than -2.5 .

Although effective treatments exist for low BMD in the general population, osteoporosis is often asymptomatic until it is advanced, and the first symptom for many affected individuals is fracture. The key to reducing the personal and public health burden of osteoporosis is early identification and treatment to prevent the occurrence of fractures. This requires recognition of high-risk patients and DXA screening to identify those with low BMD. Individuals with NF1 are at higher risk than the unaffected population to have low bone mineral density.

Vitamin D and Its Role in Bone

Vitamin D regulates calcium homeostasis and plays a key role in bone metabolism (Plum and DeLuca 2011; Rosen 2011). Although vitamin D may be obtained from food or supplements in the diet, most people synthesize most of the vitamin D they need during sunlight exposure. Vitamin D is formed in the skin by the action of ultraviolet light on 7-dehydrocholesterol. The form of vitamin D that is initially synthesized is biologically inert. It is converted by the liver into 25-hydroxy vitamin D, the major circulating form of the vitamin. 25-hydroxy vitamin D, which is also inactive, is bound to vitamin D binding protein in the blood or stored in fat and muscle tissues. In order to become physiologically active, 25-hydroxyvitamin D must be converted to 1,25-dihydroxy vitamin D by a 1- α -hydroxylase encoded by the *CYP27B1* locus. This conversion occurs primarily in the kidney, although some other cell types, such as keratinocytes and monocytes, can also produce active 1,25 dihydroxy vitamin D from its 25-hydroxy precursor. Vitamin D acts through the binding of 1,25 dihydroxy vitamin D to the vitamin D nuclear receptor (VDR), which is widely expressed throughout the body. The classical activity of vitamin D on calcium homeostasis is mediated in response to low serum calcium concentration. This stimulates release of parathyroid hormone (PTH) by the parathyroid glands, and PTH, in turn, stimulates *CYP27B1* transcription, which leads to increased production of active 1,25 dihydroxy vitamin D. The activated vitamin D then binds to VDRs in target tissues, increasing calcium absorption by the intestine, increasing calcium reabsorption by the distal renal tubule, and stimulating calcium reabsorption from bone. These actions increase the serum calcium concentration, which suppresses PTH secretion, thus dampening the system.

Serum 25-hydroxyvitamin D levels are significantly correlated with BMD and fracture risk in the general population (Vieth, 2005; Arya, 2004; van Scherr et al 2008; Sakuma et al 2011, Burgi et al 2011), but most of these studies have been done in postmenopausal women; a few have been done in older men. In a metaanalysis of 30 studies that included more than 2900 subjects, serum 25-hydroxyvitamin D levels were 0.66 of a standard deviation less in older individuals who fractured their femurs than in those who did not fracture (Weatherall et al 2000). A more recent metaanalysis of 8 studies that included over 2000 subjects 65 years of age or older (Bischoff-Ferrari et al, 2009) demonstrated a dose effect of vitamin D3: compared to calcium alone or placebo, subjects who received 482-770 IU of vitamin D3 per day had a significantly reduced risk of hip and non-vertebral fractures (pooled relative risk [RR] = 0.80; 95% confidence interval [CI], 0.72-0.89, and pooled RR = 0.82; 95% CI, 0.69-0.97, respectively), whereas subjects who received only 400 IU per day had no beneficial effect (RR = 1.02 and 1.09, respectively). Cauley et al (2010) showed that a 1 standard deviation decrease in serum 25-hydroxyvitamin D level was associated with an increased risk of hip fracture (hazard ratio = 1.60; 95% CI, 1.19-2.17) in over 2000 older male individuals.

There are very few studies of the effects of vitamin D on bone in younger adults without chronic disease, but the available data support the importance of vitamin D in maintaining bone homeostasis throughout life. An association study in 756 young Finnish army recruits demonstrated that those with lower serum 25-hydroxy vitamin D levels were more likely to suffer stress fractures during training than those with higher serum vitamin D levels (Ruohola et al, 2006). Recently, Priemel et al (2010) demonstrated that vitamin D insufficiency was very common among healthy German adults (401 males, mean age = 58.2 years, and 270 females, mean age = 68.2 years) and that 25.6% of these individuals had histopathological evidence of osteomalacia (defined as > 2% increase in osteoid volume per bone volume) in iliac crest biopsies. This was never seen in subjects whose serum 25-hydroxy vitamin D levels were > 30 ng/mL (75 nmol/L). Vitamin D status is usually estimated by measuring the concentration of 25-hydroxy vitamin D in the blood (Gascon-Barré, 2000). Although the serum concentration of 25-hydroxyvitamin D required for good health has been controversial, a consensus has now developed that maintenance of optimal BMD and fracture prevention requires a serum 25-hydroxy vitamin D concentration of at least 30-32 ng/mL (75-80 nmol/L) (IOM 2011).

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)

Bone Health in NF1

Skeletal abnormalities that occur in patients with NF1 fall into three general categories: (1) characteristic focal lesions, (2) short stature, and (3) osteomalacia, osteoporosis, or low BMD. Serious focal bone lesions are one of the cardinal features of NF1. These abnormalities, which are almost always evident in childhood, include tibial dysplasia, dysplastic scoliosis, and sphenoid wing dysplasia. There are multiple case reports of osteomalacia (Hogan et al 1986; Weinstein and Harris 1990; Abdel-Wanis and Kawahara 2002) or severe osteoporosis (Brunetti-Pierri et al 2008; Bahadir et al 2009) in people with NF1, and it seems that these cases represent the extreme end of a spectrum of generalized bone disease. Konishi et al. (1991) described a typical case of osteomalacia in an NF1 patient and reviewed 34 previously-described cases. These are usually characterized by adult-onset bone pain, impaired ambulation, multiple pseudofractures, and marked increase in osteoid on bone biopsy. In some instances, increased renal phosphate loss with hypophosphatemia or severe vitamin D deficiency and dramatic response to vitamin D therapy were noted.

Seitz et al. (2010) examined iliac crest biopsies from 14 adults with NF1 who did not have symptomatic osteomalacia or known dystrophic bone lesions. The patient samples were compared to 14 iliac crest biopsies taken at autopsy from individuals without NF1 or any disease known to affect calcium or bone homeostasis. These investigators found a decrease in bone volume and trabecular thickness, an increase in osteoclast number and surface area, an increase in osteoblast number and surface area, an increase in osteoid volume and surface area, and inhomogeneous mineral distribution with decreased calcium content in the NF1 patient biopsies. In comparison to controls, the NF1 patients who were studied had significantly lower serum 25-hydroxyvitamin D3 concentrations. The findings were similar to those reported by Brunetti-Pierri et al. (2008) in vertebral bone samples obtained from three NF1 patients known to have poor BMD during surgical correction of scoliosis.

Vitamin D Status of NF1 Patients

Five studies of serum 25-hydroxyvitamin D concentrations in people with NF1 have been published, and all found reduced average values compared to controls or higher than expected frequencies of vitamin D insufficiency/deficiency. Three of these studies included patients seen in Hamburg, Germany (Lammert et al., 2006; Tucker et al. 2009; Seitz et al., 2010), but the other two studies were of patients from Texas (Brunetti-Pierri et al., 2008) or Utah (Stevenson et al., 2011), areas with substantially more sun exposure than Hamburg. The reason for the high prevalence of vitamin D insufficiency in the NF1 population is unknown. There have been no published studies of vitamin D dietary intake, absorption, sunlight-induced synthesis, degradation, or excretion among NF1 patients.

Data on the relationship of serum vitamin D concentration to BMD in people with NF1 are inconsistent, but the reported studies have been small and the patient groups, heterogeneous. Brunetti-Pierri et al. (2008) reported that 10 of 16 NF1 patients with low bone mass were vitamin D deficient. Tucker et al. (2009) did not see an association of BMD with reduced serum 25-hydroxy vitamin D levels in unselected NF1 patients but did find an association between high PTH and low BMD. Stevenson et al. (2011) found low serum 25-hydroxyvitamin D concentrations to be frequent but no association with low BMD in a cohort of children with NF1. Unpublished data from the University of British Columbia indicate that low serum 25-hydroxy vitamin D levels are associated with low BMD in NF1 patients over 50 years of age (see below).

Vitamin D Treatment of Low BMD

Placebo-controlled clinical trials of oral vitamin D supplementation in older adults who do *not* have NF1, but who are vitamin D deficient and have low BMD, have consistently shown improvement in bone mineralization in response to therapy (Bischoff-Ferrari et al 2009; IOM 2011). For example, in a study of 3270 elderly women, Chapuy et al. (1992) showed that daily supplementation with 800 IU of vitamin D3 and 1200 mg calcium for 1.5 years resulted in a 2.7% increase in BMD at the proximal femur, compared to a 4.6% decrease in untreated controls. Hip and non-vertebral fracture rates were also significantly lower in the treated group. Similarly, significant improvements in BMD and reductions in fracture rates were seen in a trial of treatment with 700 IU vitamin D3 and 500 mg calcium in men and women over age 65 (Dawson-Hughes et al, 1997) and in a trial of treatment with 400 IU vitamin D alone in elderly Dutch women (Ooms et al, 1995). In contrast to the clear efficacy of vitamin D treatment in people with vitamin D deficiency, clinical trials of vitamin D therapy in individuals with various serum levels of vitamin D have produced somewhat equivocal results on BMD or bone loss (Chung et al. 2009). However, after reviewing the available data, a recent Institute

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)

of Medicine report (2011) concluded that vitamin D3 and calcium supplementation produces small increases in spine and total body BMD.

Vitamin D Dose Requirements for Supplementation

The response of people with vitamin D insufficiency or deficiency to treatment depends on how low the serum 25-hydroxyvitamin D concentration is at the time therapy is initiated; the greatest response is seen with the greatest deficiency (IOM 2011). Heaney et al. (2003) have shown that for a starting serum 25-hydroxyvitamin D level of 24 ng/mL (60 nmol/L), the serum concentration increases approximately (0.3 ng/mL (0.75 nmol/L) for every additional 40 IU of vitamin D taken per day. For example, to reach 30 ng/mL (75 nmol/L) from a starting serum level of 24 ng/mL (60 nmol/L) would require about 800 IU/day of supplementary vitamin D. The US National Osteoporosis Foundation recommends the minimum daily intakes of calcium and vitamin D.

The current recommended upper limit for daily vitamin D intake is 4000 IU/day (IOM 2011). Vitamin D has a wide safety range (Veith, 2006; Heaney, 2006). Vitamin D toxicity is a rare event caused by ingestion of excessively high amounts (IOM 2011). The upper value of serum 25-hydroxyvitamin D concentration that can be tolerated with causing hypercalcemia is unknown, but studies suggest that this level is above 150 ng/mL (375 nmol/L). Vitamin D overdose is easy to identify clinically because it is invariably accompanied by hypercalcemia (Veith, 2006). Oral vitamin D doses below 10,000 IU/day are usually not associated with toxicity, but doses of 50,000 IU or more per day for several weeks or months frequently produce hypercalcemia and toxic manifestations (IOM 2011).

Studies in People with NF1

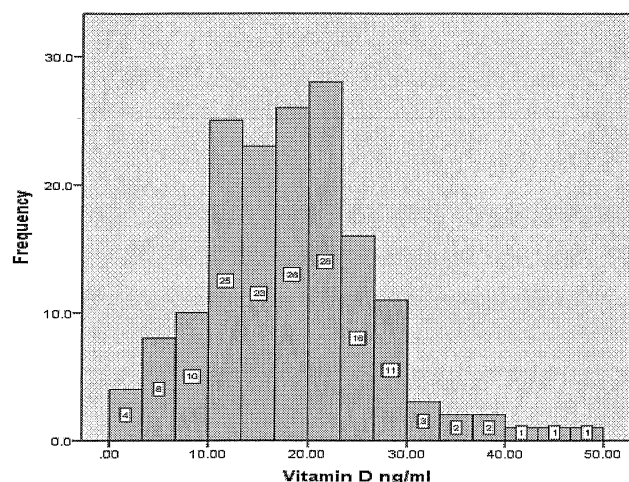
Three studies have examined the effect of supplementation with oral vitamin D (cholecalciferol) on BMD in individuals with NF1. In the first study, 8 patients with elevated serum PTH concentrations were treated with 400 IU of vitamin D daily for 4 months (Brunetti-Pierri et al 2008). No significant change in BMD was observed. In the second study, four patients whose initial BMD T-scores were below -3.0 SD were given 1000 IU vitamin D per day for 1 year (Setiz et al 2010). This treatment produced a significant increase in BMD. A pilot study from Germany (Schnabel et al., 2013) indicates that administration of vitamin D in a dose that maintains the serum 25-hydroxyvitamin D level above 30 ng/mL significantly improves BMD. This study followed BMD for two years in 36 adults with NF1 and low serum 25-hydroxy vitamin D concentrations. Nineteen of the patients received vitamin D supplementation for two years, 6 patients received supplementation for one year, and 10 patients chose not to take vitamin D supplements. Supplementation was administered in a dose that maintained the serum 25-hydroxy vitamin D level above 30 ng/mL (75 nmol/L). BMD was measured at entry and again after one and two years. The trial included 13 males and 23 females with NF1 (mean age = 45.75 years; range, 32-63 years). Ten subjects received no treatment, 6 received one year of treatment, and 19 received 2 years of treatment. The mean age and BMD were not significantly different among the three groups of NF1 patients at the time they entered the study. In comparison to untreated patients, those who were treated had significantly less reduction in BMD T-score at the hip ($p=0.014$) and at the lumbar spine ($p=0.05$). Maintenance of the BMD T-score at the hip was significantly better ($p=0.022$) in NF1 patients who were treated for 2 years than in those who were treated for 1 year. There was no association between treatment response and either age or T score at the time of entry. However, treated individuals with lower initial serum 25-hydroxy vitamin D concentrations had greater improvement in T score at the hip.

Serum 25-Hydroxy vitamin D Concentrations by Month in Individuals with NF1

158 unselected NF1 patients from the Hamburg NF Clinic, in whom the serum 25-hydroxy vitamin D had been measured at least once, were included in this analysis. In order to assess the effect of seasonality (a surrogate for sun exposure) on serum vitamin D concentration, we classified the measurements by the month in which they were obtained and calculated the mean serum 25-hydroxy vitamin D concentration for each month.

The distribution of serum 25-hydroxy vitamin D concentrations is shown in the following graph.

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)



Only 10 (6.3%) of the 158 NF1 patients tested were vitamin D sufficient (>30 ng/mL [>75 nmol/L]). The mean serum 21-hydroxy vitamin D level was below 30 ng/mL (75 nmol/L) in every month, but the lowest levels were observed in February and March.

STUDY DESIGN

The study will take place in one of 4 locations; University of British Columbia (Vancouver, CA), University of Utah (Salt Lake City, UT, USA), University of Cincinnati (Cincinnati, OH, USA), and University of Hamburg (Hamburg, Germany). Individuals will be enrolled for serum screening using a blood test to determine their level of 25-(OH) vitamin D [25(OH)D]. Those with sufficient vitamin D (≥ 30 ng/mL (75 nmol/L)) will be excluded from the clinical trial because this level of vitamin D is thought to be sufficient for maintenance of healthy bones. Those individuals with deficient vitamin D (≤ 8 ng/mL) will be excluded and be advised that treatment by their primary health care provider is indicated. The remaining individuals, with serum 25(OH) vitamin D levels between 9 and 29 ng/mL, will be treated with oral supplementation of vitamin D in the form of cholecalciferol. They will be randomized to receive either 600 IU or 4,000 IU of cholecalciferol orally on a daily basis and calcium supplementation of 400 mg daily elemental calcium per day. The primary outcome measure is bone mineral density, which will be determined by DXA scanning at the beginning and at the end of the 2-year trial. DXA is a standardized measure that uses low dose x-rays to determine the density of bones in the hip and spine. Secondary outcome measures include quality of life and history of bone fractures. Serum samples will be analyzed for 25(OH) vitamin D, calcium, and intact parathyroid hormone at the beginning, midpoint, and end of the 2-year study.

The two doses of cholecalciferol were selected with respect to standard dosages in clinical care; 600 IU per day is considered a standard supplement, whereas 4,000 IU is considered a standard therapeutic dose. A pharmacist employed by DDrops™ prepares two sets of bottles, one set has 300 IU per metered dose and the other set has 2,000 IU per metered dose. Participants are randomized to one or the other dose, and they take two measured drops orally, once a day. Randomization tables will be created by a PhD statistician. Randomization tables will include geographic location and gender, see study operations manual for further details.

There is a dropper that automatically drops out a measured amount when the bottle is turned upside down. Each bottle lasts 3 months, and a new bottle with the same dose of cholecalciferol is provided after a diary is reviewed and an updated medical history provided to the study team. A total of 4 distributions will be made over the course of this 2-year study.

The target population for this study is adults with neurofibromatosis type 1 (NF1) between the ages of 25 and 40 years at time of recruitment who are insufficient for vitamin D, as defined by serum testing. In this age group, there is a slow, steady decline of bone mineral density, and individuals with NF1 have been shown to have a higher rate of decline than the unaffected adult population (Sietz et al., 2010). Vitamin D sufficiency is theorized to diminish the rate of decline of BMD. Over a 2-year time period, the rate of BMD decline at the hip and spine will be measured and compared between

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)

the low-dose versus high-dose groups. If there is a difference then appropriate dosing of vitamin D supplementation to optimize bone health in patients with NF1 could be established.

Inclusion/Exclusion Criteria

All individuals with NF1, based on NIH diagnostic criteria, who are between the ages of 25 and 40 years, may participate in this study. All participants will be enrolled in the study and then screened for serum 25(OH)D levels. Individuals with levels between 8 and 30ng/ml are eligible for vitamin D supplementation.

Individuals will be excluded for the following reasons:

- 1) diagnosis of Paget's disease, hyperthyroidism, hyperparathyroidism, or other medical condition that affects bone health
- 2) they foresee that they will be unable to comply with the two-year study protocol
- 3) Pregnant, planning to conceive within the next two years, or is less than 6 months post-delivery or lactation.
- 4) vitamin D supplementation in the last 3 months equal to or greater than 600IU per day
- 5) oral or IV glucocorticoid use for over 3 months
- 6) bisphosphonate therapy for more than 3 months
- 7) calcitonin therapy for more than 3 months
- 8) calcium supplementation in last 3 months equal to or greater than 1000mg per day
- 9) malignant peripheral nerve sheath tumor (MPNST)
- 10) history of kidney stones in last 5 years
- 11) individuals with metal instrumentation in spine or hip that preclude accurate DXA interpretation.
- 12) inability to obtain blood samples on routine venipuncture
- 13) anti-epileptic medical therapy
- 14) anticoagulant medical therapy

Description of Recruitment Process

All of the participating centers maintain registries of affected individuals who wish to participate in studies. Individuals on these lists who meet the study inclusion criteria will be mailed an IRB-approved letter of invitation to participate in the study, as well as a consent form that further describes the study. Contact information for phone, fax, mail, and email will be included in the information package. If there has been no response from the potential participant within one month of mailing the invitation, the study coordinator will phone the potential study participant to verify that the letter of invitation was received and to address any questions there may be about the study. This process is currently in place for several studies, and has been IRB-approved in the past.

Using IRB-approved advertising material we will also advertise for participants via patient support groups and lay organizations for NF1 patients. The support groups and lay groups are well-organized to provide information on translational studies and encourage patients to seek additional information on clinical trials if they are interested in participating. In particular, The Children's Tumor Foundation (CTF) has developed a North American Registry in which patients can enroll directly with the CTF. The demographic information includes geographic location, and there will be a clause that allows contact for recruitment into clinical trials. Those living within a 250-mile radius of the 3 participating North American sites, University of Utah, University of British Columbia, and the University of Cincinnati will be contacted about possible enrollment.

All subjects will be provided participant compensation equivalent to US\$25 for enrollment and screening blood test for the determination of serum 25-OH vitamin D levels [25(OH)D]. Subjects will be offered participant compensation equivalent to US\$50 per clinical visit at the start of the study, at 12 months, and at 24 months. These visits include DXA scans on entry and exit, and blood work, physical activity survey, calcium intake questionnaire, a fracture history, a quality of life survey, and a brief clinical exam for each visit.

Description of the Informed Consent Process

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)

The study coordinator at each site will be responsible for explaining the study, answering questions, and obtaining informed consent. The principal investigator at each site will also be available for answering questions. The study will be explained in advance of the screening visit and the consent form will be signed and witnessed prior to the first screening visit. All potential study participants will be adults who are competent to understand the study and sign consent on their own behalf. Each subject will have at least one week to decide whether or not they wish to participate. Participants will have full access to the investigative team throughout the clinical trial. Coordinators at each site will telephone participants every 6 months between visits to review any issues or concerns with respect to the trial. A review of the vitamin D₃ and calcium supplementation diary will be obtained and any potential side effects or adverse effects will be documented and discussed at that time.

Screening Procedures

The consent form and informed consent process describes the screening process for this study, obviating the need for a separate consent form for screening. The screening process involves a blood draw for 25(OH)D levels, and a urine pregnancy test, where applicable. To avoid a second blood draw to obtain other serum measures of bone health for those subjects who are eligible for the study (serum calcium, serum PTH), subjects will have blood drawn for all these measures as part of the screening procedure.

All potential participants come for the initial screening. This will take about 20-60 minutes. The procedures for the screening are described below:

- Meeting with the study coordinator to sign the consent form. A clinic coordinator and/or physician will be available to verify medical history and ensure recruits are eligible to participate.
- A blood test will be performed. The amount of blood required is about three teaspoons (15ml). The blood is to screen for serum 25(OH) vitamin D level. A local serum 25 (OH) vitamin D level will be obtained and used for study enrollment. Other serum studies will be performed if the enrollee is found to be eligible for the remainder of the study. These tests include intact parathyroid hormone (a measure of bone metabolism) and calcium
- After the initial blood test, the study coordinator will provide the participant with the result of the vitamin D testing. The enrollee will learn of his or her serum vitamin D level; either sufficient ($\geq 30\text{ng/ml}$), very low ($< 8\text{ng/ml}$), or insufficient. If insufficient then the enrollee will be invited to participate in the remainder of the study.

