AD_____

Award Number: W18XWH-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 84112

REPORT DATE: October 2013

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2013	Annual	15 September 2012-14 September 2013

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
W18XWH-12-1-0487

5b. GRANT NUMBER
W18XWH-12-1-0487

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
David Viskochil, MD, PhD

E-Mail: dave.viskochil@hsc.utah.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Utah
Salt Lake City, UT 84132

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel 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 study has received an IND from the FDA to use high-dose vitamin D in the NF1 (neurofibromatosis type 1) population. Once the IND was provided by the FDA, the study was approved by the University of Utah IRB. This was reviewed by the DoD USAMRMC ORP HRPO and an amendment was submitted to the University of Utah IRB delineating duties of the Safety Monitor. The amendment was approved, which led to approval by the HRPO. The University of Hamburg has begun the process with the European Union Clinical Trials group (EurodratCT), and the group identified a need for a designated legal representative from the sponsoring agency. The DoD has reviewed this request and decided that the University of Utah is the sponsoring agency. After full review from the U of Utah office of sponsored projects (OSP), a document of agreement has been drawn up between the University of Utah as the Sponsor and the University Medical Center Hamburg-Eppendorf as the delegated institution. The final draft is under review by both organizations, and once signed, the University of Hamburg can move forward with subcontract review and signature. No funds have been allocated from Utah to the 3 participating centers.

15. SUBJECT TERMS
none provided

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
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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: 9/30/2012 -09/29/2016; 48 months)

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, CIN, HAM

Subcontracts have been compiled by the University of Utah Office of Sponsored Projects including agreement on the allocation of funding between the financial administrators from each institution. The University of Cincinnati cannot sign the agreement until the IRB is approved at the University of Cincinnati, and it will be submitted for review once the DoD Human Subjects Protection Oversight committee has completed its review and negotiated changes with the IRB from the University of Utah. Like the University of Cincinnati, the subcontract with the University of British Columbia will not be enacted until the investigators can begin the Ethics Committee approval process. The University of Hamburg has begun the process with the European Union Clinical Trials group (EurodratCT), and the group identified a need for a designated legal representative from the sponsoring agency. The DoD has reviewed this request and decided that the University of Utah is the sponsoring agency. After full review from the U of Utah office of sponsored projects (OSP), a document of agreement has been drawn up between the University of Utah as the Sponsor and the University Medical Center Hamburg-Eppendorf as the delegated institution. The final draft is under review by both organizations, and once signed, the University of Hamburg can move forward with subcontract review and signature. No funds have been allocated from Utah to the 3 participating centers.

Task I.2 (mo 2): conduct an organizational face-to-face meeting between 4 PIs and data monitor

This meeting is contingent on changes to protocol after IRB approval from all institutions, and it will be scheduled after the approval from DoD USAMRMC ORP HRPO.

Task I.3 (mo 2-3): assemble manual of operations and distribute to each site

The manual of operations will be finalized once the protocol has been approved by the DoD HSPO. A copy of the present protocol is attached.

Task I.4 (mo 1-2): establish lines of communication between PIs, coordinators, financial managers at each site

As part of the subcontracts appropriate financial managers have been identified at each of the 4 institutions. Email has been the primary line of communication. Conference calls have not been established.

Task I.5 (mo 2): establish long-term contract with courier for shipment of samples, supplies, study drug

A proposal with Markem courier is under review; however, negotiations on final pricing has not been completed, pending IRB approval. The cost quote for 69 batched shipments is $45,101.50 as of January, 2013.

Task I.6 (mo 7-48): maintain regular monthly reports regarding enrollment, data collection, and safety issues

Enrollment has not begun.

II. Major Goal - Enroll human subjects into a phase II clinical trial with vitamin D_3 supplementation

Task II.1 (mo 0-5): establish IRB approvals at 4 sites and USAMRMC ORP HRPO review

Pre-review of the protocol at the University of Utah led to the recommendation that it would review only after the protocol had been vetted through the FDA for determination of need for an IND. A proposal for exempt status was submitted in July, 2013 and denied, although an IND number (119135) was provided in August with stipulations that a number of issues be addressed. Final approval from the FDA was obtained in September, 2013, and the trial was listed by ClinicalTrials.gov (NCT01968590) in October, 2013. The IRB at the University of Utah approved the clinical trial application at the end of November, 2013. This was reformatted as an application for administrative review by the USAMRMC ORP HRPO, which has undergone

initial review. The protocol required better description of the safety monitor's role in the project, and this was put into an amendment and approved by the University of Utah IRB in February, 2014 and submitted to the HRPO for final application submission for formal review.

Task II.2 (mo 1): confirm oversight by an external safety monitor

The safety monitor is Dr. Richard Kanner from the Center for Clinical and Translational Sciences (CCTS) at the University of Utah, and he will serve as chair of a 3-member committee to oversee safety issues related to the study. They 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 as submitted to the Pediatric Clinical Trials Office (director, Dr. Michael Spigarelli), review adverse events, and monitor serum collection and disposition of samples. The amendment clarified his authority and responsibilities.

Task II.3 (mo 4-23): recruit adults with NF1 to consider participation in clinical trial

Coordinators at each site have alerted their respective adult NF1 population of the upcoming trial.

Task II.4 (mo 3): establish failsafe mechanism to determine pregnancy status prior to densitometry

Coordinators will oversee urine pregnancy testing and review history with females.

Task II.5 (mo 6-15): first enrollment period for 25(OH)D serum screening/vitamin D_3 supplementation

Cannot proceed without IRB approval at all sites.

Task II.6 (mo 18-23): second enrollment period for 25(OH)D serum screening/vitamin D_3 supplementation

N/A.

Task II.7 (mo 6-15; mo 18-23): verify enrollment with unique identifier by hard copy and electronic means

N/A.

Task II.8 (mo 5-48): maintain ongoing IRB approval

After initial approval.

Task II.9 (mo 12, 24, 36, 48): annual review by safety monitor and distributed to each IRB and USAMRMC

Per IRB application, review will take place every 6 months.

Task II.10 (mo 18-27; mo 30-35): data monitor safety assessment for loss of bone mineral density of >7% loss

N/A.

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

Task III.1 (mo 3-5): establish scheduling processes for each enrollment center

Waiting for subcontracts to be finalized so work can begin at CIN, UBC, and HAM. Scheduling processes have been included in our application for CCTS services. The application for CCTS support was reviewed by committee and approved in December, 2013.

Task III.2 (mo 3-5): complete assessment of cross-calibration of DXA machines at 4 sites

Pending subcontract completion.

Task III.3 (mo 2-5): assemble all data collection forms, blood collection kits, and CDs at each enrollment center

Data collection forms have been designed and approved by IRB at the University of Utah. Blood collection kits and CDs will be purchased and distributed once the protocol is approved by the HRPO

Task III.4 (mo 3-5): establish and verify access to the study-specific, web-based, password-protected database

Pending subcontract completion.

Task III.5 (mo 4): develop mechanism to obtain blood samples for 25(OH) vitamin D screening (ARUP Lab)
Pending final approval of contract with the shipping agency.

Task III.6 (mo 6-15; mo 18-23): obtain serum 25(OH)D on 316 enrollees across 4 enrollment centers
N/A

Task III.7 (mo 5-7): document processes for timely notification of serum 25(OH)D results and randomization
N/A

Task III.8 (mo 6-15; mo 18-23): Randomize 226 participants to either 600 IU or 4,000 IU of daily vitamin D_3
N/A

Task III.9 (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 3 time-points
N/A

IV. Major Goal - Monitor data acquired throughout the study period

Task IV.1 (mo 3-5): establish confidential procedures for monthly data acquisition monitoring and reporting
N/A

Task IV.2 (mo 3-5): establish access for the data monitoring team to the study-specific database
N/A

Task IV.3 (mo 6-48): verify quality of data acquisition with coordinators at each enrollment center
N/A

Task IV.4 (mo 18-21): perform interim analysis on a subset of enrollees at 1 year for change in BMD of hip
N/A

V. Major Goal - Provision of vitamin D_3 and calcium supplementation

Task V.1 (mo 3-5): verify formulation of vitamin D_3 in the form of Ddrops
Documentation has been provided by Ddrops on the formulation; however, they have not synthesized a batch of Ddrops for study as of yet.

Task V.2 (mo 5): distribute Ddrops from dispensing site in Ontario Canada to the University of Utah
N/A

Task V.3 (mo 2-4): establish failsafe methodology to mask the bottle of Ddrops and provide unique identifier
Pending final approval of the protocol by the HRPO

Task V.4 (mo 6-15; 18-23): randomize participants with a unique bottle number/communicate to site coordinator
N/A

Task V.5 (mo 6-47): implement methods to educate/monitor participants on aspects of vit D_3 and calcium intake
N/A

Task V.6 (mo 12-41): ensure resupply of Ddrops bottle corresponds to the initial bottle designation
N/A

Task V.7 (mo 6-48): monitor potential side effects of vit D_3 supplementation
N/A

VI. Major Goal - Establish a bio-repository of serum samples

Task VI.1 (mo 2-5): develop protocol to process samples at the CGRP freezer storage facility at the U of Utah
This protocol has been approved by the FDA and the U of Utah IRB.

Task VI.2 (mo 6-47): ensure participant identifier corresponds to consent to store samples for future studies
N/A

Task VI.3 (mo 6-47): document acceptance of storage sample in the CGRP database and vit D_3 study database
The process for storage of sample in the CGRP database has been established, but the vitD3 study database has not been established.

VII. Major Goal - Data analyses

Task VII.1 (mo 6-48): collect data on all enrollees both by hard copy forms and in the study-specific database
N/A
Task VII.2 (mo 6-48): validate data collection on a monthly basis by data monitor
N/A
Task VII.3 (mo 7-48): verify accuracy of data collection by enrollment center coordinators
N/A
Task VII.4 (mo 47-48): perform comparison of low-dose vit D_3 versus high-dose vit D_3 on data collections
N/A

Subcontracts between University 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

Organization name: University Medical Center Hamburg-Eppendorf (HAM)
Organization address: Hans-Albert Schnelle
Department of Finance
University Medical Center Hamburg-Eppendorf
Martinistrasse 52
20246 Hamburg, Germany
Investigators: Victor F. Mautner, MD
Collaborators: Said Farschtshi, MD

Attachments: Quarterly reports to the DoD

Quarterly Technical Progress Report Format
Front Cover

Award Number:	W18XWH-12-1-0487
Log Number:	Log No. A-17236
Project Title:	A PHASE II TRIAL ON THE EFFECT OF LOW-DOSE VERSUS HIGH-DOSE VITAMIN D SUPPLEMENTATION ON BONE MASS IN ADULTS WITH NF1
Principal Investigator Name:	David Viskochil MD, PhD.
Principal Investigator Organization and Address:	David Viskochil MD, PhD. University of Utah 50 N. Mario Capecchi Drive Room 2C412 SOM Salt Lake City- Utah 84132 801-581-8943
Principal Investigator Phone and Email:	801-581-8943 dave.viskochil@hsc.utah.edu
Report Date:	June 25, 2013; edited and submitted July 8, 2013
Report Period:	2nd and 3rd quarters (16 December 2012 to 15 June 2013)
Grants Officer's Representative :	Brent Brown 801-581-3003

1. Project Status

a. Accomplishments

This may include completion of milestones, objectives, and/or tasks, regulatory approval received, publication of papers, presentations at conferences, filing of intellectual property, etc. for this quarter, followed by date in DD-MMM-YYYY. Write salient bullet points to highlight the requested information.

1. Development of IRB application and response to pre-review
2. Hamburg site identified needs for
3. At the request of the U of Utah IRB, we prepared an IND waiver request to the FDA for the use of Vitamin D in the adult NF1 population.
4. Correspondence with the other 3 centers regarding study progress and IRB delays.

b. Reportable Outcomes

This may include development of a product, prototype, new methodology, or any other similar items that have resulted from this research.. Write salient bullet points to highlight the requested information.