It is expected that about two-thirds of enrollees will have insufficient vitamin D levels, thus will be eligible for the remainder of the study. Individuals with low vitamin D levels, but equal to or higher than 8ng/ml , will continue in the clinical trial with a pregnancy screening test. Those who are pregnant will have enrollment deferred to a later date. Those who are not pregnant will undergo randomization for high- versus low-dose vit D₃ supplementation. DXA scanning will be performed of the spine and left hip as the primary endpoint of the clinical trial. Those who become pregnant will be removed from the supplementation and DXA scanning while remaining on the longitudinal studies until study end. Individuals with insufficient 25(OH)vitamin D are usually treated with both vitamin D and calcium supplements. Therefore, all participants will supplement their calcium intake with 400 mg elemental calcium per day. A diary is provided to keep daily track of vitamin D and calcium supplementation. Fractures, should they occur, will also be noted in participant's diaries and conveyed to the study coordinator. Individuals who have an adequate serum 25(OH)D level, $\geq 30\text{ng/ml}$, will be given their results and followed in a registry. (see **Figure 2**). Individuals who have serum 25(OH)D levels $< 8\text{ng/ml}$, will be notified so that they can discuss more extensive treatment with their primary care provider.

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)

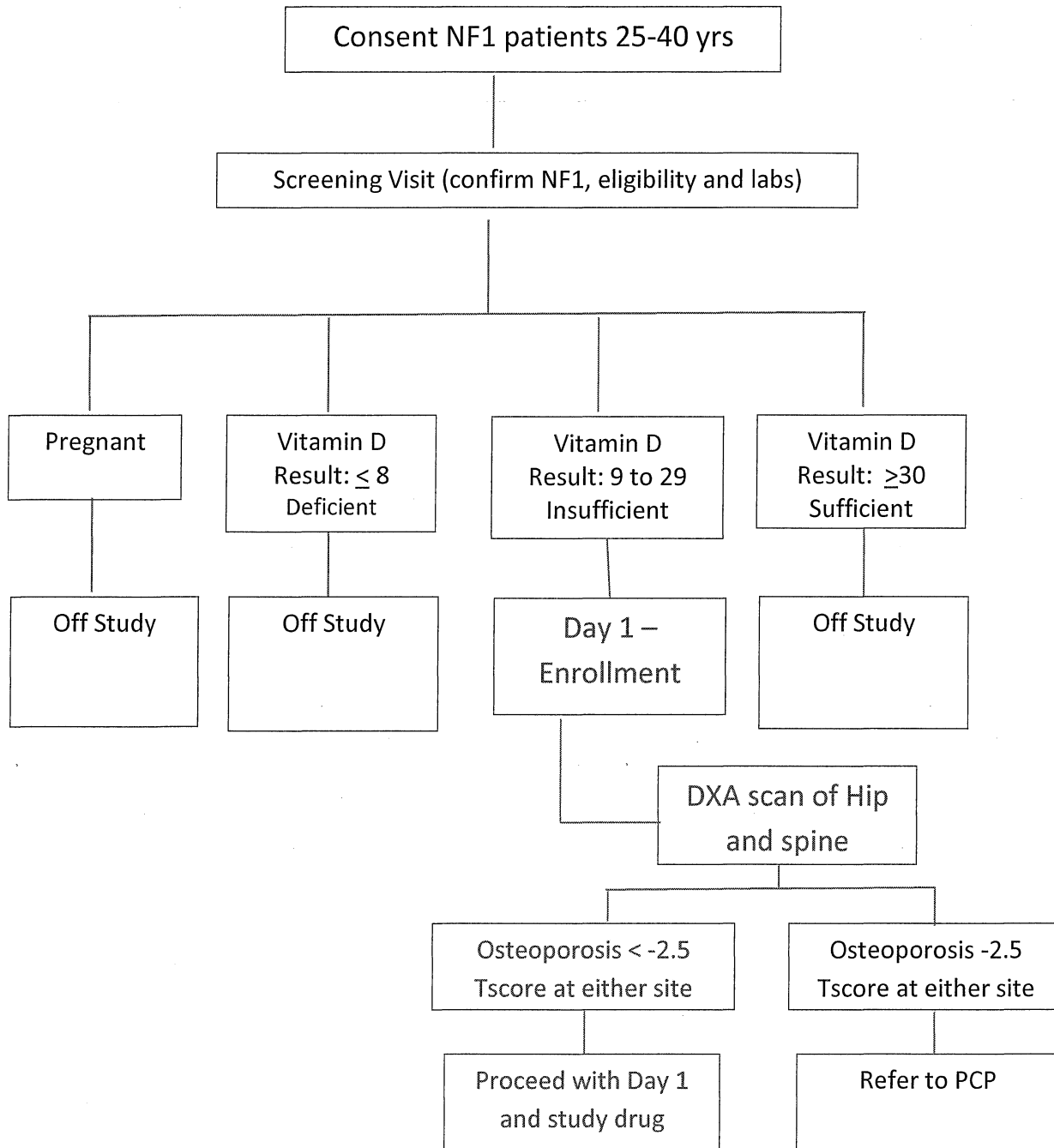


Figure 2. Study Design – 316 screened; 226 enrolled

DXA

Bone densitometry (DXA) is a painless procedure, in which a densitometry technician scans the hip and spine of the subject on a large, flat table, using cushions to position the area being scanned. There is a detector arm overhead, connected to a computer and monitor, that measures the density of bone via a process that calculates the amount of low-dose x-rays that are absorbed by the bone. Denser bone absorbs more x-rays than less dense bone. The output is a measure of bone mineral density. The data for both sites, spine and left hip, will be transferred to a CD and shipped to the the University of Utah (see study operations manual for further details). DXA scanning is a standard procedure that is performed in a medical setting. Individuals are situated on a table for scanning and the procedure is completed in less than 30 minutes. The amount of radiation will be limited to about 6 mrem. For comparison, the annual background radiation exposure from the earth and atmosphere in an average person is roughly 300 mrem.

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)

Risks/Benefits Assessment

Risk of Vitamin D Supplementation

There is a risk for vitamin D toxicity with over-supplementation; however, it is highly unlikely that treating with 4,000IU vitamin D₃/day (the higher dose in this clinical trial) will cause toxicity. In comparison to the amount of vitamin D synthesized in the skin of a young adult, the treatment dose is small. For example, the equivalent synthesized amount of vitamin D from 10-12 minutes of sun at Boston latitudes in mid-July to a Caucasian wearing a bathing suit is about 10,000-20,000 IU.

Cholecalciferol overdose can be detected by signs and symptoms of hypercalcemia. Study participants will be counselled regarding the symptoms of vitamin D overdose and will be given a card to keep with them with these symptoms summarized, and contact numbers of the appropriate coordinators as well as a 24-hour emergency contact number. Vitamin D overdose causes hypercalcemia, and calcium levels will be checked at 12 months after initiation of vitamin D₃ and calcium supplementation. Early symptoms of hypercalcemia include nausea and vomiting, weakness, headache, somnolence, dry mouth, constipation, metallic taste, muscle pain and bone pain. Late symptoms and signs of hypercalcemia include polyuria, polydipsia, anorexia, weight loss, nocturia, conjunctivitis, pancreatitis, photophobia, rhinorrhea, pruritis, hyperthermia, decreased libido, elevated BUN, albuminuria, hypercholesterolemia, elevated ALT (SGPT) and AST (SGOT), ectopic calcification, nephrocalcinosis, hypertension and cardiac arrhythmias. These symptoms will be described in lay terms and be provided to each study participant.

Whereas side effects from use of vitamin D in this trial are not anticipated, accidental overdose is always a possibility. Safety monitoring of symptoms associated with hypercalcemia will be put in place to detect early signs of overdose by clinical monitoring provided by the study coordinator at the respective sites. The amount of vitamin D in one full bottle of the higher dose of Ddrops is 750,000IU, which, if taken all at once, might cause symptoms of overdose in adults and could seriously harm a child. It is important that subjects be counselled to keep the vitamin D₃ provided in this study out of reach of children. Overdose treatment will be provided on a clinical basis, depending on symptoms. Treatment could include correcting dehydration by administering intravenous fluids, including promotion of calcium excretion by administration of intravenous normal saline. Corticosteroids may also be given.

Risk of Radiation from DXA

The amount of radiation from DXA at the spine and left hip is low (about 6 mrem) and equivalent to that of a cross-country airplane flight. Nevertheless, pregnancy tests will be obtained on all women prior to DXA and participants who are pregnant will be excluded.

Risk of Infection from Venipuncture

There is a small risk of infection after venipuncture. We will use trained phlebotomists, using appropriate technique to minimize this risk.

Risk of Teratogenicity of Vitamin D after an Unrecognized Pregnancy

There is no evidence that vitamin D, at the levels used in this clinical trial, is teratogenic. TERIS (Teratogen information system) states that:

"No controlled epidemiological studies of malformations in infants born to women who took large amounts of vitamin D during pregnancy have been reported. In one clinical series, no malformations were observed among 15 children born to hypoparathyroid women who ingested an average of 107,000 units of vitamin D per day throughout pregnancy (Goodenay & Gordon, 1971). In another series, no malformations were seen among 19 infants with elevated vitamin D levels whose mothers drank milk containing excessive vitamin D supplements (100-600 times the RDA) during pregnancy (O'Brien et al., 1993)." TERIS (2004)

Potential Benefits

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)

Participants may benefit from serum 25(OH) vitamin D screening. Those with deficient 25(OH) Vitamin D will be referred to a health care provider for medical management. Those with a sufficient level of serum 25(OH) Vitamin D will be provided that information, which may be viewed as a benefit of the screening phase of this trial.

Participants may benefit from maintenance of bone mineral density (BMD), awareness of their BMD status, and documentation of a baseline DXA scan to provide enrollees with their BMD. We anticipate that some subjects may have improved BMD after treatment with vitamin D₃, but our expectation is that it is more likely to decrease the anticipated rate of decline in BMD. Participants will benefit from surveillance of BMD that is beyond the current clinical standard of care for 25-40 year old patients. Participants who are ineligible for the clinical trial on the basis of osteoporosis may benefit from referral to clinical treatment for their osteoporosis.

The NF1 population as a whole is expected to benefit from a greater knowledge of BMD and bone health and from knowledge of the potential efficacy of several doses of vitamin D.

DATA MANAGEMENT

All data collected from this study will be maintained as both hard copy forms and electronic data entered into an NF1 database designed and maintained in the Center for Clinical & Translational Sciences at the University of Utah. This database has a tiered access with each of the four centers having password-protected access to data entered from their respective site. These data include demographic information, NF1-related manifestations, documentation of data collection points, and actual data values including serum biomarkers and bone mineral density values. The hard copy forms include surveys, questionnaires, and clinic report forms (CRFs) that will be maintained on each enrollee at the local site. Investigative teams at each site have full access to data collected from participants enrolled through their site. There is limited access to data collected from other centers. The project manager, data manager, and the data safety monitoring committee will have full access to data collected from this study, until completion.

Identifiers

Human subjects will be identified at the time of enrollment from one of the 4 centers; UBC (University of British Columbia, Canada), UTA (University of Utah, USA), CIN (University of Cincinnati, USA), and HAM (University of Hamburg, Germany). The unique identifier will include the site followed by a 3-digit number starting with 100 ascribed sequentially at the time of enrollment at each site from:

UBC-100 to UBC-XXX

UTA-100 to UTA-XXX

CIN-100 to CIN-XXX

HAM-100 to HAM-XXX

This identifier will be used on all correspondence and only the investigative team at the enrollment site will be able to link the name with the identifier.

Confidentiality

As with all studies carried out at the 4 institutions involved in this multicenter trial, every measure will be taken to protect the privacy of enrollees in this study. Each site has full integrity of enrollment, and once a patient enrolls he or she is given a unique identifier from the site that is the only information transmitted between the data collection center and other collaborating sites. Each data item is labeled only with the unique identifier and the only demographic information shared is sex, affected status, and year of birth. Data collected from each site and entered in the database is protected by standard operating procedures in place in the informatics core of the CCTS. Individual sites have measures to protect confidential information as part of any IRB-approved study in each of the respective academic institutions.

The information gathered on enrollees during this study will be kept confidential to the extent permitted by law. However, the investigator and his staff as well as regulatory personnel, the Department of Defense, the U. S. Food and Drug Administration, the Office for Human Research Protection, and each Institutional Review Board at the 4 centers will have access to confidential information that identifies the participant by name. The results of the treatment, including laboratory tests may be published for scientific purposes; however the participant's identity will not be revealed.

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)

Disposition of Data

Hard copy data from this study will be stored under the responsibility of the coordinator at each of the 4 sites. Each site has protected facilities to store data in locked cabinets within rooms that have limited access. The coordinator is responsible to oversee safe storage of the hard copy data. The electronic database is embedded in the Informatics Core at the Center for Clinical Translational Science (CCTS) at the University of Utah. Databases within the Informatics Core are designed to maintain the integrity of the data in storage. These electronic data will be protected by the data manager of the CCTS, but ownership reverts to each of the 4 principal investigators of this study (Viskochil, Friedman, Schorry, and Mautner).

This study provides an opportunity to follow a large cohort of adults with NF1 for a number of years as they age. All PIs are in agreement to maintain each enrollee in a registry/database for longitudinal studies that assess aging processes in the NF1 population. The IRB consents are drafted to reflect ongoing studies; the enrollees have an opportunity participate in a long-term registry and have their serum stored frozen for use in future studies. Data will be stored for as long as the respective institutions agree to maintain an open study.

Sharing Study Results

There are 3 instances where participants will receive information based on their enrollment in the study. The initial serum 25(OH)D will be conveyed to the enrollees as part of the screening test. Participants will know if they have sufficient vitamin D, insufficient levels, or possibly severe deficiency that requires medical intervention. Those who have 25(OH)D <8ng/ml will be notified and the coordinator will inform their primary care provider. Second, if the initial DXA scan identifies osteoporosis, the coordinator will notify the participant and their primary care provider to consider initiation of medical management, regardless of the serum 25(OH) vitamin D level. Third, the final results of each participant's BMD calculations, status of dose randomization, and final serum calcium and 25(OH) vitamin D levels will be conveyed to the participant once available after the 2-year follow-up visit. They will receive an analysis and counseling regarding the results of their bone mineral density of spine and hip as determined by DXA scanning. These results will be shared with their primary care provider and may determine long-term care management for some participants.

Laboratory Evaluations

Specimens to be Collected, Schedule of Collection, and Amount of Each Collection

As outlined in other sections, there are 3 laboratory studies to be performed at 3 collection points in the protocol. Studies include serum 25(OH) vitamin D, serum calcium, and serum iPTH at entry, 1 year, and 2 years. These values will be correlated with bone mineral density and dose of cholecalciferol as an analysis of the study. Serum will be processed from 15-ml blood draws at each of the 3 time-points. No other lab studies will be performed. These values are to help determine the effect of low- versus high-dose vitD₃ on calcium metabolism and correlate to change in bone mineral density. None of the studies are used for safety monitoring because the 2 doses of vitamin D₃ are known to be well-tolerated.

Storage

Blood samples will be processed for serum and stored in each of 4 sites. Batches of serum specimens will be shipped under dry ice to the lab processing center at the Clinical Genetics Research Program freezer storage facility at the University of Utah under the direction of David Viskochil. Aliquots will be stored in this facility for the duration of the study, and an aliquot from each thawed sample will be sent to ARUP labs for analyses of 25(OH) vitamin D, calcium, and iPTH. Serum samples processed during assessments for year 1 and year 2 will be temporarily stored at -80 degrees Celcius at the collaborating sites until they can be batch-mailed under dry ice. Once these shipments arrive at the CGRP at the University of Utah they will be logged in for continued storage and a serum aliquot will be sent to the ARUP Lab for testing before date of expiration of the sample determined by each of the 3 tests. Participants at the University of Utah only will be given an option to have the remainder of their serum samples to be stored beyond the duration of the study by signing a different consent form. This option is provided so participants can provide biologic specimens for future studies, including some studies in which their clinical information could be shared with other investigators. This long-term storage is in a -80 degree freezer in a well-demarcated tissue repository. Each sample is marked with the participant identifier (ie. UTA110) and stored in boxes that identify the NF1-vitamin D supplementation study.

Labs Performing Evaluations and Special Precautions

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)

There are no special precautions in preparing serum for the studies to be performed at ARUP Labs. ARUP Labs is a CLIA-approved facility to perform many research-related studies using testing that has been validated on a routine basis. The 3 serum assays of this study are routinely performed at ARUP Labs. There are specifications provided by ARUP to phlebotomists and laboratory technicians to optimize lab draws, storage of serum specimens, and shipping specifications.

Human Subjects and Safety Monitoring

The PI from each participating institution will provide University of Utah with a copy of the initial IRB protocol approval and the yearly IRB continuing reviews. The Study Coordinator will also submit these to the USAMRMC ORP HRPO. Registration will be halted at a participating institution if a current continuing approval is not on file at the NF Consortium Operations Center. As this trial receives funding by the US Army, approval of all protocol amendments will be obtained from the USAMRMC ORP HRPO in addition to the institutional IRB prior to implementation.

Richard Kanner, M.D. will serve as the external medical safety monitor for this study. He serves as the Research Compliance Officer of the Center for Clinical and Translational Sciences at the University of Utah who will serve as the chair of a 3-member committee to oversee safety issues related to the study. The committee will meet face-to-face or by teleconference every 6 months to review recruitment and participant enrollment, monitor summarized data collection from the 4 sites, and review adverse events. As safety monitor, Dr. Kanner shall have authority to carry out the following:

- 1) Stop the research protocol in progress;
- 2) Remove individual participants from the research protocol;
- 3) Initiate steps to protect the safety and well-being of participants until the University of Utah IRB and Human Research Protection Office (HRPO) of the U.S. Army Medical Research and Materiel Command can assess the safety monitor's report.

He and his fellow committee members have the authority to discuss the research protocol with the investigators, interview participants, and consult with others outside the study about the research.

As chair, Dr. Kanner shall have the responsibility to promptly report the committee's observations and findings to the University of Utah IRB or other designated officials at the University of British Columbia, University of Cincinnati, University of Hamburg, and the HRPO.

Dr. Viskochil has obtained approval of this trial under the auspices of the CCTS to obtain services for medical safety monitoring available to PIs with approved protocols in the CCTS. He will assess the safety aspects of this trial and safety monitor report every 6 months. This is a valid process providing the respective IRB/Human Subjects Safety Committees view this study as minimal risk or almost minimal risk.

All observed or volunteered adverse events, regardless of suspected causal relationship to study drug, will be recorded as Adverse Events on case report forms and submitted to the Data Monitor within 2 weeks of its occurrence. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbation of pre-existing illnesses will be recorded. It will be left to the investigator's clinical judgment whether or not an adverse event is of sufficient severity to require that the subject should be removed from treatment. Any safety issue deemed Unexpected and Related to Vitamin D3 supplementation would disallow continued participation in the protocol. The data safety monitoring committee would review the safety issue and inform local coordinator of the study arm assignment (low or high dose vitamin d) for the withdrawn participant.

A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these occurs, the subject will be given appropriate care under medical supervision until symptoms cease or until the condition becomes stable.

The severity of toxicities will be graded as mild, moderate, or severe.

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)

SERIOUS ADVERSE EVENT REPORTING:

SAEs must be reported to the DSMC, the FDA, and the IRB, according to the requirements described below:

FDA Notifications:

- Adverse events occurring during the course of a clinical study that meet the following criteria will be promptly reported to the FDA:
 - Serious
 - Unexpected
 - Definitely, Probably or Possibly Related to the investigational drug
- Fatal or life-threatening events that meet the criteria above will be reported within 7 calendar days after first knowledge of the event by the investigator; followed by as complete a report as possible within 8 additional calendar days.
- All other events that meet the criteria above will be reported within 15 calendar days after first knowledge of the event by the investigator.
- All other adverse events and safety information not requiring expedited reporting that occur or are collected during the course of the study will be summarized and reported to the FDA through the IND Annual Report.

IRB Notification:

Events meeting the University of Utah IRB reporting requirements (<http://irb.utah.edu/submit-application/forms/problems.php>) will be submitted through the IRB's electronic reporting system within 10 working days

FDA ANNUAL REPORTS:

An annual progress report will be submitted to the FDA within 60 days of the anniversary of the date that the IND went into effect. (21 CFR 312.33).

PROTOCOL AMENDMENTS:

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

All amendments will be submitted to the FDA for review.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

PROTOCOL DEVIATIONS:

Any protocol deviation (or violation) will be reported to the IRB as soon as possible after the PI learns of the deviation, but in all cases within 10 working days. The following deviations will be reported to the IRB:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

STATISTICAL ANALYSIS

Sample size

The sample size for this study depends on the difference in maintenance of BMD between individuals treated with 600 IU versus individuals treated with 4,000 IU. Schnabel et al (2013) showed a mean change in the hip T-score of about -

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)

0.14/year in untreated, vitamin D insufficient NF1 patients and about -0.02/year in patients who were treated with oral cholecalciferol in a dose that maintained the serum 25-hydroxyvitamin D concentration above 30 ng/mL. A key aim of this study is to simplify the supplementation of vitamin D by eliminating the ongoing serum studies to maintain serum levels above 30 ng/ml, therefore we selected 2 standard dosing schemes, a daily dose of either 600 IU cholecalciferol for our minimal supplement and a higher daily dose of 4,000 IU. 600 IU dosing is the minimum daily intake from all sources combined recommended by the US National Osteoporosis Foundation (2007). 4000 IU/day is the current upper limit recommended for daily vitamin D intake (IOM 2011) but is far below 50,000 IU/day, the intake that has been consistently associated with toxicity (IOM 2011).

No information is available on the BMD response of NF1 patients with vitamin D insufficiency to daily cholecalciferol doses of either 600 IU or 4,000 IU per day for 2 years. Brunetti-Pierri et al (2008) found no difference in BMD among individuals with NF1 and elevated serum PTH levels who were treated with 400 IU of cholecalciferol for 4 months. In a pilot study (Schnabel et al., 2013), the mean difference in the hip T-score between a vitamin D₃ treated (6 NF1 patients) and untreated (10 NF1 patients) groups was 0.12/year with a standard deviation of about 0.14. Conservatively assuming that the subjects in the trial proposed here who are given 600 IU/day and those who are given 4,000 IU/day would have a mean difference in Z-scores at the hip of 0.06/year after 2 years, we estimate that 188 subjects will need to be included in this study and followed for two years (standard deviation=0.14, $p<0.05$, one-sided) to achieve 90% power (table 1). Allowing 20% loss to follow up over the two-year treatment period, we will need to randomize 226 subjects for the trial. No adjustment of sample size for stratification of the randomization is necessary because the stratifying variables (participating center and sex) will be treated appropriately as covariates in the analysis (Kernan et al., 1999).

Table 1: Sample-size calculation based on an alpha of 0.05 (one-sided) and standard deviation of 0.14. *(These calculations were performed using <http://hedwig.mgh.harvard.edu/samplesize/size.html>.)*

Mean Difference in BMD Between Treatment Groups	Power	Sample Size Required	Sample Size Plus 10%	Sample Size Plus 20%
0.12	90%	50	55	60
0.12	80%	36	40	43
0.06	90%	188	207	226
0.06	80%	138	152	166

Safety Monitoring and Interim Analysis

Participants will be clinically monitored for signs and symptoms of hypercalcemia throughout the trial period. Interim analysis of the difference in change of BMD at the hip between subjects randomized to the 600 IU cholecalciferol and 4,000 IU cholecalciferol groups will be performed when 50 participants have completed the second DXA assessment. The trial will be stopped and all subjects offered therapy with 4,000 IU/day of cholecalciferol if the effectiveness of this treatment is clearly demonstrated ($p<0.01$).

Data Analysis

The primary endpoint for this study is the difference in BMD over the course of treatment in the two groups. We expect NF1 patients with vitamin D insufficiency randomized to 600 IU/day of cholecalciferol to show loss of BMD over the two years of study and the subjects randomized to 4,000 IU/day to either maintain their BMD or have less BMD loss over 2 years. The primary metric used to assess BMD in this analysis is the mean change in hip T-score/year, and the two groups will be compared using analysis of variance with participating center and sex as covariates. Confirmatory analyses will

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)

also be performed comparing the change in lumbar T-score/year, change in hip BMD/year, and change in lumbar BMD/year between the two treatment groups.

Descriptive univariate analyses (t-tests, χ^2 tests, or other non-parametric tests, as appropriate) will be performed on all demographic, DXA, laboratory, and questionnaire data obtained at the time of entry to assure comparability of the groups that were randomized to the two different treatments. Similar descriptive analyses will be performed on data obtained from the calcium intake as well as on measures of compliance with treatment and drop-out rates to assess comparability of the two groups at the one-year and two-year time points.

Secondary analyses will include comparison using t-tests or analysis of variance of mean change in serum 25-hydroxy vitamin D, PTH, and calcium concentrations between the two treatment groups. We will also compare changes in the subjects' assessment of their quality of life with treatment in the two groups using non-parametric statistics.

All analyses will be performed with SPSS or SAS software using standard statistical methods that have been used extensively in NF1 studies by our group over the past 20 years. These analyses will be supervised by Dr. J.M. Friedman, a collaborator and PI from the University of British Columbia site.

RECORD KEEPING:

Per 21 CFR 312.57, investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified

References

- Abdel-Wanis M, Kawahara N. (2002) "Hypophosphatemic osteomalacia in neurofibromatosis 1: hypotheses for pathogenesis and higher incidence of spinal deformity." *Med Hypotheses*. 59:183-5.
- Arya, V., R. Bhambri, et al, (2004) "Vitamin D status and its relationship with bone mineral density in healthy Asian Indians." *Osteoporos Int* 15: 56-61.
- Bahadir C, Gürleyik G, Ocak E. (2009) "Neurofibromatosis type 1 and primary hyperparathyroidism with spinal deformity and osteoporosis." *Acta Chir Belg*. 109:123-5.
- Bischoff-Ferrari, H. A., W. C. Willett, et al, (2005). "Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials." *Jama* 293(18): 2257-64.
- Bischoff-Ferrari, H. A., E. Giovannucci, et al, (2006) "Estimation of optimal serum concentrations of 25- hydroxyvitamin D for multiple health outcomes." *Am J Clin Nutr* 84: 18-28.
- Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, Wong JB, Egli A, Kiel DP, Henschkowski J. (2009) "Fall prevention with supplemental and active forms of vitamin D: a meta- analysis of randomised controlled trials." *BMJ* 339:b3692.
- Brunetti-Pierri N, Phan K, Carter S, Lewis RA, Plon S, Ellis KJ, O'Brian SE, Lee B (2008) Generalized osteopenia in neurofibromatosis type 1 patients points to an underlying disorder of skeletal homeostasis and mineralization. *Am J Hum Genet* 73:261.
- Burgi AA, Gorham ED, Garland CF, Mohr SB, Garland FC, Zeng K, Thompson K, Lappe JM. (2011) High serum 25-hydroxyvitamin D is associated with low incidence of stress fractures. *J Bone Miner Res*. Jun 22. doi: 10.1002/jbmr.451.

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)

Cauley JA, Parimi N, Ensrud KE, Bauer DC, Cawthon PM, Cummings SR, Hoffman AR, Shikany JM, Barrett-Connor E, Orwoll E. (2010) "Serum 25-Hydroxyvitamin D and the Risk of Hip and Nonspine Fractures in Older Men." *J Bone Miner Res.* 25:545-53.

Chapuy, M. C., M. E. Arlot, et al, (1992) "Vitamin D3 and calcium to prevent hip fractures in the elderly women." *N Engl J Med* 327: 1637-42.

Chung M, Balk EM, Brendel M, Ip S, Lau J, Lee J, Lichtenstein A, Patel K, Raman G, Tatsioni A, Terasawa T, Trikalinos TA. (2009) Vitamin D and Calcium: A Systematic Review of Health Outcomes, Evidence Report No. 183 (Prepared by the Tufts Evidence-based Practice Center under Contract No. HHSA 290-2007-10055-I.) Rockville, MD: Agency for Healthcare Research and Quality; AHRQ Publication No. 09-E015.

Compston, J.E. (1995) Review Article: osteoporosis, corticosteroids and inflammatory bowel disease. *Aliment Pharmacol Ther* 9: 237-250

Dawson-Hughes, B., S. S. Harris, et al, (1997) "Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older." *N Engl J Med* 337: 670-6.

Gascon-Barré M, Demers C, Ghrab O, Theodoropoulos C, Lapointe R, Jones G, Valiquette L, Ménard D. (2001) "Expression of CYP27A, a gene encoding a vitamin D-25 hydroxylase in human liver and kidney." *Clin Endocrinol (Oxf)*. 54(1):107-15.

Gilsanz, V. and T. Wren (2007) "Assessment of Bone Acquisition in Childhood and Adolescence." *Pediatrics* 119(Supplement 2): S145-149.

Heaney, R. P. (2006) "Barriers to optimizing vitamin D3 intake for the elderly." *J Nutr* 136(4): 1123-5.

Heaney, R. P., K. M. Davies, et al, (2003) "Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol." *Am J Clin Nutr* 77: 204-10.

Hogan DB, Anderson C, MacKenzie RA, Crilly RG. (1986) "Hypophosphatemic osteomalacia complicating von Recklinghausen's neurofibromatosis: increase in spinal density on treatment." *Bone* 7(1):9-12.

IOM (Institute of Medicine) (2011) Dietary reference intakes for calcium and vitamin D. Washington D C: The National Academies Press.

Illes, T., V. Halmi, et al., (2001). "Decreased bone mineral density in neurofibromatosis-1 patients with spinal deformities." *Osteoporos Int* 12(10): 823-7.

Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RJ (1999) Stratified randomization for clinical trials. *J Clin Epidemiol* 52(1):19-26.

Konishi, K., M. Nakamura, et al, (1991). "Hypophosphatemic osteomalacia in von Recklinghausen neurofibromatosis." *Am J Med Sci* 301(5): 322-8.

Lammert, M., J. M. Friedman, et al, (2006) "Vitamin D deficiency associated with number of neurofibromas in neurofibromatosis 1." *J Med Genet* 43(10): 810-3.

National Osteoporosis Foundation (2007) "Disease Facts": <http://www.nof.org/osteoporosis/diseasefacts.htm>. Accessed May 8, 2007

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)

Ooms, M. E., J. C. Roos, et al. (1995) "Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trial." *J Clin Endocrinol Metab* 80(4): 1052-8.

Plum LA and DeLuca HF. (2010) "Vitamin D, disease and therapeutic opportunities." *Nat Rev Drug Dis.* 9: 941-955.

Priemel M, von Domarus C, Klatte TO, et al. (2010) "Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients." *J Bone Miner Res* 25(2):305-312.

Rizzoli, R., J. P. Bonjour, et al. (2001) "Osteoporosis, genetics and hormones." *J Mol Endocrinol* 26(2): 79-94.

Rosen CJ. (2011) "Vitamin D Insufficiency." *N Engl J Med* 364:248-254.

Ruohola, J. P., I. Laaksi, et al (2006) "Association between serum 25(OH)D concentrations and bone stress fractures in Finnish young men." *J Bone Miner Res* 21:1483-8.

Sakuma M, Endo N, Hagino H, Harada A, Matsui Y, Nakano T, Nakamura K. (2011) "Serum 25- hydroxyvitamin D status in hip and spine-fracture patients in Japan. *J Orthop Sci.* 16:418-23.

Schnabel C, Jett K, Friedman JM, Frieling I, Kruse HP, Mautner V. (2013) Effect of vitamin D3 treatment on bone density in neurofibromatosis 1 patients: A retrospective clinical study. *J Bone Spine* 80:315-319.

Seitz S, Schnabel C, Schmidt H, Beil FT, Mautner VF, Amling M. (2008) Vitamin D deficiency, osteomalacia and high bone turnover in patients with neurofibromatosis 1. *J Bone Min Res* 2008:23S1:S126.

Slemenda, C. L., C; Peacock, M; Hui, S; Johnston, CC. (1996) "Sex steroids, bone mass, and bone loss. A prospective study of pre-, peri-, and postmenopausal women." *J Clin Invest* 97:14-21.

Stevenson, D. A., L. J. Moyer-Mileur, et al, (2007) "Bone mineral density in children and adolescents with neurofibromatosis type 1." *J Pediatr* 150:83-8.

Stevenson DA, Viskochil DH, Carey JC, Sheng X, Murray M, Moyer-Mileur L, Shelton J, Roberts WL, Bunker AM, Hanson H, Bauer S, D'Astous JL. (2011) "Pediatric 25-hydroxyvitamin D concentrations in neurofibromatosis type 1". *J Pediatr Endocrinol Metab.* 24:169-74.

Tucker et al. (2009) "Bone health and fracture rate in individuals with NF1." *J Med Genet.* 46(4):259-65.

van Schoor NM, Visser M, Pluijm SM, Kuchuk N, Smit JH, Lips P. (2008). "Vitamin D deficiency as a risk factor for osteoporotic fractures. *Bone.* 42:260-6.

Vieth, R. (2005) "The role of vitamin D in the prevention of osteoporosis." *Ann Med.* 37:278-85.

Weatherall, M. (2000) "A meta-analysis of 25 hydroxyvitamin D in older people with fracture of the proximal femur." *N Z Med J* 113:137-40.

Weinstein RS, Harris RL. (1990) "Hypercalcemic hyperparathyroidism and hypophosphatemic osteomalacia complicating neurofibromatosis." *Calcif Tissue Int.* 46:361-6.

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)

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)

Summary of Changes for Amendment V5Nov2015

- 1- Added Protocol Title to the header of each page.
- 2- Added Version and page number footer.
- 3- Study Design pg 5
 - a. Corrected vitamin D units from mg to IU
 - b. Corrected number of drops from one drop to two drops
- 4- Screening Procedures, pg 7
 - a. Removed need for fasting. Fasting status is not required.
 - b. Removed 2 week time frame, as samples are to be batch shipped.
- 5- Visit Diagram pg 8
 - a. New version was developed to better follow protocol.
- 6- Pg 9 – removed duplicate text regarding reimbursement and storage of remaining samples – both are covered later.
- 7- Laboratory: Pg 11 – Clarified only patients at the University will have the option of sample storage.
- 8- Human Subjects and Safety Monitoring pg12 and 13:
 - a. Removed Michael Spigarelli, MD and added Pediatrics Clinical Trials Office
 - b. Change chair to safety monitor for Dr. Kanner
 - c. Updated CTCAE to version 4.0

Summary of Changes for Amendment V29Feb2016

- 1- All Pages - Version date updated
- 2- All Pages – Several grammatical and readability corrections made throughout the document.
- 3- Page 1 - Cover page was added with all Versions of Protocol and IND # listed
- 4- Page 2 - Protocol Signature page added
- 5- Page 7 - Study Design:
 - a. Removed: Serum specimens will be frozen for ancillary studies and enrollees will be followed for long-term effects through a registry designed for this study and maintained at the University of Utah
 - i. Reason: no longer applicable. Samples will only be stored for study specific testing.
 - b. Removed: diet analysis and activity level questionnaires.
 - i. Reason: diet analysis questionnaire is not validated for all locations and activity level questionnaire not validated for age group.
 - c. Randomization
 - i. Removed: All randomization will be accomplished in site-specific blocks of 4 utilizing random number pre-assignments provided to each site, which will allow each site to utilize the correct blinded dose Vitamin D3. Block randomization by site (meaning equal distribution within a site is more important than equal random distribution across all sites) to account for variations in sun exposure and geographical location, while maintaining the highest protection for blinding in using a block size of
 - ii. Added: Randomization tables will be created by a PhD statistician. Randomization tables will include geographic location and gender, see study operations manual for further details.
 1. Reason: To be aligned with current operations
- 6- Page 8 - Exclusion Update:
 - a. Removed: Lack of NF1 diagnostic criteria on physical exam.
 - i. Reason: listed as an inclusion
 - b. Pregnancy language was updated to: Pregnant, planning to conceive within the next 2 years, or is less than 6 months post-delivery or lactation.
 - i. Reason: DXA is a primary end point.
 - c. Removed exclusion of 25(OH) vitamin D results as testing is completed under study protocol.
 - d. Calcium and Vitamin D supplementation changed to last 3 months
 - i. Reason: Protocol change

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)

- 7- Page 9, Telephone calls
 - a. Changed telephone participants from every 3 months to every 6 months.
 - i. Reason: protocol change.
- 8- Page 9 - Screening Procedures:
 - a. Added local serum 25(OH) vitamin D will be obtained for study enrollment.
 - i. Reason: this will allow faster recruitment of subjects from all centers.
- 9- Page 10 - Figure 2 was updated to reflect study design.
 - a. Pregnant, Deficient, or Sufficient 25(OH) vitamin D levels will not be followed.
 - b. Participants with a TScore greater than -2.5, will be referred to their primary care physician for treatment.
- 10- Page 11 - DXA –
 - a. Removed: Results of this study will not be divulged to either the participant or the investigative team. The CD will be accessed and data will be captured in the NF1 Vitamin D Study Database. Only the monitor will have access to the DXA data until the end of the study.
 - b. Added: See study operations manual for further details.
 - i. Reason: Initials DXA results will be read by local team to determine eligibility. Study operations manual allows for DXA results to be emailed or sent via CD.
- 11- Page 12 and Page 14 – Data Management
 - a. Removed: data monitoring by Pediatric Clinical Trials office at the University of Utah.
 - i. Reason: This office no longer providing this services.
 - b. Updated: full access to data collected during the study will be by the project manager, the data manager, and the data safety monitoring committee.
 - i. Reason: to be in-line with current protocol
- 12- Page 13 – Sharing Study Results
 - a. Removed the medical monitor will notify in regards to the initial DXA scan
 - i. Reasons:: DXA scans will be evaluated by local site only
- 13- Page 13 – Laboratory Storage
 - a. Removed long-term storage
 - b. Added: for the duration of the study
 - i. Reason: no longer applicable. Samples will only be stored for study specific testing.
- 14- Page 14 – Human Subjects Monitoring
 - a. Removed: data monitoring by Pediatric Clinical Trials office at the University of Utah. Also removed data monitoring of serum collection and disposition of samples.
 - i. Reason: This office no longer providing this services.
 - b. Updated Dr. Kanner and the CCTS medical safety monitoring frequency to every 6 months
 - i. Reason: better oversight
 - c. Removed: The only designed safety analysis to be performed during this study is at the time of the initial evaluation that includes serum 25(OH) vitamin D, calcium and iPTH testing, and DXA scan. The individual diary and clinical assessments will also contribute to a safety analysis. Each participant will have these studies assessed by the medical monitor. In addition to deficient vit D, abnormal calcium and/or abnormal iPTH serum levels, the finding of BMD in the osteoporosis category warrants notification of the participant's self-identified primary care provider. The medical monitor is also obligated to contact the center coordinator and the participant will be excluded from the remainder of the study.
 - i. Reason: Local sites will determine patient eligibility.
 - d. Updated: The data safety monitoring committee will review the safety issue and inform local coordinator of the study arm assignment (low or high dose vitamin d) for the withdrawn subject.
 - i. Reason: ensure blinding is broken only by data safety monitoring committee.
 - e. Removed: Medical monitor decision to break blinding
 - i. Reason: ensure blinding is broken only by data safety monitoring committee.
 - f. Removed: ability to break blinding for subjects with an adverse event while still participating in the study.
 - i. Reason: ensure blinding is broken only by data safety monitoring committee.
- 15- Page 15 – Adverse Events

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)

- a. Removed reference to CTCAE criteria
 - i. Reason: All adverse events will be graded as mild, moderate or severe.

16- Page 16 – Safety Monitoring and Interim Analysis

- a. Removed: The medical monitor will review the entry serum 25-hydroxy vitamin D levels. He will notify the participating center of any serum vitamin D levels below 8 ng/mL, and these subjects will be taken off protocol and referred for evaluation and treatment of vitamin D deficiency.
 - i. Reason: Local site will determine eligibility.
- b. Removed: and again when all subjects have completed their mid-trial (1 Year) assessments.
 - i. Reason: DXA is only performed at Day 1 and Year 2.



20 April 2016

Protocol: 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)

Dear Investigators and Study Coordinators:

This written communication is to clarify two errors found in the Protocol V10Feb 2016 Amendment 2.

- 1- On the Protocol Signature page, the protocol version is mentioned as V:10Feb2016 Amendment 3. This should be Amendment 2.
- 2- Clarification of serum 25(OH) Vitamin D result for inclusion criteria.
Participants must have a 25(OH) Vitamin D result between 9 and 29 ng/ML to enroll.
 - On Page 8 of the protocol for Inclusion/Exclusion reads:
Individuals with levels between 8 and 30ng/ml are eligible for vitamin D supplementation.

Thank you for your continued support and dedication. Please submit this letter to your IRB or ethics committee.

David H Viskochil, MD, PhD
Principal Investigator
University of Utah

Carrie Bailey, BS, CCRC
Project Manager
University of Utah

Manual of Operations

Appendix 6.2

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)

Manual of Operations

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)

Version: 29 Feb 2016

University of Utah IRB_00055719
University of Utah IRB Approval 11/20/2013
University of Utah Amendment approval 2 /11/2014

Table of Contents

CONTACT INFORMATION / SITES.....	3
GENERAL INFORMATION.....	4
STUDY ORGANIZATION AND POLICY.....	6
ESSENTIAL REGULATORY DOCUMENT EXPLANATION SHEET	7
STUDY VISITS	8
STUDY DRUG.....	12
LABORATORY PROCEDURES	15
DXA PROCEDURES.....	16
ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS	17
PROTOCOL DEVIATIONS:	21

CONTACT INFORMATION / SITES

Protocol PI/Chair: David Viskochil, Dave.Viskochil@hsc.utah.edu

Project Manager: Carrie Bailey, BS, CCRC - Carrie.Bailey@hsc.utah.edu - 8015873605

Lead site study coordinator: Carlos Barbagelata, MS

Data Safety monitor: Richard Kanner, richard.kanner@hsc.utah.edu

Data Manager: TBA

Participating Sites

University of Utah (Salt Lake City, UT, USA)

Principal Investigator: David Viskochil MD, PhD

Project Manager: Carrie Bailey, BS, CCRC

Coordinator: Carlos Barbagelata, MS

University of British Columbia (Vancouver, CA)

Principal Investigator: J.M Friedman MD. PhD

Coordinator: Patricia Birch RN

University of Cincinnati (Cincinnati, OH, USA)

Principal Investigator: Elizabeth Schorry MD.

Coordinator: Sara Manning

University of Hamburg (Hamburg, Germany)

Principal Investigator: Victor Mautner MD.

Coordinator: Claudia Wargel

Site PI contact info:

David Viskochil, MD, PhD University of Utah 295 Chipeta Way Salt Lake City, UT 84108 Phone: 801-581-8943 dave.viskochil@hsc.utah.edu	Elizabeth Schorry, MD Cincinnati Children's Hospital Medical Center 3333 Burnet Avenue - ML 4006 Cincinnati, OH 45229 Phone: 513-636-4760 elizabeth.schorry@cchmc.org
Jan Friedman, MD, PhD The University of British Columbia Box 153, Children's and Women's Hospital 4480 Oak Street Vancouver, BC V6H 3N1 jfriedman@cfri.ca	Victor-Felix Mautner MD Gebäude O 54 im UKE Martinistraße 52 20246 Hamburg Tel.: (040) 7410-53273 od. 7410-55629 v.mautner@uke.uni-hamburg.de

GENERAL INFORMATION

Each site has been sent copies of the study protocol, consent form and associated paperwork for IRB/Ethics submission.

We ask that you try to keep your IRB's /Ethics board submissions as close to the same layout /format as possible (based on your site guidelines).

Once your site has approval, please send the approved documents back to Utah for further submission to both the Department of Defense and Utah's IRB for approvals.

Note: Sites cannot enroll for this study until both approvals have been received by Utah and your site has been notified by Carrie Bailey, BS, CCRC or Dr. Viskochil that you can begin enrolling.

Description of Recruitment Process:

Recruitment will be in compliance with local site IRB requirements and GCP/ICH guidelines.

Enrollment/Eligibility:

The target population - adults with neurofibromatosis type 1 (NF1) between the ages of 25 and 40 years who are insufficient for vitamin D, as defined by serum testing at time of enrollment and meet all inclusion/exclusion criteria as defined by the protocol.

Informed Consent Process:

The study coordinator at each site will be responsible for explaining the study, answering questions, and obtaining informed consent. The principal investigator at each site will also need to be available for answering questions. The study will be explained in advance of the screening visit and the consent form will be signed and witnessed prior to the first screening visit. All potential study participants will be adults who are competent to understand the study and sign consent on their own behalf. Each subject will have at least one week to decide whether or not they wish to participate. Participants will have full access to the investigative team throughout the clinical trial.

Coordinators at each site will telephone participants every 6 months to review any issues or concerns with respect to the trial. The vitamin D₃ and calcium supplementation diary will be reviewed, and any potential side effects or adverse effects will be documented and discussed at that time.

Participant Support:

All subjects will be provided participant compensation equivalent to US\$25 for enrollment and screening blood test for the determination of serum 25(OH)D. Subjects will be offered participant compensation equivalent to US\$50 per clinical visit at the start of the study, at 12 months, and at 24 months. These visits include DXA scans on entry and exit, blood specimen on entry, 1 year, and exit at 2 years, a fracture history, a quality of life survey, and a clinical exam for each visit.