N/A

c. Progress Detail

Describe each Statement of Work (SOW) task or logical segment of work on which effort was expended during this quarterly reporting period only. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved or problems encountered. A succinct description of the methodology used shall be provided.

For an award that includes the recruitment of human subjects for clinical research or a clinical trial, (i) report progress on subject recruitment, screening, enrollment, completion, and numbers of each compared to original planned target(s), e.g., number of subjects enrolled versus total number proposed; d (ii) report amendments submitted to the IRB and USAMRMC HRPO for review, and (iii) any adverse events.

N/A

2. Future Plans

Present a brief statement of plans or milestones planned for the next quarter. If any of the plans deviate from the original approved SOW (e.g., new or modified tasks, objectives, experiments, etc), they will require review by the Grants Officer's Representative and final approval by USAMRAA Grants Officer through an award modification prior to initiating any changes.

1-We anticipate an IND waiver from the FDA for vitamin D. Once waiver is obtained the IRB application at the U of Utah will be completed and submitted for review. When it is approved we will send to the USAMRMC HRPO for secondary review.

2-We will continue to work with the University of Hamburg to obtain approval of the trial through the European union administrative process.

They are in need of a contact from the sponsoring institution to work with a community legal representative as set out in the paragraph below:

Clinical trials in the European Community (EC) are under European legislation as laid down in EudraLex Volume 10 (http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm). The rules set out there had been transferred to the national legislation in each member state, so there might be differences but substantially they are the same throughout Europe. The sponsor and the investigator are responsible for the proper conduct of a study, each representing different duties. To ensure enforceability of the sponsor's duties and liability, the sponsor must be established in the EC. Foreign sponsors must have a legal representative (LR) which is resident in the EC. The tasks of the LR are directly connected to the liability of the sponsor. The LR does not need to be a Qualified Person or an expert in clinical trials. Often specialized CROs take over this job. A proper contract must be in place, regulating all the duties and agreements between the sponsor and its LR.

The piece of legislation that regulates this matter is:

European Directive 2001/20/EC
Article 19
General provisions
This Directive is without prejudice to the civil and criminal liability of the sponsor or the investigator. To this end, the sponsor or a legal representative of the sponsor must be established in the Community.

Dr. Mautner has identified the individual in Germany to work with the US sponsor. His name is Mr. Christian Hilgenstock. We began the process of identifying a legal representative from the DoD in February, and finally arrived at the most appropriate person:

Wendy Baker
Contracting Officer
USAMRAA
301.619.2034

She was checking on her potential role on this request from Germany to serve as the liason between the sponsoring institution USAMRAA and Mr. Hilgenstock as the European legal representative of the USAMRAA. This needs to be resolved in the next quarter.

3. Problems/Issues:

Any change that is substantially different from the original approved SOW (e.g., new or modified tasks, objectives, experiments, etc.) will require review by the Grants Officer's Representative and final approval by USAMRAA Grants Officer through an award modification prior to initiating any changes.

a. Current Problems/Issues-

Provide a description of current problems or issues that may impede performance or progress of this project along with proposed corrective action. This may include administrative, technical, and/or logistical issues.

For an award that includes the recruitment of human subjects for clinical research or a clinical trial, discuss any problems or barriers encountered, if applicable, and what has been done to mitigate those issues. Discussion may highlight enrollment problems, retention problems, and actions taken to increase enrollment and/or improve retention

Waiting on the IND waiver review by the FDA then IRB approval, which is needed before we can execute the subcontracts with the 3 other sites. The subcontracts have been drawn up but not executed.

b. Anticipated Problems/Issues

Provide a description of anticipated problems or issues that have a potential to impede performance or progress. Also provide course of actions planned to mitigate problems or to take should the problem materialize.

If we do not get waiver of IND for vitamin D use in the adult NF1 population then we will need to compose an application for FDA approval to be included in the U of Utah IRB submission.

Need European Union approval from the clinical trials group at the University of Hamburg in Germany as outlined in section 2.

4. Financial Health

Comment on the financial health of the study. Was the study financially on track <u>during this quarterly reporting period</u> and <u>cumulatively</u> for completion as proposed within the period of performance? If not, describe the cause(s), whether this will have a short-term or long-term impact, the likelihood this can

be overcome, and provide remediation strategy. Provide amount expended this quarter and cumulatively. State if there was any major equipment procured, sub award implemented, and/or travel conducted.

We detailed the costs of mailing supplies to each site and mailing samples once collected through MARKEN, LLP (Global Life Science Supply Chain Solutions), Uniondale, NY

5. Personnel Effort

Provide names of current staff along with their roles and percent effort of each on this project. Add additional rows if necessary to list the complete l team. If there is more than one project on this award, break down according to each project (one table per project).

Personnel	Role	Percent Effort
David Viskochil	PI	5
Heather Hanson	Study Coord	15
David Stevenson	Co-PI	1
Michael Spigarelli	DSM	1
Austin Stevens	Data Mgr	0
Bernard LaSalle	Collab.	0

6. Protocol and Activity Status

For awards involving the use of human subjects, use of human cadavers, and/or use of animal subjects, prepare a summary in accordance with the following subsections. For all other awards, including those involving the use of human anatomical substances (such as tissue or cells or identifiable private information), mark as directed below.

a. Human Use Regulatory Protocols

TOTAL PROTOCOLS:

State the total number of human use protocols required to complete this project (e.g., 5 human subject research protocols will be required to complete the Statement of Work."). If not applicable, write "No human subjects' research will be performed to complete the Statement of Work."

One human use protocol will be needed to complete this clinical trial; however, IRB approval will need to be obtained from the University of Utah followed by the Department of Defense HRPO. Once approved at the University of Utah and the DOD we will need to proceed with each of the other sites: University of British Columbia, University of Cincinnati, and the University of Hamburg in Germany.

List all human use protocols to be performed to complete the project, and include approved target number for clinical significance, followed by type of submission and type of approval with associated dates, and performance status for each.

Protocol [HRPO Assigned Number]: *A-17236*

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)

Target required for clinical significance: 316 Screened
Target approved for clinical significance: 226 enrolled

IRB application is ready for submission to the University of Utah IRB after IND waiver for vitamin D use in the adult NF1 population is obtained from the FDA.

Status:

Provide bullet point list of performance and/or progress status relating to the above protocol and discuss recruitment number, enrollment number, drop outs, disqualified, etc. Discuss any administrative, technical, or logistical issues that may impact performance or progress of the study (e.g. slow enrollment, large dropouts, or adverse events) for the above HPRO approved protocol.

Not applicable until IRB submission.

Quarterly Technical Progress Report Format
Front Cover

Award Number:	W18XWH-12-1-0487
Log Number:	Log No. A-17236
Project Title:	A PHASE II TRIAL ON THE EFFECT OF LOW-DOSE VERSUS HIGH-DOSE VITAMIN D SUPPLEMENTATION ON BONE MASS IN ADULTS WITH NF1
Principal Investigator Name:	David Viskochil MD, PhD.
Principal Investigator Organization and Address:	David Viskochil MD, PhD. University of Utah 50 N. Mario Capecchi Drive Room 2C412 SOM Salt Lake City- Utah 84132 801-581-8943
Principal Investigator Phone and Email:	801-581-8943 dave.viskochil@hsc.utah.edu
Report Date:	September 20th, 2013; edited and submitted Sept. 26, 2013
Report Period:	4th quarter (2013 to 2013)
Grants Officer's Representative :	Brent Brown 801-581-3003

1. Project Status

a. Accomplishments

This may include completion of milestones, objectives, and/or tasks, regulatory approval received, publication of papers, presentations at conferences, filing of intellectual property, etc. for this quarter, followed by date in DD-MMM-YYYY. Write salient bullet points to highlight the requested information.

1. An IND waiver for use of cholecalciferol (vitamin D3) at the upper dose of 4,000IU, which is approved in Canada and the Institute of Medicine, was submitted to the FDA Division of Bone, Reproductive, and Urologic Products. 11-JUL-2013.
2. The waiver was denied because cholecalciferol is not marketed in the US at that dose, but an IND was provided - #119135. 12-AUG-2013
3. The FDA reviewed and advised minor changes for the protocol and consent form, which were incorporated in the U of Utah IRB application. 24-SEP-2013
4. IRB was resubmitted to the U of Utah. 25-SEP-2013
5. Clarified that the DoD does not provide a representative as a liason from the sponsoring agency to work with the European Union clinical trials representative, but it needs to come from the subcontracting entity, U of Utah. 18-JUL-2013

a. Reportable Outcomes

This may include development of a product, prototype, new methodology, or any other similar items that have resulted from this research.. Write salient bullet points to highlight the requested information.

N/A

b. Progress Detail

Describe each Statement of Work (SOW) task or logical segment of work on which effort was expended during this quarterly reporting period only. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved or problems encountered. A succinct description of the methodology used shall be provided.

For an award that includes the recruitment of human subjects for clinical research or a clinical trial, (i) report progress on subject recruitment, screening, enrollment, completion, and numbers of each compared to original planned target(s), e.g., number of subjects enrolled versus total number proposed; d (ii) report amendments submitted to the IRB and USAMRMC HRPO for review, and (iii) any adverse events.

N/A

6. Future Plans

Present a brief statement of plans or milestones planned for the next quarter. If any of the plans deviate from the original approved SOW (e.g., new or modified tasks, objectives, experiments, etc), they will require review by the Grants Officer's Representative and final approval by USAMRAA Grants Officer through an award modification prior to initiating any changes.

1- IRB application at the U of Utah has been re-submitted for review. When it is approved we will send to the USAMRMC HRPO for secondary review.

2-We will identify an official at the U of Utah willing to liason with the clinical trials group at the University of Hamburg to obtain approval of the trial through the European union administrative process as outlined in the text below:

Clinical trials in the European Community (EC) are under European legislation as laid down in EudraLex Volume 10 (http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm). The rules set out there had been transferred to the national legislation in each member state, so there might be differences but substantially they are the same throughout Europe. The sponsor and the investigator are responsible for the proper conduct of a study, each representing different duties. To ensure enforceability of the sponsor's duties and liability, the sponsor must be established in the EC. Foreign sponsors must have a legal representative (LR) which is resident in the EC. The tasks of the LR are directly connected to the liability of the sponsor. The LR does not need to be a Qualified Person or an expert in clinical trials. Often specialized CROs take over this job. A proper contract must be in place, regulating all the duties and agreements between the sponsor and its LR.

The piece of legislation that regulates this matter is:

European Directive 2001/20/EC
Article 19
General provisions
This Directive is without prejudice to the civil and criminal liability of

the sponsor or the investigator. To this end, the sponsor or a legal representative of the sponsor must be established in the Community.

Dr. Mautner has identified the individual in Germany to work with the US sponsor. His name is Mr. Christian Hilgenstock. We are working on the identification of a legal representative from the U of Utah.This needs to be resolved in the next quarter now that the IND issue has been resolved and we are moving forward on IRB approval at the U of Utah.

7. Problems/Issues:

Any change that is substantially different from the original approved SOW (e.g., new or modified tasks, objectives, experiments, etc.) will require review by the Grants Officer's Representative and final approval by USAMRAA Grants Officer through an award modification prior to initiating any changes.

a. **Current Problems/Issues-**

Provide a description of current problems or issues that may impede performance or progress of this project along with proposed corrective action. This may include administrative, technical, and/or logistical issues.

For an award that includes the recruitment of human subjects for clinical research or a clinical trial, discuss any problems or barriers encountered, if applicable, and what has been done to mitigate those issues. Discussion may highlight enrollment problems, retention problems, and actions taken to increase enrollment and/or improve retention

Waiting on the IRB approval, which is needed before we can execute the subcontracts with the 3 other sites. The subcontracts have been drawn up but not executed.

b. Anticipated Problems/Issues

Provide a description of anticipated problems or issues that have a potential to impede performance or progress. Also provide course of actions planned to mitigate problems or to take should the problem materialize.

Need European Union approval from the clinical trials group at the University of Hamburg in Germany as outlined in section 2.