Record Keeping for Study Data

Data collected from this study will be maintained as electronic data entered into a database designed and maintained in the Center for Clinical & Translational Sciences at the University of Utah. This database has a tiered access with each of the four centers having password-protected access to data entered from their respective site. These data include demographic information, NF1-related

manifestations, documentation of data collection points, and actual data values including serum biomarkers and bone mineral density values. Investigative teams at each site have full access to data collected from participants enrolled through their site. There is limited access to data collected from other centers. The project manager, data manager, and the data safety monitoring committee will have full access to data collected from this study, until completion. Electronic Case Report Forms (eCRFs) will be used for each participant. Participants must not be identified by name on any study documents that are sent off site to any agency. A Subject Identification Number (SIN) will be given by each site upon enrollment and then used to identify subjects on all associated paperwork, database, and/or regulatory documents could identify subjects.

Identifiers:

Human subjects will be identified at the time of enrollment from one of the 4 centers; UBC (University of British Columbia, Canada), UTA (University of Utah, USA), CIN (University of Cincinnati, USA), and HAM (University of Hamburg, Germany). The unique identifier will include the site followed by a 3-digit number starting with 100 ascribed sequentially at the time of enrollment at each site from:

UBC-100 to UBC-XXX

UTA-100 to UTA-XXX

CIN-100 to CIN-XXX

HAM-100 to HAM-XXX

This identifier will be used on all correspondence and only the investigative team at the enrollment site will be able to link the name with the identifier.

Disposition of Data

Electronic data from this study will be stored in the database embedded in the Informatics Core at the Center for Clinical Translational Science (CCTS) at the University of Utah.

Sharing Study Results

There are 3 instances where enrollees will receive information based on their enrollment in the study. The initial serum 25(OH)vit D will be conveyed to the enrollees as part of the screening test. Enrollees will know if they have sufficient vitamin D (no longer a participant in the trial), insufficient levels (randomized as an active participant in the trial), or severe deficiency that requires medical intervention. For participants in the trial, if the initial DXA scan identifies osteoporosis (bone mineral density T-score of ≥ -2.5), the coordinator and local physician will notify the participant and their primary care provider to consider initiation of medical management, regardless of the serum 25(OH)vit D level. Third, the final results of each participant's BMD calculations, status of vitamin D3 dose randomization, serum calcium, serum iPTH, and serum 25(OH)vit D levels will be conveyed to the participant once available after the 2-year follow-up visit. They will receive an analysis and counseling regarding the results of their bone mineral density of spine and hip as determined by DXA scanning. These results will be shared with their primary care provider and may determine long-term care management for some participants.

Safety Monitor

Richard Kanner, M.D. will serve as the external safety monitor for this study. He will review recruitment and participant enrollment and monitor summarized data collection from the 4 sites. Dr. Kanner and 2 others on the Safety Monitoring Committee will review adverse events every 6 months and compile a report outlining this data compilation. Dr. Kanner has authority to;

- 1) Stop the research protocol in progress;

- 2) Remove individual participants from the research protocol;
- 3) Initiate steps to protect the safety and well-being of participants until the University of Utah IRB and Human Research Protection Office (HRPO) of the U.S. Army Medical Research and Materiel Command can assess the safety monitor's report.

FDA ANNUAL REPORTS:

An annual progress report will be submitted to the FDA within 60 days of the anniversary of the date that the IND went into effect. (21 CFR 312.33).

PROTOCOL AMENDMENTS:

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval. All amendments will be submitted to the FDA for review.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

Safety Monitoring and Interim Analysis

Participants will be clinically monitored for signs and symptoms of hypercalcemia throughout the trial period. Interim analysis of the difference in change of BMD at the left hip and lumbar spine between subjects randomized to the 600 IU cholecalciferol and 4,000 IU cholecalciferol groups will be performed when 50 participants have completed the second DXA assessment. The trial will be stopped and all subjects offered therapy with 4,000 IU/day of cholecalciferol if the effectiveness of this treatment is clearly demonstrated ($p < 0.01$).

RECORD KEEPING:

Per 21 CFR 312.57, investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified

STUDY ORGANIZATION AND POLICY

This is a randomized clinical trial of oral vitamin D therapy in adults with NF1 and vitamin D insufficiency, comparing the effects of a 600 IU daily supplement of cholecalciferol versus a therapeutic dose of cholecalciferol (4,000 IU/day) on maintenance of bone mineral density. This is an IND study, IND Number: 119135 and the IND holder is David Viskochil, MD, PhD, University of Utah PI. This study will be conducted in compliance with FDA, GCP Guidelines, regulatory and sponsor requirements, and protocol adherence. An audit may be conducted during the course of the study to ensure protocol adherence, regulatory oversight and appropriate subject reporting to Data Management and Analysis Center and the University of Utah.

The clinical centers are responsible for recruitment, following randomization procedures, study drug dispensing, all study-related medical and laboratory and imaging procedures and protocol mandated follow up procedures for study participants.

Prior to screening procedures, all site personnel responsible for data entry must be familiar with study paperwork. Electronic clinical report forms (eCRF's) must be completed in a timely fashion with the lowest error rate attainable; addressing queries in a timely fashion, and completing required data forms. Clinical sites are responsible for maintaining current regulatory approvals for all study related activity

throughout the study. Study related activities include: annual IRB renewals, training updates, laboratory accreditation and medical license renewals, and maintenance of local clinical site regulatory binders etc.

U of U and Data Management & Analysis Center

The trial is coordinated at the University of Utah (U of U). The U of U is responsible for the overall grant administrative function and is managed under Dr. David Viskochil's leadership in the Department of Pediatrics, University of Utah. Data Management at the U of U provides a place where all data collection and/or information gathered from this trial will be stored for analysis and statistical support of this trial for the award period. Data management is under the leadership of a data manager. The data manager (TBA) will work closely with the study team to ensure that clinical sites are provided administrative, clinical and data guidance, when needed.

The U of U is responsible for insuring regulatory compliance. The U of U will ensure that serious adverse events are reported to protocol chair and protocol team, data safety monitoring committee, sponsor and FDA according to the protocol in a timely manner. The U of U assists the protocol team in the implementation of the study. The data manager and project manager will assist in quality control of data collection and will oversee the communications and governance of the study as it pertains to statistical and safety data reporting. The U of U is responsible for all regulatory reporting of the clinical sites to the DOD HRPO, sponsor, and data safety monitoring committee. Since this is an IND study using Ddrops, all safety reports will be initially reviewed by the data safety monitor and Dr. Viskochil. All safety reports will be sent to FDA by the U of U, and all study sites are responsible for providing safety reports to their regulatory agencies.

Department of Defense (DOD)

The U.S. Army (Department of Defense) is the funding agency for this NF1 Study. This trial is subject to the rules and regulations under the Army's leadership. The US Army Medical Research and Materiel Command regulate the trial. The University of Utah serves as a liaison for the NF1 study, and Dr. Viskochil will monitor and oversee regulatory mandates and compliance across all clinical sites, agencies and departments associated with this NF1 Study.

U of U Study Team

The study team will be the primary governing body of the NF1 4-center trial and will be comprised of the Principal Investigators from the 4 clinical centers; University of Utah, University of British Columbia, University of Cincinnati, and University of Hamburg. The University of Utah and NF1 protocol team will provide quarterly updates to study teams of NF1 study progress.

ESSENTIAL REGULATORY DOCUMENT EXPLANATION SHEET

All documents will be kept in the Regulatory Files for each specific protocol after submission to the University of Utah's project manager, attention Carrie Bailey in PDF format if possible to carrie.bailey@hsc.utah.edu and the data manager. This will assist you in identifying and collecting all the required regulatory documents needed to submit to the University of Utah **before** the site can conduct the study.

Regulatory Requirements based on FDA requirements and GCP guideline Regulatory Binder Index

1. Protocol	Study Protocol Study Protocol Amendments Protocol or Amendment Signature Pages Non-Disclosure Agreement
--------------------	--

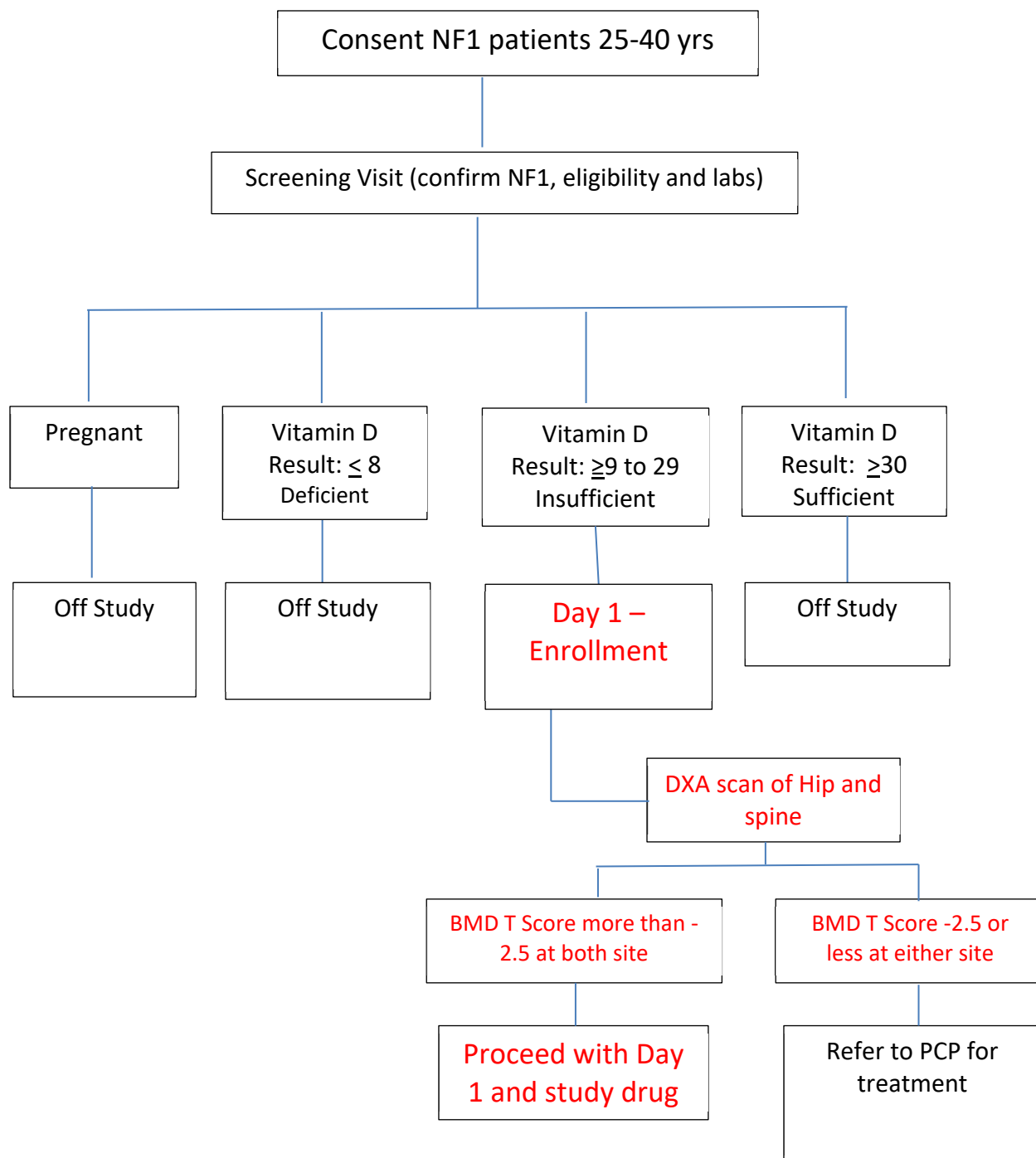
	Investigator Drug Brochure
2. 1572 Regulatory Forms/CV	Form FDA 1572 document * Curricula Vitae (signed & dated) * Medical Licenses (if applicable) * Financial Disclosure Agreement: kept in same folder, not in Regulatory File * Proof of research training*
3. Approved Consent Form(s)	Informed Consent(s)*
4. IRB Approvals and Correspondence	IRB/IEC/RAC Approvals for Protocol* Amendments, Advertisements, Renewals* IRB Correspondence (Progress reports, letters of submission for approval, IRB notification, responses to SAE reports, and IND Safety Reports, Etc.)**
5. Laboratory	Lab Certifications (CAP & CLIA) * Laboratory Normal Ranges ** CV pathologist, if applicable **
6. Study Logs	Personnel Delegation Log Monitor Site Visit Logs Site Signature Logs (may be on personnel delegation log Master Subject Logs Screening Logs Training Logs (Site initiation Visit attendance log & training certificates*)
7. Correspondence	Study related correspondence between the site, sponsor, regulatory agency, U of U, monitor, etc.
8. Serious Adverse Events (SAE)	Master SAE Reporting Form and Instructions Blank SAE Forms IND Safety Letters; DSMB reports Completed SAE Reports ** (or note where they are located)
9. Drug Accountability	Study Drug Receipt/packing invoices Study Drug Accountability Form Study Drug Supply Forms
10. Miscellaneous	Miscellaneous (CRF transmittal logs), etc.

*send to U of U initially

**send to U of U when available

STUDY VISITS

Visit Schematic



Screening Visit:

- Consent

- Verify participant meets inclusion/exclusion criteria
- Blood draw:
 - Local collection:
 - Serum 25(OH) Vitamin D level – screening only can be collected to determine eligibility.
 - Central Lab (ARUP sent to University of Utah see lab section)
 - The amount of blood required is about three teaspoons (15ml). 6ml Serum separator and 6ml plain red or serum separator tubes (see lab section for processing instructions).
 - The blood is to screen for serum 25(OH) vitamin D level. Other serum studies will be performed if the enrollee is found to be eligible for the remainder of the study. These tests include intact parathyroid hormone (a measure of bone metabolism) and calcium.
- 25 OH Vitamin D results:
 - Sufficient: $\geq 30\text{ng/ml}$ - These participants are not eligible and will be given their results and contacted yearly for a phone call or email survey.
 - Deficient: $\leq 8\text{ng/ml}$ – These participants are not eligible. They will be given their results and encouraged to follow up with his or her primary care provider for care and contacted yearly for a phone call or email survey.
 - Insufficient: 9ng/ml to 29ng/ml – These participants are eligible for enrollment.

Participants who are eligible for enrollment – Insufficient serum 25(OH) Vitamin D will return for the following assessments

Day 1:

- Pregnancy screening test. If positive results is returned, enrollment can be deferred to 6 months post-delivery and have stopped lactation.
- DXA scanning will be performed of the spine and left hip –
 - Enrollees with DXA results demonstrating osteoporosis (T-score of ≤ -2.5 are NOT eligible for study drug.
 - Participants will not be scanned if they have taken calcium in the last 24hrs or within 10 days of having any oral or IV radiologic contrast. Females will have a negative urine pregnancy test prior to the scan.
- Physical Exam
- Questionnaires:
 - Quality of Life Questionnaire
 - Fracture history
- Randomization: Vitamin D₃ supplementation either 600 IU or 4000 IU (see study drug)
- 400mg elemental calcium (e.g. 1000 mg calcium carbonate – Tums or similar) per day
- Diary: A diary is provided to keep daily track of missed vitamin D and calcium supplementation. Fractures and other adverse events will be noted in the diary.

6mo – Phone Call Visit and Study Drug Dispense

- Participants will be called to review adverse events and diary
- Dispense
 - Vitamin D₃ supplementation 600 IU or 4000 IU (see study drug)
 - 400mg elemental calcium (e.g. 1000 mg calcium carbonate – Tums or similar) per day

12 mo – 1year – Clinic Visit

- Pregnancy test. Those who are pregnant will be discontinued from study drug, whenever identified.
- Physical Exam
- Questionnaires:
 - Quality of Life Questionnaire
 - Fracture history
- Blood draw:
 - The amount of blood required is about three teaspoons (15ml). 6ml Serum separator and 6ml plain red or serum separator (see lab section for processing instructions).
 - These tests include 25(OH) vitamin D, intact parathyroid hormone (a measure of bone metabolism) and calcium.
- Dispense
 - Vitamin D₃ supplementation 600 IU or 4000 IU (see study drug)
 - 400mg elemental calcium (e.g. 1000 mg calcium carbonate – Tums or similar) per day
- Diary: Review and collect diary and dispense another year.
- Provided to keep daily track of missed vitamin D and calcium supplementation. Fractures and other adverse events should be noted on the diary.

18mo – Phone Call Visit and Study Drug Dispense

- Participants will be called to review adverse events and diary
- Dispense
 - Vitamin D₃ supplementation 600 IU or 4000 IU (see study drug)
 - 400mg elemental calcium (e.g. 1000 mg calcium carbonate – Tums or similar) per day

24 mo – 2 year – Clinic Visit

- Pregnancy test. Those who are pregnant will have discontinued from study drug.
- Physical Exam
- DXA scanning will be performed of the spine and left hip
 - Participants should not be scanned if they have taken calcium in the last 24hrs or within 10 days of having any oral or IV radiologic contrast, and females should be asked to verify there is no chance of pregnancy and/or have a negative pregnancy test prior to the scan
- Questionnaires:
 - Quality of Life Questionnaire
 - Fracture history
- Blood draw:
 - The amount of blood required is about three teaspoons (15ml). 6ml Serum separator and 6ml plain red or serum separator (see lab section for processing instructions).
 - These tests include 25 OH vitamin D, parathyroid hormone (a measure of bone metabolism) and calcium.
- Diary: Review and collect diary
- AE collection

Schedule of Events

	Screening	Day 1	Month 6	Year 1	Month 18	Year 2
Procedure						

Consent	X					
Local Vitamin D collection	X					
Central Labs ^a	X			X		X
Urine Pregnancy	X	X		X		X
DEXA Scan		X				X
Physical Exam		X		X		X
Study Medication dispense		X	X	X	X	
Study Drug Diary (dispense and collect)		X	X	X	X	Collect only
Patient Questionnaires		X		X		X
AE collection		X	X	X	X	X

^ACentral Labs: Vitamin D 25-Hydroxy and Parathyroid, intact with Calcium

STUDY DRUG

Cholecalciferol (Ddrops) are taken orally- 2 measured drops.

There is a dropper that automatically drops out a measured amount when the bottle is turned upside down. Each bottle lasts 3 months, a 6 month supply will be dispensed each dispensing period. A total of 4 distributions will be made over the course of this 2-year study. The two doses of cholecalciferol were selected with respect to standard dosages in clinical care; 600IU per day (standard supplement), and 4,000IU (therapeutic dose). The prepared bottles have a metered dose of either 300IU or 2,000IU per drop.

Participants are randomized to one or the other dose, and they take two measured drops orally, once a day. All randomization will be accomplished by a University of Utah statistical randomization. Patients will be assigned a number at randomization. All dispensing should be done using the same randomization number for the entire study.

Storage and Stability

Upon receipt of the study drug, bottles are to be stored at room temperature. Bottles should be protected from light. Bottles used for 1 subject may not be used for any other subject.

Availability

Distribution: Cholecalciferol will be distributed to site investigators directly from DDrops. Sites will be sent random labels for study drug labeling to blind study drug.

Preparation

There is a dropper that automatically drops out a measured amount when the bottle is turned upside down. Each bottle lasts 3 months.

Ordering

Initial Shipments

When a site has received local IRB approval and Sponsor IRB approval the U of U Pharmacy will ship out the Cholecalciferol for distribution.

After Sponsor IRB approval, the U of U will:

Place a call to U of U Pharmacy confirming the approval and then place the order for shipment.

Your site will be emailed the estimated day and time of arrival for the study drug.

Subsequent Shipments (active patients requiring additional Cholecalciferol supply)

If additional bottles of Cholecalciferol are required, the study site will need to complete an order form for a new shipment. Please give the U of U pharmacy 1 month notice for replacements.

For all drug shipments from U of U:

Cholecalciferol will be shipped with:

- A complete accountability record (including date of dispense, site name, quantity dispensed, and balance forward) will be recorded. Study accountability records are documented in CFR format and are kept in a secured area for duration of the study.
- Pharmacist review is required: a licensed pharmacist checks off package for accuracy of contents, authorizing order via 21 CFR compliant trial accountability log.
- Each shipment includes the following information:
 - Study number
 - IND caution statement and/or local regulatory statements
 - Drug identification
 - Lot number and expiration
 - Storage conditions
 - Dosing instructions (Take as directed per protocol)
 - (Subject ID number, initials and date dispensed will be provided by study site pharmacy)
- Enclose a packing slip that includes the quantity of drug provided with a section to be completed once received by the site coordinator. This section includes confirmation of drug receipt, verification of package contents, and instruction to fax the completed packing slip to U of U.
- Process and ship authorized and completed orders will be processed and shipped the next business morning.
- All drug orders are shipped via *FedEx for Overnight* delivery.
- Packages are tracked until confirmed delivered and delivery. Packing slips with the shipment tracking number will be part of site study drug accountability records.

Once study drug is received at the clinical trial site:

The designated site coordinator validates that contents of package matches information provided on packing slip, signs off on the packing slip, and contacts U of U via email to validate shipment has been received and is accurate.

The order transaction is completed by entering the receipt confirmation and signed packing slip into the study file.

Sites will be required to send site drug accountability records to the U of U Pharmacy on a quarterly basis. The site study drug accountability records will be checked against U of U Pharmacy study drug administration data accountability records.

Drug Destruction

Sites will be instructed to destroy unused/returned drug per institution policy and note in the accountability record after site Pharmacy Drug Destruction Policy is sent to U of U and policy placed in site Regulatory Files.

U of U Investigational Pharmacist and contact information:

Investigational Pharmacy Service

University of Utah Hospitals & Clinics

Huntsman Cancer Hospital, 1950 Circle of Hope, Suite 2110, SLC, UT 84112

Pharmacy: (801) 585-0272 Fax: (801) 581-3744

Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the Cholecalciferol using a Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at <http://ctep.cancer.gov/protocolDevelopment> for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

Example:

Investigational Agent Accountability Record Template

Site # & Name:	Protocol No:
Study drug name:	Dose Form and Strength:
Protocol Title:	Dispensing Area:
Investigator Name:	

Line No.	Date	Patient's Initials	Patient's ID No.	Dose	Quantity Dispensed or Received	Balance Forward	Manufacturer and Lot No.	Recorder's Initials
						Balance		
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								
9.								
10.								
11.								