8. Financial Health

Comment on the financial health of the study. Was the study financially on track during this quarterly reporting period and cumulatively for completion as proposed within the period of performance? If not, describe the cause(s), whether this will have a short-term or long-term impact, the likelihood this can be overcome, and provide remediation strategy. Provide amount expended this quarter and cumulatively. State if there was any major equipment procured, sub award implemented, and/or travel conducted.

No subcontracts have been executed, and the only expenses paid have been U of Utah personnel.

9. Personnel Effort

Provide names of current staff along with their roles and percent effort of each on this project. Add additional rows if necessary to list the complete l team. If there is more than one project on this award, break down according to each project (one table per project).

Personnel	Role	Percent Effort
David Viskochil	PI	5
Heather Hanson	Study Coord	15
David Stevenson	Co-PI	1
Michael Spigarelli	DSM	1
Austin Stevens	Data Mgr	0
Bernard LaSalle	Collab.	0

10. Protocol and Activity Status

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TOTAL PROTOCOLS:

State the total number of human use protocols required to complete this project (e.g., 5 human subject research protocols will be required to complete the Statement of Work."). If not applicable, write "No human subjects' research will be performed to complete the Statement of Work."

One human use protocol will be needed to complete this clinical trial; however, IRB approval will need to be obtained from the University of Utah followed by the Department of Defense HRPO. Once approved at the University of Utah and the DOD we will proceed with each of the other sites: University of British Columbia, University of Cincinnati, and the University of Hamburg in Germany.

List all human use protocols to be performed to complete the project, and include approved target number for clinical significance, followed by type of submission and type of approval with associated dates, and performance status for each.

Protocol [HRPO Assigned Number]: *A-17236*

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)

Target required for clinical significance: 316 Screened
Target approved for clinical significance: 226 enrolled

IRB application is ready for submission to the University of Utah IRB after IND waiver for vitamin D use in the adult NF1 population is obtained from the FDA.

Status:

Provide bullet point list of performance and/or progress status relating to the above protocol and discuss recruitment number, enrollment number, drop outs, disqualified, etc. Discuss any administrative, technical, or logistical issues that may impact performance or progress of the study (e.g. slow enrollment, large dropouts, or adverse events) for the above HPRO approved protocol.

Not applicable until IRB submission.

US Army Medical Research and Material Command
Office of Research Protections

Human Research Protocol Submission Form for Headquarters Level Administrative Review of Extramural* Research

PURPOSE: All United States Army Medical Research and Materiel Command (USAMRMC) supported research involving humans, human data, human specimens, or cadavers must be reviewed for compliance with Federal and Department of Defense (DoD) human subjects protection requirements and approved by the Office of Research Protections (ORP). The ORP has two human subjects protection review and compliance oversight offices, the Human Research Protections Office (HRPO) and the Clinical Investigations Regulatory Office (CIRO).

INSTRUCTIONS: Enter protocol information in the spaces provided to complete all appropriate sections of the form. Submit this completed form and the protocol documents to the electronic mailbox at usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil. An incomplete submission will result in delay in review. This form is divided into three sections: Section A requests protocol information; Section B is a checklist of documents to be submitted to the ORP, and Section C lists the reporting requirements and responsibilities of the Principal Investigator to the ORP HRPO.

NOTE: Complete a Protocol Submission Form for each human subjects research protocol performed under the DoD/USAMRMC proposal. For example, if your research proposal includes three separate research protocols, submit one completed Protocol Submission Form for each protocol.

For multi-site studies, please complete this form for the Master Protocol only at this time. Identify all participating sites in the protocol. Additional site-specific documents will be requested at a later date.

For questions regarding ORP HRPO human research protocol review requirements or assistance in completing this form, leave a message at 301-619-2165 or usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil and a staff member will contact you.

NOTE: You are reminded not to initiate the study until you receive approval from the ORP HRPO.

* *The ORP defines intramural research as research conducted by USAMRMC laboratories. All other USAMRMC managed research is considered extramural*

Protocol Submission Form

Section A: Protocol Information. The purpose of this section is to obtain administrative details for each protocol submitted to ORP. The information is required for the ORP to review and approve each research protocol and performance and collaborative site(s) associated with the study.

1. Protocol Title: A PHASE II TRIAL ON THE EFFECT OF LOW-DOSE VERSUS HIGH-DOSE VITAMIN D SUPPLEMENTATION ON BONE MASS IN ADULTS WITH NF1

2. Associated DoD/USAMRMC Proposal:

Proposal Log # Award # W18XWH-12-1-0487 (e.g. W81XWH-01-2-0004)

3. HRPO Log Number (If known): A- 17236

4. Funded Activities. Which activities in the protocol are funded by the DoD/USAMRMC?

a. X☐ All Protocol Activities
OR
b. ☐ Select activities (Describe in detail):

5. Key Study Personnel. (If more space is needed, attach additional page(s) to the end of this form)

a. List all key study personnel below, including the Principal Investigator (PI) and other study team members, along with a brief statement of their study role(s) and responsibilities. Note: Key study personnel are persons who have direct contact with subjects or their identifiable data or specimens.

Key Study Personnel (Include Degrees and Credentials)	Study Roles and Responsibilities	Primary Point of Contact (Select one)
Name: David Viskochil MD, PhD Affiliated Institution: University of Utah	Study Role(s): Principal Investigator Responsibilities: See attached Study Staff Duties.pdf for all study personnel listed	X
Name: David Stevenson MD Affiliated Institution: University of Utah	Study Role(s): Sub-Investigator Responsibilities:	☐
Name: Heather Hanson CCRC Affiliated Institution: University of Utah	Study Role(s): Coordinator Responsibilities:	☐
Name: J.M Friedman MD Affiliated Institution: University of British Columbia	Study Role(s): External Site-Principal Investigator Responsibilities:	☐
Name: Patricia Birch RN Affiliated Institution: University of British Columbia	Study Role(s): External Site-Coordinator Responsibilities:	☐

Name: David Kendler MD, FRCP Affiliated Institution: University of British Columbia	Study Role(s): External Site-Sub-Investigator Responsibilities:	☐
Name: Victor Mautner MD Affiliated Institution: University of Hamburg	Study Role(s): External Site-Principal Investigator Responsibilities:	☐
Name: Claudia Wargel RN Affiliated Institution: University of Hamburg	Study Role(s): External Site-Coordinator Responsibilities:	☐
Name: Said Farschtschi MD Affiliated Institution: University of Hamburg	Study Role(s): External Site-Sub-Investigator Responsibilities:	☐
Name: Elizabeth Schorry MD Affiliated Institution: University of Cincinnati	Study Role(s): External Site-Principal Investigator Responsibilities:	☐
Name: Sara Manning CCRC Affiliated Institution: University of Cincinnati	Study Role(s): External Site-Coordinator Responsibilities:	☐
Name: Heidi Kalkwarf PhD, RD Affiliated Institution: University of Cincinnati	Study Role(s): External Site-Sub-Investigator Responsibilities:	☐

b. List all other personnel involved in the research. (e.g., statistician, consultants, collaborators)

Other Involved Personnel	Study Roles and Responsibilities
Name: Michael Spigarelli MD Affiliated Institution: University of Utah	Study Role(s): Data Safety Monitor Responsibilities:
Name: Bernie LaSalle BS Affiliated Institution: University of Utah	Study Role(s): CCTS Collaborator Responsibilities:
Name: Richard Kanner MD Affiliated Institution: University of Utah	Study Role(s): CCTS External Medical Monitor Responsibilities:
Name: TBA Affiliated Institution: University of Utah	Study Role(s): Data management Responsibilities:

c. Conflict of Interest. Do any study personnel have a conflict of interest to declare?

X No

☐ Yes. If yes, please explain here.

6. Involved Institutions and Institutional Review Board (IRB) Reviews.

List all institution(s) involved in this protocol and the study activities occurring at each institution (Columns A and B). If employees of the institution are interacting with subjects or have access to identifiable data, complete the rest of the columns (C-J) for each institution. Identify all reviewing IRBs and the IRB actions taken regarding this protocol. If more rows are needed, attach additional page(s) to the end of the submission form. If you need assistance, please contact your local IRB office or the ORP at 301-619-2165 or usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil.

A	B	C	D	E	F	G	H	I	J
Institution *(If multi-site, include each site and site PI)*	Study Activities *(e.g. recruitment, enrollment, data/specimen collection, analysis, data storage)*	DHHS Federal Wide Assurance # (Click here to search)	Name of Reviewing IRB	IRB Approval* *(Indicate: Yes, No, Pending)*	IRB Approval Date	IRB Approval Expiration Date	Type of IRB Review *(Full Board or Expedited)*	IRB Determination	IRB Approved Waivers** *(Indicate: A, B, C, D)*
David Viskochil MD, PhD University of Utah	recruitment, enrollment, data/specimen collection, analysis, data storage	FWA00003745	University of Utah Institutional Review Board	Yes	11/22/2013	11/19/2014	Full Board	Greater Than Minimal Risk To Subjects	N/A
J.M Friedman MD University of British Columbia	recruitment, enrollment, data/specimen collection, analysis, data storage	FWA00000668	University of British Columbia Office of Research Ethics		Click here to enter a date.	Click here to enter a date.	Full Board	Choose an item.	
Victor Mautner MD University of Hamburg	recruitment, enrollment, data/specimen collection, analysis, data storage				Click here to enter a date.	Click here to enter a date.	Full Board	Choose an item.	

Elizabeth Schorry MD University of Cincinnati	recruitment, enrollment, data/specimen collection, analysis, data storage	FWA00003152	University of Cincinnati Institutional Review Board Project Assurance		Click here to enter a date.	Click here to enter a date.	Full Board	Choose an item.	

IRB Approval*: Indicate whether IRB approval has taken place or is pending. If there are any Institutional Agreements for IRB review planned, describe in the space provided.

IRB Determination: Indicate the determination made by the IRB during the initial review of the protocol. Please contact your IRB office for assistance.

IRB Approved Waivers**: In the space provided, type the letter(s) representing the waivers granted by the IRB: **A**. Waiver of the requirement to obtain informed consent from subjects; **B**. Waiver of the requirement to obtain a signed consent form from subjects; **C**. Waiver of HIPAA Authorization requirements for this protocol; **D**. Waiver of HIPAA Authorization requirements for recruitment purposes only.

Multi-Site Studies: Identify all proposed sites, site Principal Investigators, and IRBs in the above table. Additional site documents will be requested at a later date.

7. Research Monitor Requirements. If the protocol is considered greater than minimal risk to subjects, a research monitor must be identified. Please check one of the following:

a. ☐ Not applicable

b. X Protocol is greater than minimal risk (Complete the table below)

Research Monitor	Role and Responsibilities*
Name: Richard, MD Affiliated Institution: University of Utah	Study Role: External Medical Monitor Responsibilities: See attached staff list and responsibilities
Note: Please provide a current CV/Biosketch and documentation of human subjects' protection training for the Research Monitor. A Research Monitor must not be a member of the study team and is not a Clinical Research Associate (CRA). A Data Safety Monitoring Board/Data Monitoring Committee (DSMB/DMC) member may serve as the DoD required Research Monitor.	

* *Additional information about the Research Monitor's duties and responsibilities can be found in the document "**Information for Investigators: Headquarters, U. S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP) Human Research Protections Regulatory Requirements**)" found on ORP HRPO website: https://mrmc.amedd.army.mil/index.cfm?pageid=research_protections.hrpo*

8. Use of Medical Products.

a. Drugs, Biologics or Dietary Supplements. Does the protocol assess the use a drug, biologic or dietary supplement?

X Yes (If Yes, continue to question i.)
☐ No (If No, skip to question b)

i. Is the purpose of your protocol to determine the safety or effectiveness of the drug, biologic, or dietary supplement?

X Yes (If Yes, complete the table below.)
☐ No (If No, skip to question b)

ii. Does the protocol assess the use of a drug, biologic or dietary supplement that is FDA approved AND will be used in accordance with the labeling and indications as reviewed by the FDA?

☐ Yes (If Yes, protocol may be exempt from an Investigational New Drug (IND) application, continue to the table below)
X No (If No, continue to the table below)

Product Name(s)	Has the IRB/Institution or FDA evaluated whether an IND is required? *(Yes/No)*	IND Application Status *(Indicate IND#, IND pending, or IND exempt)*	Who holds the IND?
Cholecalciferol	Yes	119135	☐ Sponsor* X Investigator** ☐ Other:

*Include documentation from the sponsor or FDA identifying the IND number for this study.

b. Investigational Devices. Does the protocol assess the use of a medical device?

☐ Yes (If Yes, proceed to question i)
X No (If No, skip to Section B (Checklist of Documents to be Submitted to ORP))

i. Is the purpose of your protocol to evaluate the safety or effectiveness of a medical device as defined at 21 CFR 812?

☐ Yes (If Yes, continue to question ii)
☐ No (If No, skip to Section B, (Checklist of Documents to be Submitted to ORP)

ii. Does the protocol use a medical device that is FDA cleared AND will the device be used in accordance with the labeling and indications as reviewed by the FDA?

☐ Yes (If Yes, the protocol may be exempt from IDE requirements. Skip to Section B, (Checklist of Documents to be submitted to ORP)
☐ No (If No, complete the table below)

Device Name(s)/Manufacturer	Has the IRB/Institution or FDA evaluated whether an IDE is required? *(Yes/No)*	IDE status* *(Indicate not applicable, pending, IDE#, or IDE exempt)*	Who holds the IDE?
			☐ Sponsor ☐ Investigator ☐ Other:
			☐ Sponsor ☐ Investigator ☐ Other:
			☐ Sponsor ☐ Investigator ☐ Other:

*Sponsor/PI's Device Risk Determination for Device(s) as Used in this Study

☐ Non-Significant Risk Note: Study is subject to abbreviated IDE requirements, Provide documentation of a Non-Significant Risk determination reviewed by the convened IRB.
☐ Significant Risk Device Note: Study must have an FDA-approved IDE.
☐ Study is Exempt from IDE requirements.

NOTE: An Investigational device is a device that is the object of an investigation. When a protocol is research involving one or more subjects to determine the safety or effectiveness of a device, it is subject to the requirements of FDA's Investigational Device Exemption (IDE) regulations unless determined exempt from the requirements. If available, include documentation from the sponsor or FDA identifying the IDE status, IDE number.

Protocol Submission Form

Section B. Checklist of Documents to be Submitted to the ORP

PI Name: David Viskochil MD, PhD
Protocol 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)

The ORP reviews and approves the same documents reviewed and approved by the local Institutional Review Board (IRB). To promote a timely review, submit all IRB-approved study documents, additional applicable documents, and this Protocol Submission Form.

If your protocol meets the criteria for exemption please complete the Claim of Exemption Form found on the ORP HRPO website or submit your institution's exemption determination and associated exemption forms. Contact the ORP HRPO for exempt protocol submission instructions at usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil or 301-619-2165.

1. Institutional Review Board (IRB)-Approved Documents. Please provide all documents that were submitted to the IRB for review. These are required documents for acceptance of the protocol submission for ORP review. Please check the box beside each document included with this Protocol Submission Form.

X Research Protocol. (Please note the version(s) and date(s) of the approved protocol: original.)
X IRB Application. (If available, indicate the version(s) and date(s) of the IRB Application: original.)
X Informed Consent Document(s), HIPAA Authorization Forms, and Assent Forms. (Please note the version(s) and date(s) of the approved informed consent document(s) here: original.)
X IRB Approval Letter(s) (Original and current approval letter and amendment approval letter (if any))
X Subject recruitment material (e.g., telephone recruitment script, online or print advertising)

2. Other applicable and available study documents. If applicable and when available, submit the following research-related documents for ORP review. Please check the box beside each document included with this Protocol Submission Form.

☐ Scientific/Peer Review of Protocol
X Current Curriculum vitae or Biosketch for PI and Research Monitor (If protocol is greater than minimal risk)
X Documentation of human subjects training for the Principal Investigator, Co-Investigator, Associate Investigator(s), Research Monitor
X Study instruments and data collection forms
☐ Conflict of Interest forms (per your institutional requirements)
X Additional committee and regulatory committee approvals (e.g., radiation control committee, institutional biosafety committee, etc)
X Letter of Support from collaborating institutions
☐ Unit Commander Letter of Support (if military sites involved)
☐ Other documents signed by the subject (e.g., procedural consent, consent for sample donation, consent for testing for communicable diseases, audio/video release form)
X FDA Determination related to IND/IDE

X Medical Product Package Insert/ Investigational Brochure
☐ Device Manual
X Form FDA 1572
X Case Report Forms

3. International Sites. If your study involves international research sites, please contact the ORP HRPO for guidance on completing an international protocol submission form and requirements for international research sites. This form is found on the HRPO website: Click Here

4. Multi Site Protocols. If this is a multi-site protocol, you will be asked to provide each site's IRB approved documents (including the IRB Application) as a separate submission for ORP HRPO review. If the IRB application is unavailable for a site, complete the Site-Specific Protocol Addendum found on the HRPO website: Click Here.

5. Cadaver Research. Activities involving human cadavers supported by the USAMRMC must be reviewed for compliance with the US Army policy and approved by the ORP HRPO. Contact the ORP HRPO for cadaver protocol submission instructions at usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil or 301-619-2165.

Section C. Reporting Requirements and Responsibilities of the Principal Investigator to the USAMRMC ORP Human Research Protections Office (HRPO).

The Principal Investigator must comply with the following minimum reporting requirements. Specific reporting requirements for the protocol will be included in the HRPO Approval Memorandum. Failure to comply could result in suspension of funding.

The protocol will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.

1. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc), significant change in study design (i.e. would prompt additional scientific review) or a change that could potentially increase risks to subjects.

2. Any changes of the IRB used to review and approve the research will be promptly reported to the USAMRMC ORP HRPO.

3. All unanticipated problems involving risk to subjects or others must be promptly reported by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

4. Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the Sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.

5. A copy of the continuing review approval notification by the IRB of Record must be submitted to the HRPO as soon as possible after receipt. Please note that the HRPO also conducts random audits at the time of continuing review. Additional information and documentation may be requested at that time.

6. The final study report, including any acknowledgement documentation and supporting documents, must be submitted to the HRPO when available.

7. The knowledge of any pending compliance inspection/visit by the FDA, DHHS Office of Human Research Protections (OHRP), or other government agency concerning this research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any regulatory agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements, must be promptly reported to the HRPO.

Principal Investigator Signature Page. Please sign and scan this signature page.

I have read the above reporting requirements and responsibilities of the Principal Investigator to the USAMRMC ORP HRPO.

1-14-2014

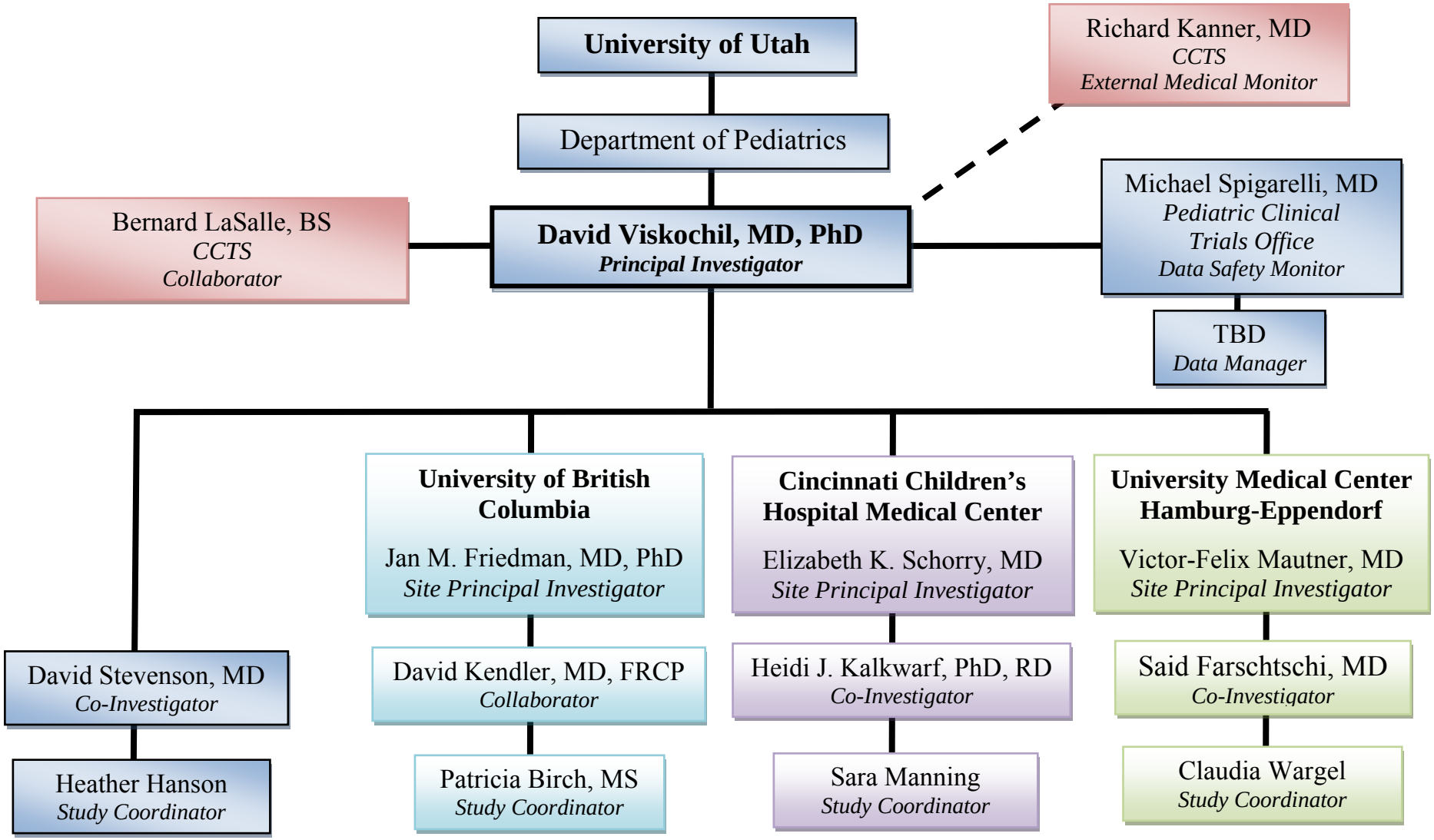
Protocol Principal Investigator Signature Date: Click here to enter a date.

Printed Name: David Viskochil

Point of Contact Regarding this Protocol Submission: David Viskochil
Study Role: PI Contact Information: david.viskochil@hsc.utah.edu
University of Utah
50 N. Mario Capecchi Dr. Rm 2C412 SOM
Salt Lake City, Utah 84132
801-581-8943

STUDY PERSONNEL AND ORGANIZATION

Study Organizational Chart



Principal Investigator/Key Personnel/Study Staff

University of Utah Personnel

David H. Viskochil, MD, PhD, Principal Investigator

Dr. Viskochil is a Professor in the Division of Medical Genetics in the Department of Pediatrics in the University of Utah. He will oversee correspondence with PIs from other sites, the data monitoring group, the shipping couriers, the ARUP lab managers, and the database manager throughout the duration of the study. At the Utah site, he will be the primary person in charge of patient recruitment, participant enrollment, clinical phenotyping, and biologic sample collection and processing. Dr. Viskochil is also the site PI at the University of Utah for the Neurofibromatosis (NF) Clinical Trial Consortium and Co-Chairs the bone committee with Dr. Elizabeth Schorry.

David A. Stevenson, MD, Co-Investigator

Dr. Stevenson is an Assistant Professor in the Division of Medical Genetics in the Department of Pediatrics in the University of Utah. Dr. Stevenson is a medical geneticist with clinical trial experience. He will participate in monthly conference calls with external collaborators to discuss study progress and issues that may arise. He will serve the primary functions of PI in the event Dr. Viskochil is unavailable.