12.								
-----	--	--	--	--	--	--	--	--

Supportive Care and Concomitant Therapy

There is no known interaction of Cholecalciferol with other concomitantly administered drugs. Prophylactic low-dose of calcium will be taken daily (400mg elemental calcium –oral).

LABORATORY PROCEDURES

Specimens to be Collected, Schedule of Collection, and Amount of Each Collection:

There are 3 laboratory studies to be performed at 3 collection points-including serum 25(OH) vitamin D, serum calcium, and serum iPTH at entry, 1 year, and 2 years. These values will be correlated with bone mineral density and dose of cholecalciferol as an analysis of the study. Serum will be processed from 15-ml blood draws at each of the 3 time-points. No other lab studies will be performed. These values are to help determine the effect of low- versus high-dose vitamin D3 on calcium metabolism and correlate to change in bone mineral density. None of the studies are used for safety monitoring because the 2 doses of vitamin D3 are known to be well-tolerated.

Collection of specimen(s)

Sample Collection Time Points

Blood samples will be obtained at baseline, 12 months and 24 months.

Vitamin D 25-Hydroxy-Serum sample collection:

- Collect: Serum separator tube.
- Unacceptable Conditions: EDTA plasma, grossly hemolyzed or lipemic specimens.
- Stability: After separation from cells: Ambient: 72 hours; Refrigerated: 1 week; frozen: 6 months

Parathyroid, intact with Calcium Serum sample collection:

- Collect: Serum Separator Tube.
- Unacceptable Conditions: Body Fluid (refer to Parathyroid Hormone, FNA, ARUP test code 2001491).
- Stability: After separation from cells: Ambient: 8 hours; Refrigerated: 48 hours; Frozen: 6 months

Handling of specimens

Vitamin D 25-Hydroxy-Serum sample collection:

- Specimen Preparation: Centrifuge at 1100-2000g for 10 minutes at 20 to 25 degrees Celsius or until there is a clear and definite separation between the cells and plasma/serum. Transfer serum to a Standard Transport Tube (STT).
- Storage/Transport Temperature: Freeze and then ship frozen on dry ice to UT for analysis.

Parathyroid, intact with Calcium Serum sample collection:

- Collect: Serum Separator Tube.
- Specimen Preparation: Allow serum specimen to clot fully at room temperature. Centrifuge at 1100-2000g for 10 minutes at 20 to 25 degrees Celsius or until there is a clear and definite separation between the cells and plasma/serum. Transfer serum to a Standard Transport Tube (STT). Transfer 2 mL or more serum or plasma to a STT.

- Storage/Transport Temperature: Frozen. Separate specimens must be submitted. Please aliquot 2 tubes.

Prepare three labels each printed with Subject Study ID., Subject DOB, day/time of sample collection (24-hour clock format, i.e., 6:30 pm = 18:30). A label example is provided below:

Subject Study ID:	Subject DOB:
Sample Type: Plasma	Investigator:
Date of sampling: (mm/dd/yy)	Time of Sampling: (hh:mm) (24-hr format)
Comments:	

Clearly label tubes and store at -80°C.

When samples from all time-points have been collected plasma samples should be shipped to Carrie Bailey on DRY ICE in a Styrofoam box. If a deep freezer is not available on site, the plasma sample should be prepared and shipped on dry ice on the same day.

Shipping and analysis of specimen(s)

Ship all specimens to the following address:

Carrie Bailey CCRC
University of Utah
Division of Medical Genetics
50 North Mario Capecchi Drive
Room 1C210 SOM
Salt Lake City- Utah 84132
Office-801-587-3605
Fax- 801-585-0269

All analyses will be performed within the ARUP Laboratories.

UA-HCG

Urine Pregnancy Test- All female subjects must have a negative urine pregnancy test to participate in the study. Those who are pregnant will have an opportunity to participate at a later date. Urine pregnancy tests will be performed at local sites.

DXA PROCEDURES

Image Acquisition

Each patient will be scanned on the same DXA system at their institution throughout the study. Scanning will include the spine and left hip. Each scanning session must include the following sequences (although additional sequences can be performed per institutional protocol):

Participants should be scanned in light-weight clothing, preferably a hospital gown or a cotton t-shirt and scrub pants. Thick clothing, clothing with decals, glitter, rhinestones and metal (snaps, zippers, bra underwire, etc) should be avoided. The proximal femur should be positioned and analyzed according to manufacturer specifications; same with lumbar spine. Scans should be acquired in Fast Array mode.

Participants should not be scanned if they have taken calcium in the last 24hrs or within 10 days of having any oral or IV radiologic contrast, and females should be asked to verify there is no chance of pregnancy and/or have a negative pregnancy test prior to the scan.

The participant information in the DXA Biography screen should include the fields listed below. All other fields should be left blank.

Field	Comment	Example
Last name	Full study ID	UBC-xxx
Sex	Select as appropriate	female
DOB	Enter month, day and year of birth	January 16 2012
Ethnicity	Select options as appropriate	white
Referring physician	The short study name that can be used to identify scans to be exported	NF1-vitD

Visit information should be entered in the Scan Properties screen.

Field	Comment	Example
Scan comment	Enter the visit number or baseline or year 2	baseline

Day 1 DXA scans should be analyzed at local sites to confirm eligibility. A sex- and race-specific T-score of ≥ -2.5 will be required for eligibility. Results of this study will not be divulged to either the participant unless the T-score is < -2.5 .

Scans of both skeletal sites, spine and left hip, will be copied to a CD and shipped to Carrie Bailey at the U of Utah.

DXA data will be merged in the NF1 Vitamin D Study database. Only the data monitor will have access to the DXA data until the end of the study.

DXA scanning is a standard procedure that is performed in a medical setting. Individuals are situated on a table for scanning and the procedure is completed in less than 30 minutes. The amount of radiation will be limited to about 6 mrem. For comparison, the annual background radiation exposure from the earth and atmosphere in an average person is roughly 300 mrem.

ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug, even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Each adverse event should be evaluated to determine:

1. SEVERITY: Mild, Moderate, Severe
2. RELATIONSHIP OR ATTRIBUTION TO THE STUDY DRUG
 - Unrelated: bears no relation to timing of medication, similar to symptoms or signs expected in the disease process, does not recur on rechallenge.
 - Unlikely: does not have temporal relationship to intervention, could readily have been produced by the subject's clinical state, environmental, or other interventions, does not reappear or worsen with reintroduction of intervention.
 - Possibly: bears relation to timing of medication, similar to symptoms or signs expected in the disease process, does not recur on rechallenge.
 - Probably: bears clear relation to timing of medication, distinct from symptoms or signs expected in the disease process, does not recur on rechallenge.
 - Definitely: bears clear relation to timing of medication, distinct from symptoms or signs expected in the disease process, occurs on rechallenge.
3. Expectedness: if the adverse event is expected or unexpected. Expected adverse events related to administration of the study drug, can be found in Investigators' brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. Expected adverse events are also summarized in protocol.
4. Duration of the adverse event: start and end dates or, if continuing at final exam/assessment of subject.
5. Action taken: this may include whether no action was taken; study drug dosage was adjusted or temporarily interrupted; study drug was permanently discontinued; whether concomitant medication was taken; non-drug therapy given; hospitalization/prolonged hospitalization.
6. Whether the adverse event constituted a serious adverse event (SAE).

Only adverse events related to study drug as ascertained by local PI, will be recorded as Adverse Events on electronic case report forms (eCRFs), and submitted to the Data Monitor within 2 weeks of its occurrence. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbation of pre-existing illnesses will be recorded. It will be left to the investigator's clinical judgment whether or not an adverse event is of sufficient severity to require that the subject be removed from treatment.

A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these occurs, the subject will be given appropriate care under medical supervision until symptoms cease or until the condition becomes stable.

Adverse events are documented after the subject begins the study treatment and monitoring for AEs are a part of each follow-up visit. Timely and complete reporting of adverse events is a critical requirement in the conduct of this clinical trial. It allows the study to track the occurrence of events of a serious nature for review by the Data Safety Monitoring Committee, sponsor (Department of Defense), regulatory agencies, institutional review boards and the investigators.

ADVERSE EVENT: TREATMENT

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment, which includes possible interruption (drug hold) or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution or until the patient meets off-study criteria as defined in protocol and assessed at all

subsequent visits. (Patients with ongoing toxicity should be followed until the toxicity stabilizes or resolves.) Please note this drug has a few weeks half-life and the **off study** follow-up phone call is scheduled 12 weeks from last study treatment while the **off treatment study visit** is scheduled 30 days from last study treatment.

PREGNANCY

Any pregnancy that occurs during study participation should be reported.

To ensure patient safety those who are pregnant will have enrollment deferred to a later date. Those who are not pregnant will undergo randomization for high- versus low-dose vitamin D3 supplementation. DXA scanning will be performed of the spine and left hip as the primary endpoint of the clinical trial. Those who become pregnant will be removed from the supplementation and DXA scanning while remaining on the longitudinal studies until study end.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications. Site study coordinator will provide pregnancy notification information and delivery documentation to the U of U data manager by email. The U of U data manager will send pregnancy information to the Study PI after receipt of information from study site coordinator.

Regulatory Notifications

Non-serious, unexpected and unrelated adverse events will be reported to the IRB per institutional standard operating procedures.

All serious, unexpected, and related adverse events will be reported to the regulatory officials and within 24 hours after the investigator is made aware of the event. Study site will be responsible for notifying individual site regulatory agencies.

SERIOUS ADVERSE EVENTS/PROCEDURES

A Serious Adverse Event (SAE) is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Hospitalizations for Medical or Surgical Procedures: any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE. If subject is hospitalized to undergo a procedure as a result of an AE, report the AE responsible for the procedure (for example, report heart condition as AE instead of coronary bypass surgery).
- Is considered a significant medical event by the investigator based on medical judgment (may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes (life threatening, death, persistent or significant disability/incapacity)).
- Pregnancy is reported as SAE if female subject becomes pregnant while receiving therapy or within 30 days after last dose of study drug. Pregnancy outcome should be reported. Abortion, whether accidental, therapeutic or spontaneous is also reported as SAE. Any congenital anomaly/birth defect in a child born to a female subject exposed to cholecalciferol is also reported as separate SAE.

Inpatient hospitalizations for the following situations **do not** qualify as serious adverse events:

1. Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions

2. Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study;
3. Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.
4. Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission (e.g., ED visit without more than 23 hours hospitalization, or < 24 hours stay for transfusions)
5. Respite care

Any serious adverse event occurring after the patient has provided informed consent and after the patient has stopped study participation must be reported if attributed to prior cholecalciferol exposure.

Documents required for SAE reporting: SAE Report Form, de-identified documents, CRF entry

Time Table for Site to notify the U of U:

- **24 hours from Day of Awareness either by telephone or email**
- **Within 3 days on written SAE report form.**

REPORTING SERIOUS ADVERSE EVENTS (SAEs)

Reporting Responsibilities

The Investigator or designee must notify the **U of U** as soon as possible by telephone or email of **all serious events** and related and unexpected adverse events. The University of Utah is responsible for notifying all required agencies of serious adverse events, related, unexpected, related AEs.

Any fatal or unexpected life-threatening events associated with the use of the drug or within 30 days of last study treatment/intervention must be reported to University of Utah within **24 hours** of Principal Investigator's initial receipt of information.

All adverse events are emailed by site study coordinator or CRA. Written documentation of Serious Adverse Events is provided on both the CRF and SAE Report Form as soon as information becomes available and completed within 24 hours of awareness. Relevant follow-up information should be submitted as soon as it becomes available.

All SAE documentation will be provided to University of Utah project manager for transmission to data safety monitoring committee, Sponsor and Protocol Team. Relevant follow-up information should be submitted as soon as it becomes available.

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse is detected, it should be followed until its resolution or until the patient meets off-study criteria and assessed at subsequent visits.

Medical records that include admission, laboratory report, progress notes and discharge summaries from the hospital should be requested. Any medical records obtained by the site in order to complete the SAE data forms should be filed in the participant's chart at the site. *Do not send copies of hospital records to U of U data manager unless specifically requested. Do send de-identified medical records to Operations Center for review. SAE Form also should contain only de-identified information and should be sent to the U of U.*

PROTOCOL DEVIATIONS:

Protocol deviations will be reported to the IRB per institutional policy.

ICF

Appendix 6.3

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)



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:

David Viskochil MD, PhD
Department of Medical Genetics
University of Utah
801-581-8943

British Columbia Principal Investigator:

Jan M. Friedman, MD, PhD
Department of Medical Genetics
University of British Columbia
604-875-2000 ext 5622

British Columbia Co-Investigator(s):

David Kendler, MD, PhD
Department of Endocrinology and Metabolism
University of British Columbia
604- 263-3661

Sponsor: US Army Department of Defense

24 Hour British Columbia emergency contact: 604-875-2157

24 Hour overall study emergency contact (in Utah): 801-581-2121

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 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 of 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/L). 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

Consent and Authorization Document

BACKGROUND

You have been invited to participate in a research study. This clinical trial is conducted in 4 locations; University of British Columbia (Vancouver, CANADA), University of Utah (Salt Lake City, UT, USA), University of Cincinnati (Cincinnati, OH, USA), and University of Hamburg (Hamburg, GERMANY). It is funded by the Department of Defense Neurofibromatosis Research Program. Before agreeing to participate in this study, it is important that you thoroughly read and understand the following information. We are asking if you want you to participate in this study because you are an adult with neurofibromatosis type 1 (NF1). Adults with NF1 have a higher risk of osteopenia and osteoporosis than the unaffected population. Osteopenia is a condition of low bone density that can lead to fragile bones and bone breakage. In general, people with NF1 also have lower serum vitamin D levels than unaffected individuals. Vitamin D is important for normal bone health, and this study will evaluate potential benefits of two doses of vitamin D supplementation in people with NF1 whose serum levels of vitamin D are insufficient.

Research is a way of gaining new knowledge. A person who participates in a research study is called a "participant". This 2-year research study is evaluating vitamin D as a possible treatment for adult NF1 individuals with an insufficient blood level of vitamin D.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of the research study, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you can refer to it while you are involved in this research study.

The research doctors will discuss other treatment options with you and/or refer you back to your regular doctor if you choose not to take part in this study.

We encourage you to take some time to think this over, to discuss it with other people and your doctor and to ask questions now and at any time in the future.

STUDY PROCEDURES

We are looking for about 320 adults with known NF1 to participate in our study. The purpose of this study is to treat about 200 adults with NF1 with two different doses of vitamin D to determine which dose of vitamin D is most appropriate to maintain bone mineral density of the spine and hip.

Participants must be between the ages of 25 and 40 years and be willing to come to one of the participating centers 3 times; at the beginning of the study, 1 year later, and 2 years later.

SCREENING

All potential participants will undergo an initial screening to determine their serum vitamin D level. The procedures for the initial screening are described below:



- You will be contacted by the study coordinator to review the details of the study. If you agree to participate then you will sign this consent form and provide it to the study coordinator who will arrange a time for your initial blood test. This can be done 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 enrollment in the study. A clinic coordinator and/or physician will review your medical history to ensure that you are eligible to participate.
- A blood sample will be collected to test your serum vitamin D level. The amount of blood required is about 3 teaspoons (15ml). To save you a lab draw, we will collect enough blood for other studies to be performed if you are eligible for the second part of the study. These additional studies include parathyroid hormone (a measure of bone metabolism), calcium.
- We will inform you of the result of you of your serum vitamin D testing within 1 month of the blood draw. There are 3 possible interpretations of your serum vitamin D level:
 - 1) sufficient (≥ 30 ng/ml)
 - 2) deficient (< 9 ng/ml), or
 - 3) insufficient (≥ 8 but < 30 ng/ml).

If you are in the group with insufficient serum vitamin D levels, you will be invited to continue in the clinical trial that includes daily vitamin D supplementation for two years. If you are in the other 2 groups you do not qualify to continue participation in the study. If you are deficient for vitamin D you may need more intensive vitamin D treatment than is provided in this study for those who are insufficient.

WHO SHOULD NOT PARTICIPATE IN THE STUDY?

There are certain medical conditions and medication use that would exclude you from the study. These include, but are not limited to:

- people who have ever taken bisphosphonates, calcitonin or glucocorticoids for over 3 months
- people who are taking some types of anti-seizure medications, blood thinners, thyroid treatments
- people who 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
- women who are pregnant because they should not have the bone density testing

This involves about 200 people with NF1 whose serum vitamin D levels are insufficient. People 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 safer than medications. For this reason, we are performing a carefully controlled trial of two doses of vitamin D. It will include controlled doses and safety checks for participants' health. This way, we will make sure that vitamin D supplementation is safe for people with NF1.



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 continue 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. The bottle given to you will have a concentration of either of 300 IU or a concentration of 2,000 IU. You will take **two** measured drops every day to equal the randomized dose of 600 IU or 4,000 IU per dose. The vitamin D is called “D-drops” and has a dropper that automatically provides a measured amount when the bottle is turned upside down. Each bottle lasts 3 months. We will provide a new bottle with the same dose of vitamin D for a total for 4 distributions over the course of this two year study.

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 your study coordinator.

The primary measure we will use in this study to determine the effectiveness of the different vitamin D doses is bone mineral density. We will test your bone mineral density at the beginning and at the end of the trial. The procedure is called DXA, and it uses low dose x-rays to measure the density of bones in the hip and spine. We will also ask you some standardized questions that assess your diet, activity level, quality of life, and history of bone fractures.

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 such as TUMS or locally available equivalent (400 mg of elemental calcium supplementation per day).

If you elect to participate in this study, we will provide you with a diary to keep daily track of your vitamin D and calcium supplementation. You will also be asked to notify your study coordinator about any fractures.

You will need to come to clinic 4 times over about 2 years, Screening, Day 1, Year 1, and Year 2. The study coordinator will call you on the phone at month 6 and month 18. Below is a list of what will happen and when during the study, called a schedule of events.



Schedule of Events

Procedure	Screening	Day 1	Month 6	Year 1	Month 18	Year 2
Consent	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
Study Medication dispense		X	X	X	X	
Study Drug Diary (dispense and collect)		X	X	X	X	Collect only
Ask questions about your health.		X	X	X	X	X

DXA scan: You will be taken to an imaging center where you will lay on your back and a scanner will pass over your body to measure total bone mineral density.

RISKS

Blood test: You may experience brief pain or possible bruising from the blood draw. There is a small risk of infection, bleeding, or swelling around the site of needle insertion.

Bone Mineral Density Test (DXA): All medical procedures attempt to minimize the amount of radiation people are exposed to, particularly for research procedures. The radiation dosage for a bone mineral density scan is about 6 mrem. For comparison, the annual background radiation exposure from the earth and atmosphere in an average person is roughly 300 mrem. The results of your bone mineral density studies performed at the beginning of study will not be known by your study team and will only be provided to you and your team at the end of the 2-year study.

Vitamin D toxicity Vitamin D overdose causes “hypercalcemia” (high levels of calcium in the blood and/or urine). The early symptoms of hypercalcemia include nausea and vomiting, weakness, headache, sleepiness, dry mouth, constipation, metallic taste, muscle and bone pain, and itching. Late 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.

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 safety monitoring. You will be asked to take note of any worrisome symptoms and contact us or your primary health provider (family doctor) if you are concerned.

REPRODUCTIVE RISKS

All women must undergo pregnancy testing prior to obtaining DXA imaging. Women who are pregnant at screening will not be eligible for the clinical trial because of the small risk of radiation from the DXA scan to cause birth defects. If you become pregnant while enrolled in this study you will need to contact the study team immediately. Pregnancy would preclude continuation of vitamin D and calcium supplementation as part of the study, and an exit DXA scan would not be performed. This action is based on 2 reasons. First, it is possible the hormone changes in pregnancy could alter your bone mineral density (BMD), and we would not be able to judge if any change on BMD were due to the vitamin D supplementation or the hormone changes associated with pregnancy. Second, if you were pregnant at the time you were scheduled for follow-up DXA imaging we would not be able to perform the second DXA imaging study due to radiation dose, even though it is low.

Pregnancy will not limit your participation to serum collection and study questionnaires while working with your primary care physician until study end.

There are no known risks from taking Vitamin D and calcium while pregnant, breast feeding or fathering a child. Therefore, birth control methods are not required for participation.

BENEFITS

Nobody knows whether or not you will benefit directly from participating in this study, and benefit cannot be guaranteed. It is likely that some participants in this study will be diagnosed with low bone mineral density and osteopenia/osteoporosis. This may be of benefit to them because this is a treatable condition. Others, who may be diagnosed with borderline low bone mineral density, will also benefit in that they may be able to prevent or slow the development of osteoporosis. Other people may receive reassurance about their bone mineral density, and may use the DXA scan(s) as a baseline for the future. You will be given all this information after the trial is completed.

You will be given a copy of your individual results for the entire study after it is over.

People enrolled in the clinical trial may benefit from improved bone mineral density from the vitamin D supplementation.

ALTERNATIVE PROCEDURES

Your participation in this research is entirely voluntary and you may withdraw from the study at any time. If you decide to enter the study but withdraw at any time in the future, there will be no penalty or loss of benefits to which you are otherwise entitled. Your future medical care will not be affected. You may also choose to discuss options for treatment with your primary care physician for different dosing of vitamin D supplementation for osteopenia and/or osteoporosis, including hormone replacement therapy and bisphosphonates.



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

PERSON TO CONTACT

If you have questions, complaints or concerns about this study, or if you think you may have been injured from being in this study, you can contact the clinical research coordinators by calling 801-585-9008. The principal investigator, Dr. David Viskochil, can be reached at 801-581-8943 during the hours of 8 am –5 pm Monday through Friday or 801-581-2121, 24 hours a day.

Institutional Review Board:

Contact the Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Participant Advocate:

You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

RESEARCH-RELATED INJURY

If you are injured from being in this study, medical care is available to you at the University of Utah as it is to all sick or injured people. The University of Utah has not set aside any money to pay the costs for such care. The University will work with you to address costs from injuries. Costs would be charged to you or your insurance company (if you have insurance), to the study sponsor or other third party (if applicable), to the extent those parties are responsible for paying for medical care you receive. Since this is a research study, some health insurance plans may not pay for the costs. By signing this consent form you are not giving up your right to pursue legal action against any parties involved with this research

The University of Utah is a part of the government. If you are injured in this study, and want to sue the University or the doctors, nurses, students, or other people who work for the University, special laws may apply. The Governmental Immunity Act of Utah is a law that controls when a person needs to bring a claim against the government, and limits the amount of money a person may recover. See sections 63G -7-101 to -904 of the Utah Code

STUDY SERUM SAMPLES

Your blood samples will be kept at the University of Utah for one year in case it is necessary to check the findings. If you would like to have your blood samples saved for future related studies, you will have to sign a separate consent form (IRB 7551). The serum will then remain frozen in the Clinical Genetics Research Program under the direction of Dr. David Viskochil, and located at the University of Utah.



UNFORESEEABLE RISKS

Unforeseeable risks may exist and, realistically, the Investigator cannot guarantee that unknown problems will not occur. There may be unforeseeable risks to the woman or fetus from participation in this research from a DXA scan.

RIGHT OF INVESTIGATOR TO WITHDRAW PARTICIPANTS

The study doctor can withdraw you without your approval. Possible reasons for withdrawal include failure to comply with study visits or study drug.

If you are withdrawn from the study, you may be asked to complete the final visit.

COSTS AND COMPENSATION TO PARTICIPANTS

All participants will receive US\$25 for the initial enrollment. For those who undergo DXA scan, an additional US\$50 will be provided. At the 1-year assessment, compensation of US\$50 will be provided. At the 2-year exit assessment, compensation of US\$70 will be provided. This is to partially compensate for time, parking expenses, and gas. People may also be compensated for extended travel expenses. We will discuss this with you in advance of your appointment and will let you know in writing what the travel compensation would be. Payment will be mailed to you after you participate in each assessment.

You will not be charged for the serum studies, DXA scans, vitamin D supplementation, or the calcium supplement.

NEW INFORMATION

Sometimes during the course of a research project, new information becomes available about the vitamin D that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study.

NUMBER OF PARTICIPANTS

We plan to enroll approximately 320 participants from 4 different study sites.

AUTHORIZATION FOR USE OF YOUR PROTECTED HEALTH INFORMATION

Signing this document means you allow us, the researchers in this study, and others working with us to use some information about your health for this research study.

This is the information we will use and include in our research records:

- Demographic and identifying information like name, address, telephone number, and email address
- Social Security Number – This is needed to reimburse you for visits.
- Related medical information about you like medical history, allergies, current and past medications or therapies, and information from physical examinations, such as blood pressure reading, heart rate, temperature, and lab results



- All tests and procedures that will be done in the study

How we will protect and share your information:

- We will do everything we can to keep your information private but we cannot guarantee this. Study information will be kept in a secured manner and electronic records will be password protected. Study information may be stored with other information in your medical record. Other doctors, nurses, and third parties (like insurance companies) may be able to see this information as part of the regular treatment, payment, and health care operations of the hospital. We may also need to disclose information if required by law.
- A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.
- In order to conduct this study and make sure it is conducted as described in this form, the research records may be used and reviewed by others who are working with us on this research:
 - Members of the research team and University of Utah Health Sciences Center
 - The University of Utah Institutional Review Board (IRB), which reviews research involving people to make sure the study protects your rights.
 - U.S. Food and Drug Administration (FDA), a federal agency that needs to confirm the accuracy of the results;
 - U.S. Army Medical Research & Materiel Command, the funding agency that has oversight of conduct of the study and protection of human subjects;
- If we share your identifying information with groups outside of University of Utah Health Sciences Center, they may not be required to follow the same federal privacy laws that we follow. They may also share your information again with others not described in this form.
- If you do not want us to use information about your health, you should not be part of this research. If you choose not to participate, you can still receive health care services at University of Utah Health Sciences Center.

What if I decide to Not Participate after I sign the Consent and Authorization Form?

You can tell us anytime that you do not want to be in this study and do not want us to use your health information. You can also tell us in writing. If you change your mind, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.

This authorization does not have an expiration date.



You have a right to information used to make decisions about your health care. However, your information from this study will not be available during the study; it will be available after the study is finished.

CONSENT

By signing this form, you are consenting to participate.

Please review the following before signing:

- I have read and understood the subject information and consent form.
- I understand that my participation in this study is voluntary and that I can refuse to participate or to withdraw from this study at any time without influencing the medical care I receive
- I understand that I am not waiving any of my legal rights by signing this consent form.
- I understand that the information collected for this study will be kept confidential and will only be used for scientific objectives.
- I have been told that I will receive a dated and signed copy of this form.
- I have read this form and freely consent to participate in this study.

I agree to take part in this research study and authorize you to use and disclose health information about me for this study, as you have explained in this document.

Participant's Name

Participant's Signature

Date

Name of Person Obtaining Authorization and Consent

Signature of Person Obtaining Authorization and Consent

Date

Demographic Information (optional):

Gender: _____ Female Race: _____ American Indian or Alaskan Native

_____ Male _____ Asian or Pacific Islander

Date of Birth: _____ _____ Black

_____ Hispanic

_____ White



Ethnicity: _____ Hispanic or Latino
 _____ Not Hispanic or Latino

_____ Respectfully decline to provide demographic information



CINCINNATI CHILDREN'S HOSPITAL
INFORMED CONSENT FORM

STUDY 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)

STUDY NUMBER: 2014-2634

FUNDING ORGANIZATION: U.S. Department of Defense

Elizabeth K. Schorry, M.D.
Name of Principal Investigator

513-636-4760 during daytime; 24 hr number: 513-636-4200, request genetics physician on call.
Telephone Number

INTRODUCTION

We are asking you to be in a research study so that we can learn new information that may help others. If you decide not to be in this study, we will still take good care of you. If you decide to be in this study, you may change your mind at any time during the study and you can stop being in the study. Take all the time you need to make your choice. Ask us any questions you have. It is also okay to ask more questions after you decide to be in the study. You can ask questions at any time.

WHY ARE WE DOING THIS RESEARCH?

In this research study we want to learn more about Vitamin D, bone density, and neurofibromatosis. Research is a way of gaining new knowledge. Adults with NF1 have a higher risk of osteopenia and osteoporosis than people who do not have NF. Osteopenia is a condition of low bone density that can lead to fragile bones and bone breakage. In general, people with NF1 also have lower vitamin D levels in their blood than people who do not have NF1. Vitamin D is important for normal bone health, and this study will test the possible benefits of two different doses of vitamin D in people with NF1 who have insufficient (not enough) blood levels of vitamin D.

We are asking you and other people with NF1 to be in the research, because you are an adult with NF1 who might be at risk for low bone density.

WHO IS IN CHARGE OF THE RESEARCH?

Dr. Elizabeth Schorry is the researcher at Cincinnati Children's Hospital Medical Center (CCHMC) that is in charge of this study.

There are 3 other centers also participating in this study: University of Utah (the lead institution for the study); University of British Columbia (Vancouver, Canada); and University of Hamburg

(Hamburg, Germany).

CCHMC is being paid by the U.S. Department of Defense (NF Research Program) to do this study.

WHO SHOULD NOT BE IN THE STUDY

You can **not** be in this study if you have any of the following:

- Age less than 25 years or more than 40 years
- Currently pregnant or planning a pregnancy in the next 2 years
- People who have ever taken bisphosphonates (such as Fosamax, Boniva, Actonel, Atelvia and/or Relcast), calcitonin (such as Fortical and/or Miacalcin) or glucocorticoids (steroids) for over 3 months
- People who are taking some types of anti-seizure medications, blood thinners, thyroid treatments
- People who have medical conditions that may affect bone health such as Paget's disease, high thyroid or parathyroid problems, kidney failure, or history of a kidney stone within the last 5 years

HOW MANY PEOPLE WILL BE IN THE STUDY?

We plan to screen 80 people on the clinical trial. A total of 320 people will be screened in 4 participating centers in the US, Canada, and Germany, with about 200 total participating in the trial.

WHAT WILL HAPPEN IN THE STUDY?

The research staff will explain each visit to you and may give you a handout that explains each visit in more detail. You will be able to ask questions to make sure that you understand what will happen.

We are looking for about 320 (80 from Cincinnati) adults with known NF1 to participate in our study. The purpose of this study is to treat about 200 adults with NF1 with two different doses of vitamin D to determine which dose of vitamin D is most appropriate to maintain bone mineral density of the spine and hip. Participants must be between the ages of 25 and 40 years and be willing to come to one of the participating centers 3 times: at the beginning of the study, 1 year later, and 2 years later.

SCREENING

All potential participants will have an initial screening to test their blood vitamin D level.

The procedures for the initial screening are described below:

- You will be contacted by the study coordinator to review the details of the study. If you agree to participate then you will sign this consent form and provide it to the study coordinator who will arrange a time for your initial blood test. This can be done 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 enrollment in the study. A clinic coordinator and/or physician will review your medical history to ensure that you are eligible to participate.

- A blood sample will be collected to test your serum vitamin D level. The amount of blood required is about 3 teaspoons (15ml). To save you a lab draw, we will collect enough blood for other studies to be performed if you are eligible for the second part of the study. These additional studies include parathyroid hormone (a measure of bone metabolism), calcium, and a second study of serum vitamin D to be performed at the central study clinical laboratory.
- We will inform you of the result of you of your serum vitamin D testing within 1 month of the blood draw. There are 3 possible interpretations of your serum vitamin D level:
 - 1) sufficient (≥ 30 ng/ml)
 - 2) deficient (< 9 ng/ml), or
 - 3) insufficient (≥ 9 but < 30 ng/ml).

If you are in the group with insufficient serum vitamin D levels, you will be invited to continue in the clinical trial that includes daily vitamin D supplementation for two years. If you are in the other 2 groups you do not qualify to continue participation in the study. If you are deficient for vitamin D you may need more intensive vitamin D treatment than is provided in this study for those who are insufficient.

CLINICAL TRIAL

This involves about 320 people (80 from Cincinnati) with NF1 whose serum vitamin D levels are insufficient. People 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 safer than medications. For this reason, we are performing a carefully controlled trial of two different doses of vitamin D. It will include safety checks for participants' health. This way, we will make sure that vitamin D supplementation is safe for people with NF1.

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 continue 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. The bottle given to you will have a concentration of either of 300 IU or a concentration of 2,000 IU. You will take **two** measured drops every day to equal the randomized dose of 600 IU or 4,000 IU per dose. The vitamin D is called "D-drops" and has a dropper that automatically provides a measured amount when the bottle is turned upside down. Each bottle lasts 3 months. We will provide a new bottle with the same dose of vitamin D for a total for 4 distributions over the course of this two year study.

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 your study coordinator.

The primary measure we will use in this study to determine the effectiveness of the different vitamin D doses is bone mineral density. We will test your bone mineral density at the beginning and at the end of the trial. The procedure is called DXA, and it uses low dose x-rays to measure the density of bones in the hip and spine. We will also ask you some standardized questions that assess your diet, activity level, quality of life, and history of bone fractures.

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. Therefore, we will give all participants a calcium supplement of 1,000 mg per day (400 mg of elemental calcium supplementation per day).

If you elect to participate in this study, we will provide you with a diary to keep daily track of your vitamin D and calcium supplementation. You will also be asked to notify your study coordinator about any fractures.

You will need to come to clinic 4 times over about 2 years, Screening, Day 1, Year 1, and Year 2. The study coordinator will call you on the phone at month 6 and month 18. A list of what will happen and when during the study is in the schedule of events.

See Appendix A Schedule of Events

WHAT ARE THE GOOD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

Nobody knows whether or not you will benefit directly from participating in this study, and benefit cannot be guaranteed. You will receive two DEXA scans and several blood tests free of charge during this study. It is likely that some participants in this study will be diagnosed with low bone mineral density and osteopenia or osteoporosis. This may be of benefit to them because this is a treatable condition. Others, who may be diagnosed with borderline low bone mineral density, will also benefit in that they may be able to prevent or slow the development of osteoporosis. Other people may receive reassurance about their normal bone mineral density, and may use the DXA scan(s) as a baseline for the future. You will be given all this information after the trial is completed.

People enrolled in the clinical trial may benefit from improved bone mineral density from the vitamin D supplementation.

You will be given a copy of your individual results for the entire study after it is over.

Being in this study may not help you right now. When we finish the study, we hope that we will know more about bone density in people with NF1. This may help other people with NF1 later on.

WHAT ARE THE BAD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

Blood test: You may experience brief pain or possible bruising from the blood draw. There is a small risk of infection, bleeding, or swelling around the site of needle insertion.

Bone Mineral Density Test (DXA): All medical procedures attempt to minimize the amount of radiation people are exposed to, particularly for research procedures. The radiation dosage for a bone mineral density scan is about 6 mrem. For comparison, the annual background radiation exposure from the earth and atmosphere in an average person is roughly 300 mrem. The results of your bone mineral density studies performed at the beginning of study will not be known by your study team and will only be provided to you and your team at the end of the 2-year study.

Vitamin D toxicity Vitamin D overdose causes “hypercalcemia” (high levels of calcium in the blood and/or urine). The early symptoms of hypercalcemia include nausea and vomiting, weakness, headache, sleepiness, dry mouth, constipation, metallic taste, muscle and bone pain, and itching. Late 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.

The risk of vitamin D toxicity with the doses used 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 safety monitoring. You will be asked to take note of any worrisome symptoms and contact us or your primary health provider (family doctor) if you are concerned.

There may be other risks that we do not know about yet.

REPRODUCTIVE RISKS

All women must undergo pregnancy testing prior to obtaining DXA imaging. Women who are pregnant at screening will not be eligible for the clinical trial because of the small risk of radiation from the DXA scan to cause birth defects. If you become pregnant while enrolled in this study you will need to contact the study team immediately. Pregnancy would mean that you would need to stop the study vitamin D and calcium supplements (and start on prenatal Vitamins instead), and an exit DXA scan would not be performed. This action is based on 2 reasons. First, it is possible the hormone changes in pregnancy could alter your bone mineral density (BMD), and we would not be able to judge if any change on BMD were due to the vitamin D supplementation or the hormone changes associated with pregnancy. Second, if you were pregnant at the time you were scheduled for follow-up DXA imaging we would not be able to perform the second DXA imaging study due to radiation dose, even though it is low.

Pregnancy will not prevent your participation in blood collection and study questionnaires until the end of the study.

There are no known risks from taking Vitamin D and calcium while pregnant, breast feeding or fathering a child. Therefore, birth control methods are not required for participation.

WHAT OTHER CHOICES ARE THERE?

Instead of being in this study, you can choose not to be in it. Your physicians in the NF clinic will continue to provide your medical care, regardless of whether you choose to be in the study.

WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE? Your participation in this research is entirely voluntary and you may withdraw from the study at any time. If you decide to enter the study but withdraw at any time in the future, there will be no penalty or loss of benefits to which you are otherwise entitled. Your future medical care will not be affected. You may also choose to discuss options for treatment with your primary care physician for different dosing of vitamin D supplementation for osteopenia and/or osteoporosis, including hormone replacement therapy and bisphosphonates.

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

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE?

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

Your confidentiality will be respected. All study visits will be performed in a private room. No information that discloses your identity will be released or published. Any information about you being sent to the University of Utah will be identified by number, not by name or birth date. However, research records and medical records identifying you may be inspected in the presence of the Investigator or his designate by representatives of the Research Ethics Board or Institutional Review Boards of the participating centers, for the purpose of monitoring the research. In addition, representatives of the funding agency are eligible to review the records in the presence of the Principal Investigator. However, no records that identify your name or initials will be allowed to leave the Investigators' offices.

The United States Food and Drug Administration (FDA) may inspect study records that include information that identifies study participants. Records about you will be kept in locked filing cabinets and on computers protected with passwords. Results of the study may be published; however, your name and other identifying information will be kept private. We will do everything we can to keep your records private, but cannot guarantee this.

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.

WHAT IF WE LEARN NEW INFORMATION DURING THE RESEARCH?

The study doctor will tell you if they find out about new information from this or other studies that may affect your health, safety or willingness to stay in this study. During the course of this research project, new information may become available about the treatment of vitamin D that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study.

WILL IT COST YOU ANYTHING EXTRA TO BE IN THE RESEARCH STUDY?

You will not be charged for the serum studies, DXA scans, vitamin D supplementation, or the calcium tablets. If you are being seen for a regular physician visit at the NF Clinic during the study, you and your insurance will still be billed for the clinic visit. However, if you are seen for only a research visit, there will be no charge.

WILL YOU BE PAID TO BE IN THIS RESEARCH STUDY?

You will be reimbursed for your time, effort and travel while you are in this research study. All participants will receive US\$25 for the initial enrollment. For those who undergo DXA scan, an additional US\$50 will be provided. At the 1-year assessment, compensation of US\$50 will be provided. At the 2-year exit assessment, compensation of US\$70 will be provided. This is to partially compensate for time, parking expenses, and gas. People may also be compensated for extended travel expenses if you live a far distance away. We will discuss this with you in advance of your appointment and will let you know in writing what the travel compensation would be. Payment will be mailed to you after you participate in each assessment.

Tissues or body fluids collected for this research may result in the development of a product that could be patented/licensed and sold. You will not be paid if this happens.

WHAT HAPPENS IF YOU ARE INJURED FROM BEING IN THIS STUDY?

If you believe that you have been injured as a result of this research you should contact the study doctor, Dr. Elizabeth Schorry (513-636-4760), as soon as possible to discuss the concerns. You may also contact the study coordinator, Melissa Kahler, at 513-636-9938 for advice. Treatment for injuries is available at CCHMC or at UC Hospital. If you go to the Emergency Room or to another hospital or doctor it is important that you tell them that you are in a research study. If possible, you should give them a copy of this consent form.

CCHMC follows a policy of making all decisions about compensation for the medical treatment of physical injuries that happened during or were caused by research on an individual basis.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

For questions, concerns, or complaints about this research study you can contact the study person listed on page 1 of this document.

If you would like to talk to someone that is not part of the research staff or if you have general questions about your research study rights or questions, concerns, or complaints about the research, you can call the CCHMC Institutional Review Board at 513-636-8039.

AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH

To be in this research study you must also give your permission (or authorization) to use and disclose (or share) your "protected health information" (called PHI for short).

What protected health information will be used and shared during this study?

CCHMC will need to use and share your PHI as part of this study. This PHI will come from:

- Your CCHMC medical records
- Your research records

The types of information that will be used and shared from these records include:

- Laboratory test results, diagnosis, and medications
- Reports and notes from clinical and research observations
- Imaging (like CT scans, MRI scans, x-rays, etc.) studies and reports
- If applicable, information concerning HIV testing or the treatment of AIDS or AIDS-related conditions, drug or alcohol abuse, drug-related conditions, alcoholism, and/or psychiatric/psychological conditions (but not psychotherapy notes).

Who will share, receive and/or use your protected health information in this study?

- Staff at all the research study sites (including CCHMC)
- Personnel who provide services to you as part of this study
- Other individuals and organizations that need to use your PHI in connection with the research, including people at the sponsor and organizations that the sponsor may use to oversee or conduct the study.
- The members of the CCHMC Institutional Review Board and staff of the Office of Research Compliance and Regulatory Affairs.
- U.S. Food and Drug Administration (FDA), a federal agency that needs to confirm the accuracy of the study results
- U.S. Army Medical Research & Material Command, the funding agency that has oversight of conduct of the study and protection of human subjects.

How will you know that your PHI is not misused?

People that receive your PHI as part of the research are generally limited in how they can use your PHI. In addition, most people who receive your PHI are also required by federal privacy laws to protect your PHI. However, some people that may receive your PHI may not be required to protect it and may share the information with others without your permission, if permitted by the laws that apply to them.

Can you change your mind?

You may choose to withdraw your permission at any time. A withdrawal of your permission to use and share your PHI would also include a withdrawal from participation in the research study. If you wish to withdraw your permission to use and share PHI you need to notify the study doctor, listed on the first page of this document, in writing. Your request will be effective immediately and no new PHI about you will be used or shared. The only exceptions are (1) any use or sharing of PHI that has already occurred or was in process prior to you withdrawing your permission and (2) any use or sharing that is needed to maintain the integrity of the research.

Will this permission expire?

Your permission will expire at the end of the study. If the study involves the creation or maintenance of a research database repository, this authorization will not expire.

Will your other medical care be impacted?

By signing this document you agree to participate in this research study and give permission to CCHMC to use and share your PHI for the purpose of this research study. If you refuse to sign this

document you will not be able to participate in the study. However, your rights concerning treatment not related to this study, payment for services, enrollment in a health plan or eligibility of benefits will not be affected.

You can choose to have us inform your primary care physician of your study participation:

- ☐ No, please do NOT inform my primary care physician
☐ Yes, please inform my primary care physician

My physician's name is: _____

My physician's contact info/ telephone # is: _____

STUDY SERUM SAMPLES

Your blood samples will be kept at the University of Utah for one year in case it is necessary to check the findings. If you would like to have your blood samples saved for future related studies, you can sign and date below. The serum will then remain frozen in the Clinical Genetics Research Program under the direction of Dr. David Viskochil, and located at the University of Utah.

Sign and date	
	I <u>DO</u> agree for my samples to be kept for future related studies
	I <u>DO NOT</u> agree for my samples to be kept for future related studies

SIGNATURES

The research team has discussed this study with you and answered all of your questions. Like any research, the researchers cannot predict exactly what will happen. Once you have had enough time to consider whether you should participate in this research you will document your consent by signature below.

Please review the following Check List before signing:

- I have read and understood the subject information and consent form.
- I understand that my participation in this study is voluntary and that I can refuse to participate or to withdraw from this study at any time without influencing the medical care I receive
- I understand that I am not waiving any of my legal rights by signing this consent form.
- I understand that the information collected for this study will be kept confidential and will only be used for scientific objectives.
- I have been told that I will receive a dated and signed copy of this form.
- I have read this form and freely consent to participate in this study.

I agree to take part in this research study and authorize you to use and disclose health information about me for this study, as you have explained in this document.

Participant's Name

Participant's Signature

Date

Name of Person Obtaining Authorization and Consent

Signature of Person Obtaining Authorization and Consent

Date

Subject Information (optional):

Gender: _____ Female
 _____ Male

Race: _____ Caucasian (white)
 _____ Asian or Pacific Islander
 _____ African American/Black
 _____ American Indian

Date of Birth: _____

Ethnicity: _____ Hispanic or Latino
 _____ Not Hispanic or Latino

_____ Respectfully decline to provide demographic information

Appendix A

Schedule of Events

Procedure	Screening	Day 1	Month 6	Year 1	Month 18	Year 2
Consent	X					
Blood collection	X					
Urine Pregnancy	X	X		X		X
DXA Scan		X				X
Physical Exam		X		X		X
Questionnaires		X		X		X
Study Medication dispense		X	X	X	X	
Study Drug Diary (dispense and collect)		X	X	X	X	Collect only
Ask questions about your health.		X	X	X	X	X

DXA scan: You will be taken to an imaging center where you will lay on your back and a scanner will pass over your body to measure total bone mineral density.