Michael G. Spigarelli, MD, PhD, Data Safety Monitor

Dr. Spigarelli is a Professor of Pediatrics in the Department of Pediatrics at the University of Utah. He is the Chief of both the Division of Clinical Pharmacology and of Adolescent Medicine in the Department of Pediatrics. In addition, he is the Director of the Pediatric Clinical Trials Office in the Department of Pediatrics. Dr. Spigarelli will oversee activities of the data monitoring team, which includes 1) retrieval of serum values from ARUP and communication of those results to the site coordinators, 2) randomization of those enrollees who are eligible to participate in the trial, 3) enter lab data for years 1-3 into the database, 4) perform quality checks on the acquired data, 5) evaluate quality and completeness of data 6) collect and communicate safety-related data, including adverse events and protocol deviations to the medical monitor, and 7) obtain DXA scan data to perform interim analysis.

Bernard A. LaSalle, BS, Collaborator

Dr. LaSalle is the Director of Operations for the Center for Clinical and Translational Science(CCTS) at the University of Utah. Mr. LaSalle oversees all aspects of databases maintained in the CCTS. He will maintain the NF Database for the purpose of this study. His efforts are subsumed under the CCTS funding from National Center for Research Resources (UL1-RR025764 and C06-RR11234), providing the clinical trial is approved by the CCTS Executive Committee.

Heather Hanson, Study Coordinator

Ms. Hanson is a Clinical Research Coordinator in the Division of Medical Genetics in the Department of Pediatrics at the University of Utah. She will submit IRB applications as requested, search and find patients for the study, collect all data for the patients enrolled, arrange travel, collect and track all data, perform telephone and general mail communications with patients and co-investigators, coordinate the handling and shipping of biologic specimens, verify accuracy of entered data, coordinate all computer related activities including exporting data in viable and usable formats to all consultants, and assist the investigators as needed.

TBD, Data Manager

A Data Manager will work directly with Dr. Spigarelli to obtain serum values and enter laboratory data in the CCTS NF database for years 1-4. He or she will determine completeness and quality of data collections, and oversee the appropriate posting of safety-related data.

Cincinnati Children's Hospital Medical Center Personnel

Elizabeth K. Schorry, MD, Site Principal Investigator

Dr. Schorry is an Associate Professor of Clinical Pediatrics at the Cincinnati Children's Hospital Medical Center. She is also the Director of both the Neurofibromatosis Clinic and Adult Neurofibromatosis Clinic at the Cincinnati Children's Hospital Medical Center. She has collaborated with the University of Utah investigators on multiple studies involving NF1-related bone disorders. She serves as the Principal Investigator of the Cincinnati Children's Hospital Medical Center Site for the NF Clinical Trials Consortium, and has a long-term involvement in NF1 clinical trials. Her role is instrumental in development of techniques enhance recruitment. At her site, Dr. Schorry will oversee patient recruitment, participant enrollment, clinical phenotyping, and biologic sample collection and processing.

Heidi J. Kalkwarf, PhD, RD, Co-Investigator

Dr. Kalwarf is a Research Professor of Pediatrics in the Division of General and Community Pediatrics at the Cincinnati Children's Hospital Medical Center. She has worked closely with Dr. Schorry for a number of years and is presently a collaborator with Dr. Viskochil on a NF1-related scoliosis study funded by the NIH. She has actively participated in trial design and has agreed to serve as the lead densitometrist for the present study. She will provide consultation services for oversight of all aspects of bone density data collection, and she will play a major role in the final data analyses.

Sara Manning, Study Coordinator

Ms. Manning is a Study Coordinator in the Division of Human Genetics at the Cincinnati Children's Hospital Medical Center and has worked with Dr. Schorry in the past. She will submit IRB applications as requested, recruit and enroll patients for the study, collect all data for the patients enrolled, arrange travel, collect and track all data, perform telephone and general mail communications with patients and co-investigators, coordinate the handling and shipping of biologic specimens, verify accuracy of entered data, coordinate all computer related activities including exporting data in viable and usable formats to all consultants, complete clinic report forms (CRFs), and assist the investigators as needed.

University of British Columbia (UBC) Personnel

Jan M. Friedman, MD, PhD, FAAP, Site Principal Investigator

Dr. Friedman is a Professor in the Department of Medical Genetics at the University of British Columbia. He also is the Acting Executive Director of the Child and Family Research Institute and the Acting Associate Dean of Research in the Faculty Medicine at the University of Columbia. Dr. Friedman is a Medical Geneticist. He has served many years as the Director of the NF Clinic at UBC and continues extensive research in various aspects of NF1. His role is instrumental in trial design and statistical analysis. He will oversee patient recruitment, participant enrollment, clinical phenotyping, and biologic sample collection and processing. He will take the lead role in data analysis at the end of the study.

David Kendler, MD, FRCP(c), Co-Investigator

Dr. Kendler is the Director of the Prohealth Clinical Research Centre and an Associate Professor in the Division of Endocrinology at the University of British Columbia. He will serve as collaborator on the interpretation of data from this study. He oversees the personnel and functioning of the Bone Densitometry Core affiliated with the clinical departments. His efforts are subsumed by costs associated with DXA scanning in approved and funded studies at UBC.

Patricia Birch, Study Coordinator

Ms. Birch is a Study Coordinator in the Medical Genetics Research Unit ath the University of British Columbia and has worked with Dr. Friedman over 20 years. She will submit IRB applications as requested, recruit and enroll patients for the study, collect all data for the patients enrolled, arrange travel, collect and track all data, perform telephone and general mail communications with patients and co-investigators, coordinate the handling and shipping of biologic specimens, verify accuracy of entered data, coordinate all computer related activities including exporting data in viable and usable formats to all consultants, complete clinic report forms (CRFs), and assist the investigators as needed.

University Medical Center Hamburg-Eppendorf Personnel

Victor-Felix Mautner, Site Principal Investigator

Dr. Mautner is a Professor of Neurology at the University Hospital Hamburg-Eppendorf. He is also the Director of the Neurofibromatosis Program Klinikum Nord and the Head of the Oupatient Department. He has been involved in NF-related research for over 20 years and has completed numerous clinical trials specifically related to the conditions of NF1, NF2, and schwannomatosis. He is head of the Neurofibromatosis Program Klinikum Nord, Hamburg, and serves as medical advisor for two lay-group organizations. His role is instrumental in trial design and recruitment of patients throughout Germany. He will oversee patient recruitment, participant enrollment, clinical phenotyping, and biologic sample collection and processing.

Said Farschtschi, MD, Co-Investigator

Dr. Farschtschi is a Medical Doctor at the University Hospital Hamburg-Eppendorf and is working closely with Dr. Mautner in the Department of Medicine and the Neurofibromatosis Program at Klinikum Nord, Hamburg. Dr. Farschtschi has been working in Hamburg NF-outpatient department as a medical student for one year and he was trained to do clinical examinations and treat NF1 adult patients. He was involved in vitamin D supplementation studies during this period. He has also been connected to the German Lay Organization (Bundesverband Neurofibromatose), where he worked for their Newsletter. His role will be to work closely with the study coordinator and Dr. Mautner in the recruitment and assessment of study participants.

Claudia Wargel, Study Coordinator

Ms. Wargel is a Study Coordinator at the University Hospital Hamburg-Eppendorf and works with Dr. Maunter in the Neurofibromatosis Program. She will submit IRB applications as requested, recruit and enroll patients for the study, collect all data for the patients enrolled, arrange travel, collect and track all data, perform telephone and general mail communications with patients and co-investigators, coordinate the handling and shipping of biologic specimens, verify accuracy of entered data, coordinate all computer related activities including exporting data in viable and usable formats to all consultants, complete clinic report forms (CRFs), and assist the investigators as needed. S

External Medical Monitor

Richard Kanner, MD, External Medical Monitor

Dr. Kanner is a Research Compliance Officer in the University of Utah's Center for Clinical and Translational Science Patient Interaction Core. He serves as the medical monitor for those studies performed under the auspices of the CCTS at the University of Utah that are deemed by the IRB as "almost minimal risk." He will serve this function providing that each IRB deems this study as minimal risk or slightly more than minimal risk. His efforts are subsumed under the CCTS funding from National Center for Research Resources (UL1-RR025764 and C06-RR11234), providing the clinical trial is approved by the CCTS Executive Committee.

Study Management Plan

As a 4-center consortium spanning 8 time zone, each of the academic centers will utilize high-speed internet for electronic communication as a means of sharing observations and needs. There will be 4 distinct email lists; study-wide personnel, coordinators, all co-investigators and collaborators, and a more restricted PI-only group. In addition to email correspondence, there will be monthly teleconference calls initiated by Dr. Viskochil for all the PIs and the data monitor to review a standing agenda. This has worked well with the NINDS-sponsored NF1-Spine study that includes 3 of the 4 centers that are collaborating on this study. Mr. LaSalle has designed the Spine study database, and will use similar design processes to develop the Vitamin D NF1 Study Database as part of the Informatics Core of the CCTS at the University of Utah. This database will have tiered access to shared data, but each of the 4 enrolling centers has full access to the data submitted from their web-based data entry portal. Lab values and DXA data will be stored in a separate portal, and no investigative team will have access to these data until the end of the study. Only the database manager (Mr. LaSalle) and data monitor (Dr. Spegarelli) will have access to these data.

Communication between the coordinators at each center with the data monitoring group is especially important because of the need to relay eligibility status and randomization outcome. The coordinator is responsible for assigning a local identifier at the time of participant enrollment. A tracking system with alert capability will be developed in the first 2 months of funding as part of a manual of operations. With respect to the initial serum specimen that defines subsequent enrollment into the vit D_3 supplementation trial, this tracking system will jointly notify coordinator, data monitor, and specimen receiving at the CGRP freezer storage facility that a serum sample has been shipped. Once a sample is transferred to ARUP a lab tracking system will be activated to document that the sample was received and processed. Only the medical monitor will receive the actual results from 25(OH)D screening. Once the medical monitor is alerted that the screening serum 25(OH)D test is complete, the monitor will retrieve the value and determine eligibility for continued enrollment in the vitamin D supplementation clinical trial. The coordinator must then be notified of eligibility and randomization status. Each of these communication points will require an acknowledgment by a responsible team member, and lack of response in a timely manner will constitute a protocol deviation.

The DXA data will be collected on site and electronic data will be stored at the densitometry site and a CD harboring the electronic information will be shipped by courier to the medical monitor for validation of scan quality and data entry into the database. In addition to validation and entry of data, analysis of the mid-study DXA scan will be performed for safety issues (loss of more than 7% bone mineral density requires and alert to the coordinator and PI at the respective site). This communication will be by phone and electronically transmitted via personal health information (HPI)-protected internet connections. The CDs containing electronic DXA data will be stored with the data monitor after entry into the database. Survey data will be captured by hard copy and entered into the database through password-protected portals at each of the 4 enrollment centers. The coordinator is responsible for this data web-based entry and a copy of the hard-copy forms are sent to the data monitor on a monthly basis.

The data monitor will generate a monthly report documenting the data that has been entered into the database, but not the content of the data. This includes lab entries, surveys, and DXA scans. The coordinator from the University of Utah will document and provide a monthly report on the serum specimens that are collected and stored in the CGRP freezer collection repository. These reports are reviewed by conference call and entered in the administrative record retained in a correspondence folder of the study database.

Serum specimens stored in the repository will be used only for approved future research. The samples will remain frozen in the -80 degree Celcius freezer until requests for access are made to the executive committee comprised of the 4 PIs who must be in full consensus for serum to be used for other research purposes.

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 Summary

IRB Approval Date:	11/20/2013
University of Utah IRB #:	IRB_00055719
Sponsor:	
Principal Investigator:	David Viskochil
Internal Staff and Sub-Investigators:	David Stevenson David Viskochil Michael Spigarelli Heather Hanson Bernie LaSalle
External Sub-Investigators:	J.M Friedman Victor Mautner Elizabeth Schorry

This document was created using the ERICA Online System at the University of Utah. The document is created from study information approved by the IRB on the date listed above. Any alteration to the original content of this document may not be considered to represent the study as approved by the IRB.

Background and Introduction

Neurofibromatosis 1 (NF1)

NF1 is a genetic condition that affects 1 in 3000 people worldwide. NF1 is caused by a constitutional heterozygous "loss of function" mutation in the *NF1* gene on chromosome 17q11.2. The *NF1* gene product is a component of the Ras signaling pathway, which plays a fundamental role in control of cellular proliferation and differentiation. Clinical features of NF1 vary greatly among individuals with this condition, but different manifestations tend to have age-related penetrance. Characteristic pigmentary lesions of the skin (café-au-lait macules and intertriginous freckling) are the most frequent signs of NF1 of children, and almost all older patients have numerous cutaneous neurofibromas, benign Schwann cell tumours that give neurofibromatosis its name. However, NF1 is a multisystem disease, and many patients also have other features such as optic nerve gliomas, learning disabilities, bone abnormalities, and/or vasculopathies. Most people with NF1 are shorter than expected for their families, and, as described below, almost all affected individuals develop osteopenia or osteoporosis by the time they are 50 years old.

Bone Mineral Density (BMD) and Osteoporosois

Bone mass is accumulated in childhood and adolescence, and peak bone mass is normally reached by approximately age 25 years. Once peak bone mass is achieved, bone is continually remodeled by a balance of absorption and deposition to maintain bone homeostasis. The maintenance of normal BMD in younger adults reduces the risk of osteoporosis later in life. After menopause in women and with aging in men, bone mass is lost, mainly due to sex hormone deficiency.

Osteoporosis is a systemic condition of low bone mass and deterioration of bone structure. Osteoporosis produces bone fragility and an increased risk of non-traumatic, "osteoporotic" fractures. Osteoporosis is common in the general population, affecting 1 in 5 women and 1 in 14 men in the US (National Osteoporosis Foundation, 2007). Osteoporosis is diagnosed on the basis of abnormally low BMD (WHO, 1998). Dual-energy x-ray absorptiometry (DXA) is the preferred method for assessing BMD, its changes over time, and its response to treatment (Rosenthall et al, 1999; Dasher et al 2011). DXA is commonly used to measure BMD at the hip, lumbar spine and wrist. BMD is measured in gm/cm$_2$, 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 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 (WHO, 1998).

In the general population, BMD is largely under genetic control. It is estimated that genetic factors contribute at least 50%, and perhaps as much as 80%, to variability in peak bone mass (Patel et al, 2000; Ralston and Uitterlinden 2010). Other factors that may affect bone mass include treatment with certain drugs, such as glucocorticoids and some anticonvulsants, physical

activity, body weight, and dietary calcium or vitamin D intake (Ralston and Uitterlinden 2010).

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. Unfortunately, however, NF1 is not recognized as a risk factor in either osteoporosis guidelines (Brown et al, 2002; Brown et al, 2006; National Osteoporosis Foundation, 2006) or NF1 care guidelines (www.geneclinics).

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. 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 (Plum and DeLuca 2011; Rosen 2011).

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. 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). 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 histolopathogical 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).

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. There are multiple case reports of osteomalcia (Hogan et al 1986; Weinstein and Harris 1990; Abdel-Wanis and Kawahara 2002; Chadha et al 2009) 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. Lower than expected BMD has been observed among people with NF1 of all ages (Illes et al 2001; Kuorilehto et al 2005; Lammert et al 2005; Stevenson et al 2005; Stevenson et al 2007; Dulai et al 2007; Seitz et al 2010).

Vitamin D Status of NF1 Patients

Serum 25-hydroxyvitamin D concentrations in people with NF1 show reduced average values compared to controls, thus they have higher than expected frequencies of vitamin D insufficiency/deficiency (Illes et al 2001; Lammert et al 2006; Brunetti-Pierri et al 2008; Tucker et al 2009; Seitz et al 2010; Stevenson et al 2011). Three of these studies included patients recruited 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.

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.

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 D_3 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 D_3 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). 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). The US National Osteoporosis Foundation recommends the minimum daily intakes of 1000 mg calcium and 600 IU vitamin D for adults in the 19-50 year old age range. 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). The upper value of serum 25-hydroxyvitamin D concentration that can be tolerated without 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).

Two previous 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.

In studies performed in Hamburg, Germany, by our co-investigator, Dr. Victor Hamburg, 36 adults with NF1 and low serum 25-hydroxy vitamin D concentrations were followed for 2 years by BMD analysis. 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 two 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. A similar trend was observed at the spine. These data (Schnabel et al., 2013) support the development of a clinical trial to assess the potential preservation of BMD in adult patients with NF1 who use either a supplemental dose of vitamin D versus a therapeutic dose of vitamin D.

Purpose and Objectives

This is a two-year prospective, double-blind trial of two different doses of vitamin D supplementation in adults with neurofibromatosis type 1 (NF1) who are insufficient in serum 25-(OH) vitamin D

[25(OH)D] at the time of enrollment.

OBJECTIVE

Osteoporosis and vitamin D insufficiency are common manifestations of NF1, 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 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, 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. All participants will also take an oral calcium supplement (400 mg elemental calcium) daily.

Study Population

Age of Participants: between the ages of 25 and 40 years

Sample Size:

At Utah:	approximately 80
All Centers:	320

Inclusion Criteria:

All individuals with NF1 (neurofibromatosis type 1), based on NIH diagnostic criteria, who are between the ages of 25 and 40 years, are potentially eligible for this study. Exclusion criteria will be reviewed prior to enrollment. All eligible participants will be enrolled in the study and then screened for serum 25(OH) vitamin D levels. Individuals with levels between 9 and 29ng/ml are eligible to receive vitamin D supplementation at one of 2 doses.

Exclusion Criteria:

Individuals will be excluded from treatment for the following reasons:

1. lack of NF1 diagnostic criteria on physical examination

2. diagnosis of Paget's disease, hyperthyroidism, hyperparathyoroidism or other medical condition that affects bone health
3. they foresee that they will be unable to comply with the two-year study protocol
4. they are pregnant at the time of DXA scanning
5. their initial screening 25(OH) vitamin D level is either equal to or over 30ng/ml (sufficient)
6. their initial screening 25(OH) vitamin D level is either equal to or less than 8ng/ml (deficient)
7. vitamin D supplementation in the last 6 months equal to or greater than 600IU per day
8. oral or IV glucocorticoid use for more than 3 months
9. bisphosphonate therapy for more than 3 months
10. calcitonin therapy for more than 3 months
11. calcium supplementation in last 6 months equal to or greater than 1000mg per day
12. malignant peripheral nerve sheath tumor
13. history of kidney stones in the last 5 years
14. individuals with metal instrumentation in spine or hip that preclude accurate DXA interpretation.
15. inability to obtain blood samples on routine venipuncture
16. anti-epileptic medical therapy
17. anticoagulant medical therapy
18. pregnancy within the past 12 months

Design

Phase II Clinical Trial

Study Procedures

Recruitment/Participant Identification 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 NF1-related studies.

Using IRB-approved advertising material (sample advertisement included at the end of this attachment), we will 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 4 participating sites, University of Utah, University of British Columbia, Hamburg University, and the University of Cincinnati will be contacted about possible enrollment.

Informed Consent:

Description of location(s) where consent will be obtained:

Consent will be obtained at clinical trial research-designated areas at each facility. At the University of Utah, consent will be obtained in the CCTS outpatient facility.

Description of the consent process(es), including the timing of consent:

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 3 months 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.

Procedures:

Description of the 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 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 3 months to review any issues or concerns with respect to the trial. A review of the vitamin D_3 and calcium supplementation diary will be obtained and any potential side effects or adverse effects will be documented and discussed at that time.

Enrollment and 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 serum 25(OH) vitamin D levels on all enrollees. 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 a second tube drawn for serum preparation and freezing as part of the initial sampling.

All participants in the trial come for the initial screening, which 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 physician will verify medical history and perform brief physical examination to ensure recruits have NF1 and are eligible to participate.
- Blood will be drawn by a trained phlebotomist. The amount of blood required is about six teaspoons (30 ml). Serum will be prepared for 25(OH) vitamin D screening performed at a central laboratory (A.R.U.P., University of Utah). Other serum studies will be performed if the enrollee is found to be eligible for the remainder of the study. These tests include parathyroid hormone and calcium. Recruits need to have been fasting for 4 hours before the blood draw.
- After results from the initial blood test are obtained, the study coordinator will provide the participant with the result of the 25(OH) vitamin D testing. The enrollee will learn of his or her serum vitamin D level; either sufficient ($\geq$30ng/ml), very low (<8ng/ml), or insufficient. If insufficient then the enrollee will be invited to participate in the remainder of the study.

Individuals who have an adequate serum 25(OH)D level, $\geq$30ng/ml, will be given their results and followed in a registry. No further studies will be performed on these enrollees; however, they will be maintained in a registry with linked serum sample deposited in a tissue repository until the end of the 4-year study. Individuals who have serum 25(OH)D levels deemed to be in the osteomalacia range, <8ng/ml, will be notified so that they can discuss more extensive treatment with their primary care provider. It is expected that about two-thirds of enrollees will fit the "insufficient" category of serum vitamin D levels, thus will be eligible for the remainder of the study.

Study Protocol

At the Utah site, participants will come to the Center for Clinical Translation Sciences (CCTS) outpatient site for further studies, including a urine pregnancy test. Those who are pregnant at screening will not be included in the study, but will be included in the registry. Those who are not pregnant will enter the study and undergo simple randomization for high- versus low-dose cholecalciferol (vitamin D3) supplementation by the study monitoring group in site-specific blocks of 4 utilizing random number pre-assignments. Those who become pregnant will be removed from the supplementation and DXA scanning while remaining on the longitudinal studies until study end. Each participant will be instructed by the study coordinator at the respective sites on how to take the solution of vitamin D in the form of Ddrops. 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. DXA scanning will be performed of the spine and left hip as the primary endpoint of the clinical trial in routine fashion. Surveys will be administered and collected.

Bone densitometry (DXA scanning) is the primary outcome measure. It 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. 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.

All participants will receive US$25 for the screening test and $50 for the initial assessment and $70 for each of the remaining 2 assessment visits (at the beginning, end of 1 year, and at the last visit at 24 months). This is to partially compensate for time, parking expenses, and gas. People may also be compensated for travel, which will be discussed in advance of the initial appointment and enrollees will be notified in writing what the travel compensation will be. Participants will not be charged for the vitamin D, the calcium supplement, the blood tests, the DXA scan, or the urine pregnancy test. Participants will be notified of their serum 25(OH) vitamin D level and results of pregnancy testing; however, they will not be notified of other serum study results or DXA scan results until they have completed the 2-year study.

Participants will return to the CCTS every 6 months until the study is completed at 24 months. At each visit, the participant and clinic coordinator will review medical history and medication diary. Surveys will be performed and serum sampling will be obtained for safety studies only at the 12-month assessment visit. Vitamin Ddrops will be distributed to the participants every 6 months at these visits. The exit DXA scan will be performed at the 24-month assessment visit except for those who become pregnant while enrolled. A brief physical examination will be performed at each visit and information entered on physical examination forms. Participants, study coordinators, and investigators at each site will not know the dose of vitamin D or the results of DXA scan and intermediate serum sample results.

Serum samples from the initial blood draw will be kept in the bone repository lab for one year after the study is completed to ensure appropriate data analysis. Participants will be provided an opportunity to have their serum sample frozen and stored indefinitely for future studies by signing a seperate consent form. This is a serum sample. It will not be saved as DNA material and will not be used in such a manner in future research. The serum will be stored frozen in the Clinical Genetics Research Program under the direction of Dr. David Viskochil, and located at the University of Utah. Participants will have an opportunity to choose how they would like their sample used for future research. It can be as an anonymous sample in which only age, sex, and NF1 status is available to the investigator, or it can be linked to clinical information but remain confidential.

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 cholecalciferol 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 vit D_3

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 long-term in this facility, 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 Celsius 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 are given an option to have the remainder of their serum samples to be stored beyond the duration of the study. This is a separate consent process under University of Utah IRB #7551 (PI-Viskochil). Other sites may elect to enroll participants under separate IRB, as well. This option is provided so participants can contribute 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 (i.e. UTA110) and stored in boxes that identify the NF1-vitamin D supplementation study.