UofU Letter of Initial Contact

Appendix 6.4

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)

You Are Invited to Participate in a Research Study

“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)”

What is this research study?

This is a randomized clinical trial of oral vitamin D therapy in adults with NF1 and vitamin D insufficiency. We are looking for about 320 adults with known NF1 to participate in this study. The purpose of this study is to treat adults with two different doses of vitamin D to determine which dose is most appropriate to maintain bone mineral density of the spine and hip.

What would be expected of me?

All study patients are expected to attend 3 study visits over 2 years, adhere to study guidelines and answer the required questionnaires for the duration of the study.

You may be eligible to take part in this Study if:

- You are 25-40 years of age
- You have Neurofibromatosis Type 1 (NF1)
- You are willing to come to a clinic 3 times (Beginning, 1 year later, and 2 years later)
- Not on Vitamin D or calcium
- You have insufficient serum vitamin D levels on a blood sample

Will it cost me anything?

There is no cost to you.

What are the risks?

- Vitamin D Toxicity: The risk for vitamin D toxicity through supplementation in the study is **low**. We will assess for this through safety monitoring.
- Radiation: As part of the study, you will receive a Bone Mineral Density Test (DXA). The radiation levels of this test are minimal (6mrem).
- Reproductive Risks: Hormone changes during pregnancy can alter bone density, which can alter our results. If you are pregnant during the DXA scan, there is a small chance for a birth defect to become present.

Are there any benefits?

Some people enrolled in this clinical trial may benefit from improved bone mineral density from the vitamin D supplementation. However, benefits cannot be guaranteed.

If you are interested in learning more about this vitamin D study, please contact:

Please contact Jenny Billy at (801) 585-9008, or Sarah Couchon at (801) 585-3822, or Maggie Kuenzi at (801) 585-9183.

You will be contacted 1 week after this advertisement has been mailed to answer any questions.

REDCap Data Collection Forms

Appendix 6.5

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)

Adverse Events Log

Participant ID

Adverse Events Log

Only report AE's related to Vitamin D or SAE

AE term

Serious Adverse Event

- ☐ yes
☐ no

Severity

- ☐ Mild
☐ Moderate
☐ Severe
☐ Life Threatening
☐ Death

Relationship

Only probably or definitely related need to be recorded

- ☐ Unrelated
☐ Unlikely
☐ Possibly
☐ Probably
☐ Definitely

Action taken with Study Medication

- ☐ None Continue dose
☐ Interrupted On hold
☐ Reduced Cut back on dose
☐ Discontinued

Other action

- ☐ None
☐ Prescription
☐ OTC / non-RX
☐ Hospitalization
☐ Other - Complete Comment Form

Outcome

- ☐ Complete recovery w/o residual effect
☐ Recovered with residual effect
☐ Recovered with persistent effect
☐ Not yet recovered
☐ Died

Start Date

(mm/dd/yyyy)

Ongoing

- ☐ Yes
☐ No

Stop Date

(mm/dd/yyyy)

Adverse Event 2

AE term

Serious Adverse Event

Severity

- ☐ Mild
☐ Moderate
☐ Severe
☐ Life Threatening
☐ Death

Relationship

- ☐ Unrelated
☐ Unlikely
☐ Possibly
☐ Probably
☐ Definitely

Action taken with Study Medication

- ☐ None Continue dose
☐ Interrupted On hold
☐ Reduced Cut back on dose
☐ Discontinued

Other action

- ☐ None
☐ Prescription
☐ OTC / non-RX
☐ Hospitalization
☐ Other - Complete Comment Form

Outcome

- ☐ Complete recovery w/o residual effect
☐ Recovered with residual effect
☐ Recovered with persistent effect
☐ Not yet recovered
☐ Died

Start Date
(mm/dd/yyyy)

Ongoing

- ☐ Yes
☐ No

Stop Date
(mm/dd/yyyy)

Adverse Event 3

AE term

Serious Adverse Event

Severity	☐ Mild ☐ Moderate ☐ Severe ☐ Life Threatening ☐ Death
Relationship	☐ Unrelated ☐ Unlikely ☐ Possibly ☐ Probably ☐ Definitely
Action taken with Study Medication	☐ None Continue dose ☐ Interrupted On hold ☐ Reduced Cut back on dose ☐ Discontinued
Other action	☐ None ☐ Prescription ☐ OTC / non-RX ☐ Hospitalization ☐ Other - Complete Comment Form
Outcome	☐ Complete recovery w/o residual effect ☐ Recovered with residual effect ☐ Recovered with persistent effect ☐ Not yet recovered ☐ Died
Start Date (mm/dd/yyyy)	
Ongoing	☐ Yes ☐ No
Stop Date (mm/dd/yyyy)	
Adverse Event 4	
AE term	
Serious Adverse Event	
Severity	☐ Mild ☐ Moderate ☐ Severe ☐ Life Threatening ☐ Death
Relationship	☐ Unrelated ☐ Unlikely ☐ Possibly ☐ Probably ☐ Definitely

Action taken with Study Medication

- ☐ None Continue dose
☐ Interrupted On hold
☐ Reduced Cut back on dose
☐ Discontinued

Other action

- ☐ None
☐ Prescription
☐ OTC / non-RX
☐ Hospitalization
☐ Other - Complete Comment Form

Outcome

- ☐ Complete recovery w/o residual effect
☐ Recovered with residual effect
☐ Recovered with persistent effect
☐ Not yet recovered
☐ Died

Start Date
(mm/dd/yyyy)

Ongoing

- ☐ Yes
☐ No

Stop Date
(mm/dd/yyyy)

Adverse Event 5

AE term

Serious Adverse Event

Severity

- ☐ Mild
☐ Moderate
☐ Severe
☐ Life Threatening
☐ Death

Relationship

- ☐ Unrelated
☐ Unlikely
☐ Possibly
☐ Probably
☐ Definitely

Action taken with Study Medication

- ☐ None Continue dose
☐ Interrupted On hold
☐ Reduced Cut back on dose
☐ Discontinued

Other action

- ☐ None
☐ Prescription
☐ OTC / non-RX
☐ Hospitalization
☐ Other - Complete Comment Form

Outcome	☐ Complete recovery w/o residual effect ☐ Recovered with residual effect ☐ Recovered with persistent effect ☐ Not yet recovered ☐ Died
---------	--

Start Date (mm/dd/yyyy)	_____
----------------------------	-------

Ongoing	☐ Yes ☐ No
---------	---

Stop Date (mm/dd/yyyy)	_____
---------------------------	-------

Adverse Event 6

AE term	_____
---------	-------

Serious Adverse Event	_____
-----------------------	-------

Severity	☐ Mild ☐ Moderate ☐ Severe ☐ Life Threatening ☐ Death
----------	---

Relationship	☐ Unrelated ☐ Unlikely ☐ Possibly ☐ Probably ☐ Definitely
--------------	---

Action taken with Study Medication	☐ None Continue dose ☐ Interrupted On hold ☐ Reduced Cut back on dose ☐ Discontinued
------------------------------------	---

Other action	☐ None ☐ Prescription ☐ OTC / non-RX ☐ Hospitalization ☐ Other - Complete Comment Form
--------------	--

Outcome	☐ Complete recovery w/o residual effect ☐ Recovered with residual effect ☐ Recovered with persistent effect ☐ Not yet recovered ☐ Died
---------	--

Start Date (mm/dd/yyyy)	_____
----------------------------	-------

Ongoing	☐ Yes ☐ No
---------	---

Stop Date
(mm/dd/yyyy)

Adverse Event 7

AE term

Serious Adverse Event

Severity

- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Life Threatening
- ☐ Death

Relationship

- ☐ Unrelated
- ☐ Unlikely
- ☐ Possibly
- ☐ Probably
- ☐ Definitely

Action taken with Study Medication

- ☐ None Continue dose
- ☐ Interrupted On hold
- ☐ Reduced Cut back on dose
- ☐ Discontinued

Other action

- ☐ None
- ☐ Prescription
- ☐ OTC / non-RX
- ☐ Hospitalization
- ☐ Other - Complete Comment Form

Outcome

- ☐ Complete recovery w/o residual effect
- ☐ Recovered with residual effect
- ☐ Recovered with persistent effect
- ☐ Not yet recovered
- ☐ Died

Start Date
(mm/dd/yyyy)

Ongoing

- ☐ Yes
- ☐ No

Stop Date
(mm/dd/yyyy)

Clinical Trial Blood Collection Form

Participant ID

Urine Pregnancy Test

Urine Pregnancy Test

- ☐ positive
☐ negative

If no, explain:

If yes, date collected:

Lot # of pregnancy test

Expiration date of pregnancy test

Blood Collection sample obtained

Blood Collection sample obtained

- ☐ Yes
☐ No

If no, explain

If yes, date drawn

Calcium Lab Value

(8.4-10.2 mg/dL)

Calcium Normal?

- ☐ Normal
☐ Abnormal*
☐ ND*

If Abnormal

- ☐ NCS*
☐ AE*

PTH Lab Value

(15-65 mg/dL)

PTH Normal?

- ☐ Normal
☐ Abnormal*
☐ ND*

If Abnormal

- ☐ NCS*
☐ AE*

Vitamin D Lab Value	
	(mg/dL (eligible 9-29ng/ml))
Vitamin D Normal?	☐ Normal ☐ Abnormal* ☐ ND*
If Abnormal	☐ NCS* ☐ AE*
Date serum was frozen?	
Date serum was shipped to the University of Utah?	
Mode of shipment	
Shipment tracking number	

Clinical Trial Fracture Form

Participant ID

Have you ever broken a bone?

- ☐ No (skip the rest of this page)
☐ Yes

Event 1

Age at Fracture

Location Code (use multiple codes for multiple simultaneous fractures)

(select as many as apply)

- ☐ toes/foot
☐ ankle
☐ tibia
☐ fibula
☐ lower leg unspecified
☐ hips/pelvis
☐ spine/neck
☐ ribs
☐ skull/face
☐ shoulder
☐ humerus
☐ radius
☐ ulna leg unspecified
☐ lower arm unspecified
☐ wrist
☐ hand/fingers
☐ other
☐ uncertain which

Fracture Type Code

(select as many as apply)

- ☐ simple
☐ compound (through the skin)
☐ complete
☐ incomplete
☐ stress/fatigue
☐ pathologic (due to disease)
☐ multiple
☐ unknown

Trauma description code

(select as many as apply)

- ☐ Yes - Certain Trauma (MVA, fall)
☐ No - No trauma (apparently minimal reason for break)
☐ Unknown level of trauma

Treatment description code

(select as many as apply)

- ☐ casting
☐ pins/plates
☐ graft
☐ surgery unspecified
☐ other (specify)
☐ unknown

Please specify other treatment code

(enter if selected other for treatment code)

Complications Code
(select as many as apply)

- ☐ none (bone set, no sequelae)
- ☐ infection
- ☐ won't heal
- ☐ pain in area of fracture
- ☐ limited motion/functional impairment
- ☐ other (specify)

Please specify other complications code

Where was treatment and where were X-rays taken?

Event 2

Age at Fracture

Location Code (use multiple codes for multiple simultaneous fractures)

(select as many as apply)

- ☐ toes/foot
- ☐ ankle
- ☐ tibia
- ☐ fibula
- ☐ lower
- ☐ hips/pelvis
- ☐ spine/neck
- ☐ ribs
- ☐ skull/face
- ☐ shoulder
- ☐ humerus
- ☐ radius
- ☐ ulna leg unspec
- ☐ lower arm unspec
- ☐ wrist
- ☐ hand/fingers
- ☐ other
- ☐ uncertain which

Fracture Type Code
(select as many as apply)

- ☐ simple
- ☐ compound (through the skin)
- ☐ complete
- ☐ incomplete
- ☐ stress/fatigue
- ☐ pathologic (due to disease)
- ☐ multiple
- ☐ unknown

Trauma description code
(select as many as apply)

- ☐ Yes
- ☐ No
- ☐ Unkonwn

Treatment description code
(select as many as apply)

- ☐ casting
- ☐ pins/plates
- ☐ graft
- ☐ surgery unspec.
- ☐ other (specify)
- ☐ unknown

Please specify other treatment code

Complications Code
(select as many as apply)

- ☐ none (bone set, no sequelae)
- ☐ infection
- ☐ won't heal
- ☐ pain in area of fracture
- ☐ limited motion/functional impairment
- ☐ other (specify)

Please specify other treatment code

Where was treatment and where were X-rays taken?

Event 3

Age at Fracture

Location Code (use multiple codes for multiple simultaneous fractures)

(select as many as apply)

- ☐ toes/foot
- ☐ ankle
- ☐ tibia
- ☐ fibula
- ☐ lower
- ☐ hips/pelvis
- ☐ spine/neck
- ☐ ribs
- ☐ skull/face
- ☐ shoulder
- ☐ humerus
- ☐ radius
- ☐ ulna leg unspec
- ☐ lower arm unspec
- ☐ wrist
- ☐ hand/fingers
- ☐ other
- ☐ uncertain which

Fracture Type Code
(select as many as apply)

- ☐ simple
- ☐ compound (through the skin)
- ☐ complete
- ☐ incomplete
- ☐ stress/fatigue
- ☐ pathologic (due to disease)
- ☐ multiple
- ☐ unknown

Trauma description code
(select as many as apply)

- ☐ Yes
- ☐ No
- ☐ Unkonwn

Treatment description code
(select as many as apply)

- ☐ casting
- ☐ pins/plates
- ☐ graft
- ☐ surgery unspec.
- ☐ other (specify)
- ☐ unknown

Please specify other treatment code

Complications Code
(select as many as apply)

- ☐ none (bone set, no sequelae)
- ☐ infection
- ☐ won't heal
- ☐ pain in area of fracture
- ☐ limited motion/functional impairment
- ☐ other (specify)

Please specify other treatment code

Where was treatment and where were X-rays taken?

Event 4

Age at Fracture

Location Code (use multiple codes for multiple simultaneous fractures)

(select as many as apply)

- ☐ toes/foot
- ☐ ankle
- ☐ tibia
- ☐ fibula
- ☐ lower
- ☐ hips/pelvis
- ☐ spine/neck
- ☐ ribs
- ☐ skull/face
- ☐ shoulder
- ☐ humerus
- ☐ radius
- ☐ ulna leg unspec
- ☐ lower arm unspec
- ☐ wrist
- ☐ hand/fingers
- ☐ other
- ☐ uncertain which

Fracture Type Code
(select as many as apply)

- ☐ simple
- ☐ compound (through the skin)
- ☐ complete
- ☐ incomplete
- ☐ stress/fatigue
- ☐ pathologic (due to disease)
- ☐ multiple
- ☐ unknown

Trauma description code
(select as many as apply)

- ☐ Yes
- ☐ No
- ☐ Unkonwn

Treatment description code
(select as many as apply)

- ☐ casting
- ☐ pins/plates
- ☐ graft
- ☐ surgery unspec.
- ☐ other (specify)
- ☐ unknown

Please specify other treatment code

Complications Code
(select as many as apply)

- ☐ none (bone set, no sequelae)
- ☐ infection
- ☐ won't heal
- ☐ pain in area of fracture
- ☐ limited motion/functional impairment
- ☐ other (specify)

Please specify other treatment code

Where was treatment and where were X-rays taken?

Event 5

Age at Fracture

Location Code (use multiple codes for multiple simultaneous fractures)

(select as many as apply)

- ☐ toes/foot
- ☐ ankle
- ☐ tibia
- ☐ fibula
- ☐ lower
- ☐ hips/pelvis
- ☐ spine/neck
- ☐ ribs
- ☐ skull/face
- ☐ shoulder
- ☐ humerus
- ☐ radius
- ☐ ulna leg unspec
- ☐ lower arm unspec
- ☐ wrist
- ☐ hand/fingers
- ☐ other
- ☐ uncertain which

Fracture Type Code
(select as many as apply)

- ☐ simple
- ☐ compound (through the skin)
- ☐ complete
- ☐ incomplete
- ☐ stress/fatigue
- ☐ pathologic (due to disease)
- ☐ multiple
- ☐ unknown

Trauma description code
(select as many as apply)

- ☐ Yes
- ☐ No
- ☐ Unkonwn

Treatment description code
(select as many as apply)

- ☐ casting
- ☐ pins/plates
- ☐ graft
- ☐ surgery unspec.
- ☐ other (specify)
- ☐ unknown

Please specify other treatment code

Complications Code
(select as many as apply)

☐ none (bone set, no sequelae)

☐ infection

☐ won't heal

☐ pain in area of fracture

☐ limited motion/functional impairment

☐ other (specify)

Please specify other treatment code

Where was treatment and where were X-rays taken?

Clinical Trial Medical History

Participant ID

Is there medical history to record?

☐ Yes

☐ No

Term/ Surgery 1

Term/ Surgery

Start Month

☐ unk

☐ Jan

☐ Feb

☐ Mar

☐ Apr

☐ May

☐ Jun

☐ Jul

☐ Aug

☐ Sep

☐ Oct

☐ Nov

☐ Dec

Start Year

(Year)

Ongoing

☐ Yes

☐ No

☐ Unknown

Stop Date

Term/ Surgery 2

Term/ Surgery

Start Month

☐ unk

☐ Jan

☐ Feb

☐ Mar

☐ Apr

☐ May

☐ Jun

☐ Jul

☐ Aug

☐ Sep

☐ Oct

☐ Nov

☐ Dec

Start Year	
	(Year)
Ongoing	☐ Yes ☐ No ☐ Unknown
Stop Date	

Term/ Surgery 3

Term/ Surgery	
Start Month	☐ unk ☐ Jan ☐ Feb ☐ Mar ☐ Apr ☐ May ☐ Jun ☐ Jul ☐ Aug ☐ Sep ☐ Oct ☐ Nov ☐ Dec
Start Year	
	(Year)
Ongoing	☐ Yes ☐ No ☐ Unknown
Stop Date	

Term/ Surgery 4

Term/ Surgery	
---------------	-------------

Start Month

- ☐ unk
- ☐ Jan
- ☐ Feb
- ☐ Mar
- ☐ Apr
- ☐ May
- ☐ Jun
- ☐ Jul
- ☐ Aug
- ☐ Sep
- ☐ Oct
- ☐ Nov
- ☐ Dec

Start Year

(Year)

Ongoing

- ☐ Yes
- ☐ No
- ☐ Unknown

Stop Date

Term/ Surgery 5

Term/ Surgery

Start Month

- ☐ unk
- ☐ Jan
- ☐ Feb
- ☐ Mar
- ☐ Apr
- ☐ May
- ☐ Jun
- ☐ Jul
- ☐ Aug
- ☐ Sep
- ☐ Oct
- ☐ Nov
- ☐ Dec

Start Year

(Year)

Ongoing

- ☐ Yes
- ☐ No
- ☐ Unknown

Stop Date

Term/ Surgery 6

Term/ Surgery

Start Month

- ☐ unk
- ☐ Jan
- ☐ Feb
- ☐ Mar
- ☐ Apr
- ☐ May
- ☐ Jun
- ☐ Jul
- ☐ Aug
- ☐ Sep
- ☐ Oct
- ☐ Nov
- ☐ Dec

Start Year

(Year)

Ongoing

- ☐ Yes
- ☐ No
- ☐ Unknown

Stop Date

Term/ Surgery 7

Term/ Surgery

Start Month

- ☐ unk
- ☐ Jan
- ☐ Feb
- ☐ Mar
- ☐ Apr
- ☐ May
- ☐ Jun
- ☐ Jul
- ☐ Aug
- ☐ Sep
- ☐ Oct
- ☐ Nov
- ☐ Dec

Start Year

(Year)

Ongoing

- ☐ Yes
- ☐ No
- ☐ Unknown

Stop Date

Term/ Surgery 8

Term/ Surgery

Start month

- ☐ unk
- ☐ Jan
- ☐ Feb
- ☐ Mar
- ☐ Apr
- ☐ May
- ☐ Jun
- ☐ Jul
- ☐ Aug
- ☐ Sep
- ☐ Oct
- ☐ Nov
- ☐ Dec

Start Year

(Year)

Ongoing

- ☐ Yes
- ☐ No
- ☐ Unknown

Stop Date

Term/ Surgery 9

Term/ Surgery

Start Month

- ☐ unk
- ☐ Jan
- ☐ Feb
- ☐ Mar
- ☐ Apr
- ☐ May
- ☐ Jun
- ☐ Jul
- ☐ Aug
- ☐ Sep
- ☐ Oct
- ☐ Nov
- ☐ Dec

Start Year

(Year)

Ongoing

- ☐ Yes
- ☐ No
- ☐ Unknown

Stop Date

Term/ Surgery 10

Term/ Surgery

Start Month

- ☐ unk
- ☐ Jan
- ☐ Feb
- ☐ Mar
- ☐ Apr
- ☐ May
- ☐ Jun
- ☐ Jul
- ☐ Aug
- ☐ Sep
- ☐ Oct
- ☐ Nov
- ☐ Dec

Start Year

(Year)

Ongoing

- ☐ Yes
- ☐ No
- ☐ Unknown

Stop Date

Term/ Surgery 11

Term/ Surgery

Start Month

- ☐ unk
- ☐ Jan
- ☐ Feb
- ☐ Mar
- ☐ Apr
- ☐ May
- ☐ Jun
- ☐ Jul
- ☐ Aug
- ☐ Sep
- ☐ Oct
- ☐ Nov
- ☐ Dec

Start Year

(Year)

Ongoing

- ☐ Yes
- ☐ No
- ☐ Unknown

Stop Date

Term/ Surgery 12

Term/ Surgery

Start Month

- ☐ unk
- ☐ Jan
- ☐ Feb
- ☐ Mar
- ☐ Apr
- ☐ May
- ☐ Jun
- ☐ Jul
- ☐ Aug
- ☐ Sep
- ☐ Oct
- ☐ Nov
- ☐ Dec

Start Year

(Year)

Ongoing

- ☐ Yes
- ☐ No
- ☐ Unknown

Stop Date

Term/ Surgery 13

Term/ Surgery

Start Month

- ☐ unk
- ☐ Jan
- ☐ Feb
- ☐ Mar
- ☐ Apr
- ☐ May
- ☐ Jun
- ☐ Jul
- ☐ Aug
- ☐ Sep
- ☐ Oct
- ☐ Nov
- ☐ Dec

Start Year

(Year)

Ongoing

- ☐ Yes
- ☐ No
- ☐ Unknown

Stop Date

Term/ Surgery 14

Term/ Surgery

Start Month

- ☐ unk
- ☐ Jan
- ☐ Feb
- ☐ Mar
- ☐ Apr
- ☐ May
- ☐ Jun
- ☐ Jul
- ☐ Aug
- ☐ Sep
- ☐ Oct
- ☐ Nov
- ☐ Dec

Start Year

(Year)

Ongoing

- ☐ Yes
- ☐ No
- ☐ Unknown

Stop Date

Term/ Surgery 15

Term/ Surgery

Start Month

- ☐ unk
- ☐ Jan
- ☐ Feb
- ☐ Mar
- ☐ Apr
- ☐ May
- ☐ Jun
- ☐ Jul
- ☐ Aug
- ☐ Sep
- ☐ Oct
- ☐ Nov
- ☐ Dec

Start Year

(Year)

Ongoing

- ☐ Yes
- ☐ No
- ☐ Unknown

Stop Date

Term/ Surgery 16

Term/ Surgery

Start month

- ☐ unk
- ☐ Jan
- ☐ Feb
- ☐ Mar
- ☐ Apr
- ☐ May
- ☐ Jun
- ☐ Jul
- ☐ Aug
- ☐ Sep
- ☐ Oct
- ☐ Nov
- ☐ Dec

Start Year

(Year)

Ongoing

- ☐ Yes
- ☐ No
- ☐ Unknown

Stop Date

Term/ Surgery 17

Term/ Surgery

Start Month

- ☐ unk
- ☐ Jan
- ☐ Feb
- ☐ Mar
- ☐ Apr
- ☐ May
- ☐ Jun
- ☐ Jul
- ☐ Aug
- ☐ Sep
- ☐ Oct
- ☐ Nov
- ☐ Dec

Start Year

(Year)

Ongoing

- ☐ Yes
- ☐ No
- ☐ Unknown

Stop Date

Term/ Surgery 18

Term/ Surgery

Start Month

- ☐ unk
☐ Jan
☐ Feb
☐ Mar
☐ Apr
☐ May
☐ Jun
☐ Jul
☐ Aug
☐ Sep
☐ Oct
☐ Nov
☐ Dec

Start Year

(Year)

Ongoing

- ☐ Yes
☐ No
☐ Unknown

Stop Date

Clinical Trial Off Treatment Form

Participant ID

Date of last dose of study medication:

Reason why the participant is off treatment:

- ☐ Completed the study drug, 24 month study visit.
- ☐ Due to Side Effects (check all that apply)
- ☐ Patient/parent/guardian withdrawal from study
- ☐ Non-compliance that, in the opinion of the investigator, does not allow for ongoing participation.
- ☐ Physician determination that is not in the patient's best interest to remain on treatment.
- ☐ Patient is prescribed a non-allowed concomitant medicine during study.
- ☐ Death-complete death form
- ☐ Other

Other reason why participant is off treatment

Side effects:

- ☐ drug-related adverse events
- ☐ not drug-related adverse events
- ☐ Serious Adverse Event:
- ☐ Patients who have experienced a vitamin D-associated toxicity requiring a dose modification/interruption after dose reduction.
- ☐ Other

Other side effects:

Death Form

Participant ID

Death Form CRF

NOTE: If death occurred within 3 months of the study drug therapy, complete a MedWatch Form and notify the University of Utah within 24 hour.

Report Date

Date of death

Status in study at time of death:

- ☐ On protocol treatment
- ☐ Within 30 days of the last dose of protocol treatment
- ☐ More than 30 days from the last dose of protocol treatment
- ☐ Before protocol treatment started

Choose one of the following reasons for primary cause of death

- ☐ Neurofibromatosis Type 1 - related issue
- ☐ Concomitant condition
- ☐ Treatment toxicity
- ☐ Other: (Provide stated cause of death.)

Stated cause of death:

Demographics

Participant ID

Date of Birth

Gender

- ☐ Male
☐ Female

Race (Choose one)

- ☐ White (European, Middle Eastern or North American)
☐ Black, African American, Haitian
☐ Native Hawaiian, Other Pacific Islander (Samoan, Guamanian)
☐ Asian (Cambodian, Indian, Chinese, Japanese, Korean, Malaysian, Pakistani, Filipino, Vietnamese and Thai)
☐ American Indian or Alaska Native
☐ Unknown

Ethnicity (choose one)

- ☐ Hispanic/Latino
☐ Non-Hispanic
☐ Unknown

DEXA Form

Participant ID	
Bone densitometry completed?	Yes No
If yes, date performed	
If no, explain	
Total Spine BMD	
Total Spine T-score	
Left Hip BMD density	
Left Hip T-score:	

Drug Replacement Form

Participant ID

Date replacement drug dispensed

Replacement Ddrop bottle ID

ID of bottle being replaced.
If unknown, enter unk

Reason replacement Ddrop dispensed:

Is reason for Ddrop replacement result of an adverse
event

☐ Yes
☐ No

Was Adverse event recorded in project?

☐ Yes
☐ No

Person authorizing Ddrop replacement

Physical Exam Form

Participant ID

Assessment Date:

General Appearance

☐ Normal ☐ Abnormal
☐ Not Done

If Abnormal or Not Done, please comment

Cardiovascular

☐ Normal ☐ Abnormal
☐ Not Done

If Abnormal or Not Done, please comment

Dermatologic

☐ Normal ☐ Abnormal
☐ Not Done

If Abnormal or Not Done, please comment

Head, Eyes, Ears, Nose & Throat

☐ Normal ☐ Abnormal
☐ Not Done

If Abnormal or Not Done, please comment

Respiratory

☐ Normal ☐ Abnormal
☐ Not Done

If Abnormal or Not Done, please comment

Gastrointestinal

☐ Normal ☐ Abnormal
☐ Not Done

If Abnormal or Not Done, please comment

Musculoskeletal

☐ Normal ☐ Abnormal
☐ Not Done

If Abnormal or Not Done, please comment

Scoliosis > 20 degrees

☐ Present ☐ Absent
☐ Not Done

If Abnormal, entering degree of scoliosis

If Not Done, please comment

Neurological / Psychological

☐ Normal

☐ Abnormal

☐ Not Done

If Abnormal or Not Done, please comment

Dermal Neurofibromas

☐ Normal

☐ Abnormal

☐ Not Done

If Abnormal, please select one of the following:

☐ 1-10

☐ 11-1000

☐ > 1001

If Abnormal or Not Done, please comment

Plexiforms Neurofibromas

☐ Normal

☐ Abnormal

☐ Not Done

Plexiforms Neurofibromas Description

If Not Done, please comment

Systolic Blood Pressure

Diastolic Blood Pressure

Pill Diary

Participant ID	
Start Date	
Stop Date:	
Number of calcium doses missed in 6 months	
Number of missed Vitamin D doses in 6 months	(times)

Notes

Rand 36 Item SF Health Survey Instrument (Version 1.0) (Quality of Life Questionnaire)

Participant ID _____

1. In general, would you say your health is:

- ☐ 1 Excellent
☐ 2 Very good
☐ 3 Good
☐ 4 Fair
☐ 5 Poor

2. Compared to one year ago, how would you rate your health in general now?

- ☐ 1 Much better now than one year ago
☐ 2 Somewhat better now than one year ago
☐ 3 About the same
☐ 4 Somewhat worse now than one year ago
☐ 5 Much worse now than one year ago

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (Choose one answer for each question.)

3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports

- ☐ 1 Yes, limited a lot
☐ 2 Yes, limited a little
☐ 3 No, not limited at all

4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

- ☐ 1 Yes, limited a lot
☐ 2 Yes, limited a little
☐ 3 No, not limited at all

5. Lifting or carrying groceries

- ☐ 1 Yes, limited a lot
☐ 2 Yes, limited a little
☐ 3 No, not limited at all

6. Climbing several flights of stairs

- ☐ 1 Yes, limited a lot
☐ 2 Yes, limited a little
☐ 3 No, not limited at all

7. Climbing one flight of stairs

- ☐ 1 Yes, limited a lot
☐ 2 Yes, limited a little
☐ 3 No, not limited at all

8. Bending, kneeling, or stooping

- ☐ 1 Yes, limited a lot
☐ 2 Yes, limited a little
☐ 3 No, not limited at all

9. Walking more than a mile

- ☐ 1 Yes, limited a lot
☐ 2 Yes, limited a little
☐ 3 No, not limited at all

10. Walking several blocks

- ☐ 1 Yes, limited a lot
☐ 2 Yes, limited a little
☐ 3 No, not limited at all

11. Walking one block

☐ 1 Yes, limited a lot
☐ 2 Yes, limited a little
☐ 3 No, not limited at all

12. Bathing or dressing yourself

☐ 1 Yes, limited a lot
☐ 2 Yes, limited a little
☐ 3 No, not limited at all

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Choose one answer for each question.)

13. Cut down the amount of time you spent on work or other activities

☐ 1 Yes
☐ 2 No

14. Accomplished less than you would like

☐ 1 Yes
☐ 2 No

15. Were limited in the kind of work or other activities

☐ 1 Yes
☐ 2 No

16. Had difficulty performing the work or other activities (for example, it took extra effort)

☐ 1 Yes
☐ 2 No

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (Choose one answer for each question.)

17. Cut down the amount of time you spent on work or other activities

☐ 1 Yes
☐ 2 No

18. Accomplished less than you would like

☐ 1 Yes
☐ 2 No

19. Didn't do work or other activities as carefully as usual

☐ 1 Yes
☐ 2 No

20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? (Choose one answer.)

☐ 1 Not at all
☐ 2 Slightly
☐ 3 Moderately
☐ 4 Quite a bit
☐ 5 Extremely

21. How much bodily pain have you had during the past 4 weeks? (Choose one answer.)

☐ 1 None
☐ 2 Very mild
☐ 3 Mild
☐ 4 Moderate
☐ 5 Severe
☐ 6 Very severe

22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Choose one answer.)

☐ 1 Not at all
☐ 2 A little bit
☐ 3 Moderately
☐ 4 Quite a bit
☐ 5 Extremely

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks . . . (Choose one answer for each question.)

- | | |
|---|---|
| 23. Did you feel full of pep? | ☐ 1 All of the time
☐ 2 Most of the time
☐ 3 A good bit of the time
☐ 4 Some of the time
☐ 5 A little of the time
☐ 6 None of the time |
| 24. Have you been a very nervous person? | ☐ 1 All of the time
☐ 2 Most of the time
☐ 3 A good bit of the time
☐ 4 Some of the time
☐ 5 A little of the time
☐ 6 None of the time |
| 25. Have you felt so down in the dumps that nothing could cheer you up? | ☐ 1 All of the time
☐ 2 Most of the time
☐ 3 A good bit of the time
☐ 4 Some of the time
☐ 5 A little of the time
☐ 6 None of the time |
| 26. Have you felt calm and peaceful? | ☐ 1 All of the time
☐ 2 Most of the time
☐ 3 A good bit of the time
☐ 4 Some of the time
☐ 5 A little of the time
☐ 6 None of the time |
| 27. Did you have a lot of energy? | ☐ 1 All of the time
☐ 2 Most of the time
☐ 3 A good bit of the time
☐ 4 Some of the time
☐ 5 A little of the time
☐ 6 None of the time |
| 28. Have you felt downhearted and blue? | ☐ 1 All of the time
☐ 2 Most of the time
☐ 3 A good bit of the time
☐ 4 Some of the time
☐ 5 A little of the time
☐ 6 None of the time |
| 29. Did you feel worn out? | ☐ 1 All of the time
☐ 2 Most of the time
☐ 3 A good bit of the time
☐ 4 Some of the time
☐ 5 A little of the time
☐ 6 None of the time |

30. Have you been a happy person?

☐ 1 All of the time
☐ 2 Most of the time
☐ 3 A good bit of the time
☐ 4 Some of the time
☐ 5 A little of the time
☐ 6 None of the time

31. Did you feel tired?

☐ 1 All of the time
☐ 2 Most of the time
☐ 3 A good bit of the time
☐ 4 Some of the time
☐ 5 A little of the time
☐ 6 None of the time

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

☐ 1 All of the time
☐ 2 Most of the time
☐ 3 Some of the time
☐ 4 A little of the time
☐ 5 None of the time

(Choose one number)

How TRUE or FALSE is each of the following statements for you.

(Choose one number for each question.)

33. I seem to get sick a little easier than other people

☐ 1 Definitely true
☐ 2 Mostly true
☐ 3 Don't know
☐ 4 Mostly false
☐ 5 Definitely false

34. I am as healthy as anybody I know

☐ 1 Definitely true
☐ 2 Mostly true
☐ 3 Don't know
☐ 4 Mostly false
☐ 5 Definitely false

35. I expect my health to get worse

☐ 1 Definitely true
☐ 2 Mostly true
☐ 3 Don't know
☐ 4 Mostly false
☐ 5 Definitely false

36. My health is excellent

☐ 1 Definitely true
☐ 2 Mostly true
☐ 3 Don't know
☐ 4 Mostly false
☐ 5 Definitely false

RAND® is a registered trademark. Copyright © 1994-2010 RAND Corporation. RAND Health is a research division of the RAND Corporation. Used with permission
http://www.rand.org/health/surveys_tools/mos/mos_core_36item.html

Randomization Form

Participant ID

There is an issue with the Trial Inclusion/Exclusion form.

This participant cannot be randomized until the Inclusion/Exclusion form has been completed, confirmed and submitted. All of the Inclusion responses must be 'Yes', all of the exclusion responses must 'No', and Form Status must be "Complete".

There is an issue with the Vitamin D Local Collection form.

This participant cannot be randomized if vitamin D level is less than 9 or greater than 29 ng/dL'

Randomize

☐ 1
☐ 2

SAE

Participant ID

SAE

Event term

Severity - select one:

- ☐ Grade 2 - Moderate
☐ Grade 3 - Severe
☐ Grade 4 - Life threatening
☐ Grade 5 - Death

Date of onset:

Relationship to study drug (select one):

- ☐ Inpatient visit or hospital admission
☐ Prescription medication
☐ ER or out-patient visit
☐ Procedure performed
☐ Other

Other action taken/ corrective therapy

Action taken regarding study drug (select one):

- ☐ Reduced
☐ Interrupted
☐ Discontinued
☐ None

Outcome

- ☐ Resolved
☐ Continuing (at this report date)
☐ Recovered with residual effect
☐ Required or prolonged hospitalization
☐ Resulted in permanent or severe disability
☐ Required intervention to prevent permanent damage or disability
☐ Died-Complete Death Form

Date of resolution

Date recovered with residual effect

Date resulted in permanent or severe disability

Date of death

Is the event an expected side effect of Vitamin D?

- ☐ Yes
☐ No

SAE form was completed and sent to University of Utah
(University of Utah fax # 1-801-585-0269 or E-mail)

☐ Yes
☐ No

Date of signature

Study Drug Compliance Form

Participant ID

Vitamin D

Is subject taking protocol prescribed study drug Ddrop dose?

- ☐ Yes
☐ No

If no, select reason here:

- ☐ Withdrew from Study
☐ Dose Reduction (Complete AE form)
☐ Toxicity (Complete AE form)
☐ Drug Shortage (complete Protocol Deviation form)
☐ Other (Complete Comment form)

Participant returned the "D" drop bottle?

- ☐ Yes
☐ No

Participant returned the completed dosing Ddrop Diary?

- ☐ Yes
☐ No

Calcium supplement

Is subject taking protocol prescribed study drug Calcium dose?

- ☐ Yes
☐ No

If no, select reason here:

- ☐ Withdrew from Study
☐ Dose Reduction (Complete AE form)
☐ Toxicity (Complete AE form)
☐ Drug Shortage (complete Protocol Deviation form)
☐ Other (Complete Comment form)

Signature date

Study Drug Dispensing Form

Participant ID

Vitamin D

Have you retrieved the assigned study drug bottles for this participant?

☐ Yes
☐ No

Randomized Ddrops bottle identification number (bottle 1)

Date dispensed (bottle 1)

Randomized Ddrops bottle identification number (bottle 2)

Date dispensed (bottle 2)

If no, explain

Calcium supplement

Did participant receive calcium supplement of 1000 mg/day?

☐ Yes
☐ No

Date dispensed

If no, explain

Signature date

Trial Inclusion-exclusion

Participant ID

Inclusion Criteria

All inclusion criteria must be checked "YES"

	Yes	No
1. Signed informed consent/assent statements by parent or legal guardian.	☐	☐
2. Is the patient > 24 years 12 months and < 40 years at time of study enrollment?	☐	☐
3. Does the subject meet all diagnostic criteria of individuals with NF1 on physical examination?	☐	☐

Exclusion Criteria

All exclusion criteria must be checked "NO" in order for a participant to be eligible.

	Yes	No
1. Is pregnant, planning to conceive within the next two years, or is less than 6 months post-delivery or lactation?	☐	☐
2. Has had or having thyroid therapy?	☐	☐
3. Has he or she used high dose steroids?	☐	☐
4. Taken vitamin D supplementation in the last 3 months? (add date below)	☐	☐
5. Has he or she has had calcium supplementation in last 6 months equal to or greater than 1000mg elemental = 2500mg calcium carbonate?	☐	☐
6. Has he or she has had bisphosphonate therapy?	☐	☐
7. He or she foresees that they will be unable to comply with the two?year study protocol?	☐	☐

- | | | |
|---|-----------------------|-----------------------|
| 8. He or she has a malignant peripheral nerve sheath tumor? | ☐ | ☐ |
| 9. Has he or she has a history of kidney stones and/or hypercalciuria? | ☐ | ☐ |
| 10. Has he or she has metal instrumentation in spine or hip that precludes accurate DXA interpretation? | ☐ | ☐ |
| 11. Has he or she had anti-epileptic therapy? | ☐ | ☐ |
| 12. He or she has had anticoagulant therapy? | ☐ | ☐ |
| 13. He or she is unable to comply for blood samples on routine venipuncture | ☐ | ☐ |
| 14. He or she has a diagnosis of Paget's disease, hyperthyroidism, hyperparathyroidism, or other medical conditions that affect bone health | ☐ | ☐ |

a. Date of last dose of vitamin D supplementation:

Principal Investigator Signature Date

Trial Protocol Deviations Log

Participant ID

Protocol Deviation 1

Protocol deviation

Visit

Category

- ☐ Eligibility enrollment
- ☐ Protocol procedure / assessment
- ☐ Dosing schedule / Administration
- ☐ Missed Visit
- ☐ Out of window follow-up visit schedule
- ☐ Other (specify below)

Please list other category

Reason

- ☐ Subject illness
- ☐ Subject unable to comply
- ☐ Laboratory error
- ☐ Investigator / study decision
- ☐ Other

Please list other reason

Impact subject safety

- ☐ Yes
- ☐ No

Affect scientific integrity of study

- ☐ Yes
- ☐ No

Protocol Deviation 2

Protocol deviation

Visit

Category

- ☐ Eligibility enrollment
- ☐ Protocol procedure / assessment
- ☐ Dosing schedule / Administration
- ☐ Missed Visit
- ☐ Out of window follow-up visit schedule
- ☐ Other (specify below)

Please list other category

Reason	☐ Subject illness ☐ Subject unable to comply ☐ Laboratory error ☐ Investigator / study decision ☐ Other
--------	---

Please list other reason

Impact subject safety	☐ Yes ☐ No
-----------------------	---

Affect scientific integrity of study	☐ Yes ☐ No
--------------------------------------	---

Protocol Deviation 3

Protocol deviation

Visit

Category	☐ Eligibility enrollment ☐ Protocol procedure / assessment ☐ Dosing schedule / Administration ☐ Missed Visit ☐ Out of window follow-up visit schedule ☐ Other (specify below)
----------	--

Please list other category

Reason	☐ Subject illness ☐ Subject unable to comply ☐ Laboratory error ☐ Investigator / study decision ☐ Other
--------	---

Please list other reason

Impact subject safety	☐ Yes ☐ No
-----------------------	---

Affect scientific integrity of study	☐ Yes ☐ No
--------------------------------------	---

Protocol Deviation 4

Protocol deviation

Visit

Category

- ☐ Eligibility enrollment
- ☐ Protocol procedure / assessment
- ☐ Dosing schedule / Administration
- ☐ Missed Visit
- ☐ Out of window follow-up visit schedule
- ☐ Other (specify below)

Please list other category

Reason

- ☐ Subject illness
- ☐ Subject unable to comply
- ☐ Laboratory error
- ☐ Investigator / study decision
- ☐ Other

Please list other reason

Impact subject safety

- ☐ Yes
- ☐ No

Affect scientific integrity of study

- ☐ Yes
- ☐ No

Protocol Deviation 5

Protocol deviation

Visit

Category

- ☐ Eligibility enrollment
- ☐ Protocol procedure / assessment
- ☐ Dosing schedule / Administration
- ☐ Missed Visit
- ☐ Out of window follow-up visit schedule
- ☐ Other (specify below)

Please list other category

Reason

- ☐ Subject illness
- ☐ Subject unable to comply
- ☐ Laboratory error
- ☐ Investigator / study decision
- ☐ Other

Please list other reason

Impact subject safety

- ☐ Yes
☐ No

Affect scientific integrity of study

- ☐ Yes
☐ No

Protocol Deviation 6

Protocol deviation

Visit

Category

- ☐ Eligibility enrollment
☐ Protocol procedure / assessment
☐ Dosing schedule / Administration
☐ Missed Visit
☐ Out of window follow-up visit schedule
☐ Other (specify below)

Please list other category

Reason

- ☐ Subject illness
☐ Subject unable to comply
☐ Laboratory error
☐ Investigator / study decision
☐ Other

Please list other reason

Impact subject safety

- ☐ Yes
☐ No

Affect scientific integrity of study

- ☐ Yes
☐ No

Protocol Deviation 7

Protocol deviation

Visit

Category

- ☐ Eligibility enrollment
☐ Protocol procedure / assessment
☐ Dosing schedule / Administration
☐ Missed Visit
☐ Out of window follow-up visit schedule
☐ Other (specify below)

Please list other category	
Reason	☐ Subject illness ☐ Subject unable to comply ☐ Laboratory error ☐ Investigator / study decision ☐ Other
Please list other reason	
Impact subject safety	☐ Yes ☐ No
Affect scientific integrity of study	☐ Yes ☐ No

Vitamin D Local Collection

Participant ID	
Vitamin D (LOCAL RESULT)* screening only - Lab Value	(ng/dL (eligible if 9-29 ng/dL))
Vitamin D Screening Normal?	☐ Normal ☐ Abnormal* ☐ ND*
If Abnormal	☐ NCS* ☐ AE*