Labs Performing Evaluations and Special Precautions

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.

Procedures performed for research purposes only:

Statistical Methods, Data Analysis and Interpretation

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. Preliminary data showed a mean change in the hip T-score of about -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 and 4,000 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. The mean difference in the hip T-score between the treated and untreated groups in the pilot study 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 (See table below). 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.

Table: 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

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 maintain their BMD, or at least to show less loss. The primary metric used to assess BMD in this analysis is the mean change in hip Z-score/year, and the two groups will be compared using analysis of variance with participating center and sex as covariates. Confirmatory analyses will also be performed comparing the change in lumbar Z-score/year, change in hip BMD/year, and change in lumbar BMD/year between the two treatment groups.

Descriptive univariate analyses (t-tests, X^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, activity and UV exposure questionnaires 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.

Electronic
RESEARCH INTEGRITY AND COMPLIANCE
THE UNIVERSITY OF UTAH

Date: Tuesday, January 07, 2014 10:57:04 AM

Print Close

IRB_00055719 **Created:** 2/24/2012 4:00 PM

PI: David Viskochil M.D., Ph.D. **Submitted:** 2/5/2013

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)

1. Contacts and Title

1. Principal Investigator:

David Viskochil

Email	Training	CoI Date
dave.viskochil@hsc.utah.edu	5/14/2012 SMN	11/4/2013

a. Position of Principal Investigator:

- (●) **Faculty**
- ( ) Student
- ( ) Staff
- ( ) Resident/Fellow
- ( ) Other

If Other, describe:

b. Will the Principal Investigator consent participants? (●) **Yes** ( ) No

2. Contact Person(s) (if different from the PI):

Name	Email	Training
Heather Hanson	heather.hanson@hsc.utah.edu	1/28/2013 SMN

3. Internal Staff and Sub-Investigator(s) (Within the University of Utah):

Name	Email	Training	Obtaining Consent	CoI Date
Heather Hanson	heather.hanson@hsc.utah.edu	1/28/2013 SMN	☑	11/4/2013
Bernie LaSalle	bernie.lasalle@hsc.utah.edu	10/9/2013 MN	☐	11/12/2013
Michael Spigarelli	michael.spigarelli@hsc.utah.edu	3/29/2011 M	☐	9/6/2013
David Stevenson	david.stevenson@hsc.utah.edu	7/16/2012 MN	☑	11/15/2013
David Viskochil	dave.viskochil@hsc.utah.edu	5/14/2012 SMN	☑	11/4/2013

4. External Sub-Investigator(s) (Investigators outside the University of Utah):

Last Name	First Name	Affiliation
Friedman	J.M	University of British Columbia
Mautner	Victor	University of Hamburg
Schorry	Elizabeth	University of Cincinnati

5. Faculty Sponsor (if needed):

6. Guests:

Last Name	First Name	E-Mail

There are no items to display

7. What type of application is being submitted?

New Study Application (or Amendment/Continuing Review)

8. Title Of 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)

9. Study Purposes and Objectives:

This is a two-year prospective, double-blind trial of two different doses of vitamin D supplementation in adults with neurofibromatosis type 1 (NF1) who are insufficient in serum 25-(OH) vitamin D [25(OH)D] at the time of enrollment.

OBJECTIVE

Osteoporosis and vitamin D insufficiency are common manifestations of NF1, 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 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, 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. All participants will also take an oral calcium supplement (400 mg elemental calcium) daily.

10. Background and Introduction:

Neurofibromatosis 1 (NF1)

NF1 is a genetic condition that affects 1 in 3000 people worldwide. NF1 is caused by a constitutional heterozygous "loss of function" mutation in the *NF1* gene on chromosome 17q11.2. The *NF1* gene product is a component of the Ras signaling pathway, which plays a fundamental role in control of cellular proliferation and differentiation. Clinical features of NF1 vary greatly among individuals with this condition, but different manifestations tend to have age-related penetrance. Characteristic pigmentary lesions of the skin (café-au-lait macules and intertriginous freckling) are the most frequent signs of NF1 of children, and almost all older patients have numerous cutaneous neurofibromas, benign Schwann cell tumours that give neurofibromatosis its name. However, NF1 is a multisystem disease, and many patients also have other features such as optic nerve gliomas, learning disabilities, bone abnormalities, and/or vasculopathies. Most people with NF1 are shorter than expected for their families, and, as described below, almost all affected individuals develop osteopenia or osteoporosis by the time they are 50 years old.

Bone Mineral Density (BMD) and Osteoporosois

Bone mass is accumulated in childhood and adolescence, and peak bone mass is normally reached by approximately age 25 years. Once peak bone mass is achieved, bone is continually remodeled by a balance of absorption and deposition to maintain bone homeostasis. The maintenance of normal BMD in younger adults reduces the risk of osteoporosis later in life. After menopause in women and with aging in men, bone mass is lost, mainly due to sex hormone deficiency.

Osteoporosis is a systemic condition of low bone mass and deterioration of bone structure. Osteoporosis produces bone fragility and an increased risk of non-traumatic, "osteoporotic" fractures. Osteoporosis is common in the general population, affecting 1 in 5 women and 1 in 14 men in the US (National Osteoporosis Foundation, 2007). Osteoporosis is diagnosed on the basis of abnormally low BMD (WHO, 1998). Dual-energy x-ray absorptiometry (DXA) is the preferred method for assessing BMD, its changes over time, and its response to treatment (Rosenthall et al, 1999; Dasher et al 2011). DXA is commonly used to measure BMD at the hip, lumbar spine and wrist. BMD is measured in gm/cm_2, 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 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 (WHO, 1998).

In the general population, BMD is largely under genetic control. It is estimated that genetic factors contribute at least 50%, and perhaps as much as 80%, to variability in peak bone mass (Patel et al, 2000; Ralston and Uitterlinden 2010). Other factors that may affect bone mass include treatment with certain drugs, such as glucocorticoids and some anticonvulsants, physical activity, body weight, and dietary calcium or vitamin D intake (Ralston and Uitterlinden 2010).

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. Unfortunately, however, NF1 is not recognized as a risk factor in either osteoporosis guidelines (Brown et al, 2002; Brown et al, 2006; National Osteoporosis Foundation, 2006) or NF1 care guidelines (www.geneclinics).

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. 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 (Plum and DeLuca 2011; Rosen 2011).

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. 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). 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 histolopathogical 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).

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. There are multiple case reports of osteomalcia (Hogan et al 1986; Weinstein and Harris 1990; Abdel-Wanis and Kawahara 2002; Chadha et al 2009) 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. Lower than expected BMD has been observed among people with NF1 of all ages (Illes et al 2001; Kuorilehto et al 2005; Lammert et al 2005; Stevenson et al 2005; Stevenson et al 2007; Dulai et al 2007; Seitz et al 2010).

Vitamin D Status of NF1 Patients

Serum 25-hydroxyvitamin D concentrations in people with NF1 show reduced average values compared to controls, thus they have higher than expected frequencies of vitamin D insufficiency/deficiency (Illes et al 2001; Lammert et al 2006; Brunetti-Pierri et al 2008; Tucker et al 2009; Seitz et al 2010; Stevenson et al 2011). Three of these studies included patients recruited 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.

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.

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 D_3 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 D_3 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). 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). The US National Osteoporosis Foundation recommends the minimum daily intakes of 1000 mg calcium and 600 IU vitamin D for adults in the 19-50 year old age range. 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). The upper value of serum 25-hydroxyvitamin D concentration that can be tolerated without 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).

Two previous 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.

In studies performed in Hamburg, Germany, by our co-investigator, Dr. Victor Hamburg, 36 adults with NF1 and low serum 25-hydroxy vitamin D concentrations were followed for 2 years by BMD analysis. 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 two 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. A similar trend was observed at the spine. These data (Schnabel et al., 2013) support the development of a clinical trial to assess the potential preservation of BMD in adult patients with NF1 who use either a supplemental dose of vitamin D versus a therapeutic dose of vitamin D.

IRB_00055719 **Created:** 2/24/2012 4:00 PM

PI: David Viskochil M.D., Ph.D. **Submitted:** 2/5/2013

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)

2. Study Location and Sponsors

1. **Department:**
   PEDIATRICS
2. **Location of Study:**

   University of Utah's Covered Entity (Health sciences, hospitals, and clinics)
3. **Is this a Multicenter Study (i.e., the study involves other sites with other PIs):**

   (●) **Yes** ( ) No

   a. **If yes, are you the lead investigator of this study, or is this the central location for the study?**

      (●) **Yes** ( ) No
4. **Indicate other locations that are participating in the study for which you, as the PI, are responsible:**

	Site Name	Other Site	Site Investigator	Investigator/Main Contact
View	Other	University of British Columbia	yes	J.M. Friedman, MD PhD
View	Other	University of Cincinnati	yes	Elizabeth Schorry MD
View	Other	University of Hamburg	yes	Victor Mautner MD

   a. **How will adverse events, unanticipated problems, interim results, and changes to the research be communicated between the participating sites and the Principal Investigator?**
   All observed or volunteered adverse events, regardless of suspected causal relationship to study drug, will be recorded as Adverse Events in the case report forms (CRFs) 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 on the CRF. The Data Monitor will review the adverse events and communicate with the PI/study coordinator at each of the 4 participating sites. It will be left to the investigator's clinical judgment whether or not an adverse event is of sufficient severity to require that the participant should be removed from the trial, and if other participants should be notified of the event if related to the study. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these occurs, the participant will be given appropriate care under medical supervision until symptoms cease or until the condition becomes stable.

   The severity of toxicities will be graded in accordance with the Common Terminology Criteria for Adverse Event (CTCAE) version 3.0 (http://ctep.info.nih.gov).
5. **Indicate the source(s) of funding obtained or applied for to support this study.**

	Sponsor	Sponsor Type	Sponsor Contact Information
View	ARMY MEDICAL RESEARCH & MATERIEL COMMAND	Federal Government	MCMR- AAA-R US Dept of Defense Office of Navel Research Seattle regional office of reserach 300 5th ave st 710 Seattle WA- 98104

6. **Does this study have functions assigned to a Contract Research Organization (CRO)?**
   ( ) Yes (●) **No**

   If yes, CRO Contact Information:
7. **Does this study involve use of the Utah Population Database (UPDB)?**
   ( ) Yes (●) **No**

Addition of a Site

a. Site Name:
Other

If Other, provide full site name: University of British Columbia

b. Site address:
2329 West Mall Vancouver, B.C., Canada V6T 1Z4

c. Site phone number: 604-875-2000

d. Does this site have an investigator?
(●) **Yes** ( ) No

Enter the investigator's or main contact's name:
J.M. Friedman, MD PhD

e. Select the study procedures that will be conducted at this site:

Recruitment
Consent/Enrollment
Research observation/intervention with participants
Data collection
Data analysis

If Other, describe:

Addition of a Site

a. Site Name:
Other

If Other, provide full site name: University of Cincinnati

b. Site address:
2600 Clifton Ave., Cincinnati OH 45221

c. Site phone number: 513-556-6000

d. Does this site have an investigator?
(●) **Yes** ( ) No

Enter the investigator's or main contact's name:
Elizabeth Schorry MD

e. Select the study procedures that will be conducted at this site:

Recruitment
Consent/Enrollment
Research observation/intervention with participants
Data collection
Data analysis

If Other, describe:

Addition of a Site

a. Site Name:
Other

If Other, provide full site name: University of Hamburg

b. Site address:
Edmund-Siemers-Allee 1, 20146 Hamburg, Germany

c. Site phone number: +49 40/42838 ext. 0

d. Does this site have an investigator?
(●) **Yes** ( ) No

Enter the investigator's or main contact's name:
Victor Mautner MD

e. Select the study procedures that will be conducted at this site:

Recruitment
Consent/Enrollment
Research observation/intervention with participants
Data collection
Data analysis

If Other, describe:

Sponsor Information

a. Sponsor:
ARMY MEDICAL RESEARCH & MATERIEL COMMAND
Previously, the following data was entered on your IRB application:

b. Sponsor Contact Information:
MCMR- AAA-R
US Dept of Defense
Office of Navel Research
Seattle regional office of reserach
300 5th ave st 710
Seattle WA- 98104

c. If the funding type is "Federal Agency, or federal flow through", provide the following information:

Grant Number:
W81XWH1210487

Grant Awardee (Institution and Investigator):
David Viskochil MD
Univeisty of Utah

Effective Start Date: 9/15/2012

Effective End Date: 9/14/2016

d. Are you working on this study with the University of Utah Office of Sponsored Projects to obtain this funding?
(●) **Yes** ( ) No

If no, please explain:

IRB_00055719 **Created:** 2/24/2012 4:00 PM

PI: David Viskochil M.D., Ph.D. **Submitted:** 2/5/2013

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)

3. Participants

1. **Ages of Participants:**
   18 and older (Consent form needed)

2. **Specific age range of participants (e.g., 7-12 years old, 60+, etc.):**
   between the ages of 25 and 40 years

3. **Indicate any vulnerable participant groups (other than children) included:**

   None

   If "Other", please specify:

   If "None" and no children are involved, answer the following question.
   Has the participant selection process overprotected potential subjects who are considered vulnerable so that they are denied opportunities to participate in research?
   ○ Yes ◉ **No**

4. **Number of participants to be enrolled during the entire study:**

   At Utah: approximately 80

   All Centers:320

5. **Characteristics of Participants / Inclusion Criteria:**

   All individuals with NF1 (neurofibromatosis type 1), based on NIH diagnostic criteria, who are between the ages of 25 and 40 years, are potentially eligible for this study. Exclusion criteria will be reviewed prior to enrollment. All eligible participants will be enrolled in the study and then screened for serum 25(OH) vitamin D levels. Individuals with levels between 9 and 29ng/ml are eligible to receive vitamin D supplementation at one of 2 doses.

6. **Participant Exclusion Criteria:**

   Individuals will be excluded from treatment for the following reasons:

   1. lack of NF1 diagnostic criteria on physical examination
   2. diagnosis of Paget's disease, hyperthyroidism, hyperparathyoroidism or other medical condition that affects bone health
   3. they foresee that they will be unable to comply with the two-year study protocol
   4. they are pregnant at the time of DXA scanning
   5. their initial screening 25(OH) vitamin D level is either equal to or over 30ng/ml (sufficient)
   6. their initial screening 25(OH) vitamin D level is either equal to or less than 8ng/ml (deficient)
   7. vitamin D supplementation in the last 6 months equal to or greater than 600IU per day
   8. oral or IV glucocorticoid use for more than 3 months
   9. bisphosphonate therapy for more than 3 months
   10. calcitonin therapy for more than 3 months
   11. calcium supplementation in last 6 months equal to or greater than 1000mg per day
   12. malignant peripheral nerve sheath tumor
   13. history of kidney stones in the last 5 years
   14. individuals with metal instrumentation in spine or hip that preclude accurate DXA interpretation.
   15. inability to obtain blood samples on routine venipuncture
   16. anti-epileptic medical therapy
   17. anticoagulant medical therapy
   18. pregnancy within the past 12 months

7. **Is a substantial percentage of the participant population anticipated to be non-English speaking?**

   ○ Yes ◉ **No**

IRB_00055719 **Created:** 2/24/2012 4:00 PM

PI: David Viskochil M.D., Ph.D. **Submitted:** 2/5/2013

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)

4. Study Information

1. **Design of Study (select all that apply):**
   Phase II Clinical Trial
   If Other, describe:

2. **Does your study involve the use of any placebo?**
   ○ Yes ◉ **No**

3. **Length of entire study, from initiation through closeout:** 4 years

4. **How will participants be recruited or identified for inclusion in the study?**

   a. **Select all methods that will be used:**
   In-person contact (e.g., patients, students, etc.)
   Written advertising (flyers, brochures, website postings, newspaper ads, etc.)
   From a database or participant pool for which participants have given prior permission to be contacted for research studies

   b. **Describe the recruitment/participant identification process in detail (e.g. who will review charts or records, who can refer participants to the study, where will flyers be posted, how often will recruitment letters be sent, when will follow-up phone calls be made, etc.):**

   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 NF1-related studies.

   Using IRB-approved advertising material (sample advertisement included at the end of this attachment), we will 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 4 participating sites, University of Utah, University of British Columbia, Hamburg University, and the University of Cincinnati will be contacted about possible enrollment.

5. **How will consent be obtained?**
   Informed Consent Process (with or without a document)

6. **Describe all the procedures chronologically, from screening/enrollment through study closeout, which will be completed in the research project.**

   Description of the 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 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 3 months to review any issues or concerns with respect to the trial. A review of the vitamin D_3 and calcium supplementation diary will be obtained and any potential side effects or adverse effects will be documented and discussed at that time.

   Enrollment and 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 serum 25(OH) vitamin D levels on all enrollees. 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 a second tube drawn for serum preparation and freezing as part of the initial sampling.

   All participants in the trial come for the initial screening, which 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 physician will verify medical history and perform brief physical examination to ensure recruits have NF1 and are eligible to participate.
   - Blood will be drawn by a trained phlebotomist. The amount of blood required is about six teaspoons (30 ml). Serum will be prepared for 25(OH) vitamin D screening performed at a central laboratory (A.R.U.P., University of Utah). Other serum studies will be performed if the enrollee is found to be eligible for the remainder of the study. These tests include parathyroid hormone and calcium. Recruits need to have been fasting for 4 hours before the blood draw.
   - After results from the initial blood test are obtained, the study coordinator will provide the participant with the result of the 25(OH) vitamin D testing. The enrollee will learn of his or her serum vitamin D level; either sufficient ($\geq$30ng/ml), very low (<8ng/ml), or insufficient. If insufficient then the enrollee will be invited to participate in the remainder of the study.

Individuals who have an adequate serum 25(OH)D level, ≥30ng/ml, will be given their results and followed in a registry. No further studies will be performed on these enrollees; however, they will be maintained in a registry with linked serum sample deposited in a tissue repository until the end of the 4-year study. Individuals who have serum 25(OH)D levels deemed to be in the osteomalacia range, <8ng/ml, will be notified so that they can discuss more extensive treatment with their primary care provider. It is expected that about two-thirds of enrollees will fit the "insufficient" category of serum vitamin D levels, thus will be eligible for the remainder of the study.

Study Protocol

At the Utah site, participants will come to the Center for Clinical Translation Sciences (CCTS) outpatient site for further studies, including a urine pregnancy test. Those who are pregnant at screening will not be included in the study, but will be included in the registry. Those who are not pregnant will enter the study and undergo simple randomization for high- versus low-dose cholecalciferol (vitamin D3) supplementation by the study monitoring group in site-specific blocks of 4 utilizing random number pre-assignments. Those who become pregnant will be removed from the supplementation and DXA scanning while remaining on the longitudinal studies until study end. Each participant will be instructed by the study coordinator at the respective sites on how to take the solution of vitamin D in the form of Ddrops. 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. DXA scanning will be performed of the spine and left hip as the primary endpoint of the clinical trial in routine fashion. Surveys will be administered and collected.

Bone densitometry (DXA scanning) is the primary outcome measure. It 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. 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.

All participants will receive US$25 for the screening test and $50 for the initial assessment and $70 for each of the remaining 2 assessment visits (at the beginning, end of 1 year, and at the last visit at 24 months). This is to partially compensate for time, parking expenses, and gas. People may also be compensated for travel, which will be discussed in advance of the initial appointment and enrollees will be notified in writing what the travel compensation will be. Participants will not be charged for the vitamin D, the calcium supplement, the blood tests, the DXA scan, or the urine pregnancy test. Participants will be notified of their serum 25(OH) vitamin D level and results of pregnancy testing; however, they will not be notified of other serum study results or DXA scan results until they have completed the 2-year study.

Participants will return to the CCTS every 6 months until the study is completed at 24 months. At each visit, the participant and clinic coordinator will review medical history and medication diary. Surveys will be performed and serum sampling will be obtained for safety studies only at the 12-month assessment visit. Vitamin Ddrops will be distributed to the participants every 6 months at these visits. The exit DXA scan will be performed at the 24-month assessment visit except for those who become pregnant while enrolled. A brief physical examination will be performed at each visit and information entered on physical examination forms. Participants, study coordinators, and investigators at each site will not know the dose of vitamin D or the results of DXA scan and intermediate serum sample results.

Serum samples from the initial blood draw will be kept in the bone repository lab for one year after the study is completed to ensure appropriate data analysis. Participants will be provided an opportunity to have their serum sample frozen and stored indefinitely for future studies by signing a seperate consent form. This is a serum sample. It will not be saved as DNA material and will not be used in such a manner in future research. The serum will be stored frozen in the Clinical Genetics Research Program under the direction of Dr. David Viskochil, and located at the University of Utah. Participants will have an opportunity to choose how they would like their sample used for future research. It can be as an anonymous sample in which only age, sex, and NF1 status is available to the investigator, or it can be linked to clinical information but remain confidential.

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 cholecalciferol 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 vit D_3 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 long-term in this facility, 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 Celsius 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 are given an option to have the remainder of their serum samples to be stored beyond the duration of the study. This is a separate consent process under University of Utah IRB #7551 (PI-Viskochil). Other sites may elect to enroll participants under separate IRB, as well. This option is provided so participants can contribute 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 (i.e. UTA110) and stored in boxes that identify the NF1-vitamin D supplementation study.

Labs Performing Evaluations and Special Precautions

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.

7. Are all procedures for research purposes only (non-standard or non-standard of care procedures)?

(•) **Yes** ( ) No

If no, list the procedures that are performed for research purposes only (non-standard or non-standard of care procedures):

8. Is there a safety monitoring plan for this study?

(•) **Yes** ( ) No

9. Provide a summary of the statistical methods, data analysis, or data interpretation planned for this study. Factors for determining the proposed sample size (e.g., power) should be stated.

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. Preliminary data showed a mean change in the hip T-score of about -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 and 4,000 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. The mean difference in the hip T-score between the treated and untreated groups in the pilot study 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 (See table below). 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.

Table: 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

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 maintain their BMD, or at least to show less loss. The primary metric used to assess BMD in this analysis is the mean change in hip Z-score/year, and the two groups will be compared using analysis of variance with participating center and sex as covariates. Confirmatory analyses will also be performed comparing the change in lumbar Z-score/year, change in hip BMD/year, and change in lumbar BMD/year between the two treatment groups.

Descriptive univariate analyses (t-tests, X^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, activity and UV exposure questionnaires 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.

IRB_00055719 **Created:** 2/24/2012 4:00 PM

PI: David Viskochil M.D., Ph.D. **Submitted:** 2/5/2013

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)

Consent Process

1. **The following investigators and internal staff will obtain consent (as indicated on the Contacts and Title Page):**

   Heather Hanson
   David Stevenson
   David Viskochil

   List by name, role, and affiliation any others who will obtain consent (e.g. Dr. John Smith, Co-Investigator, etc.).

2. **Describe the location(s) where consent will be obtained.**
   Consent will be obtained at clinical trial research-designated areas at each facility. At the University of Utah, consent will be obtained in the CCTS outpatient facility.

3. **Describe the consent process(es), including the timing of consent. Describe whether there is a waiting period between the consent process and obtaining consent from the participant (i.e., any time between informing participants and actually obtaining consent).**
   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 3 months 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.

4. **Describe what measures will be taken to minimize the possibility of coercion or undue influence.**
   All potential study participants will be adults who are competent to understand the study and sign consent on their own behalf.

5. **Describe the provisions that are made to allow adequate time to exchange information and questions between the investigator and participant.**
   Each subject will have at least one week to decide whether or not they wish to participate.

6. **Will a legally authorized representative (LAR) be used?**

   ○ Yes ◉ **No**

   If yes, describe when the use of an LAR might arise in this study population and what the frequency of an LAR will be during the enrollment period.

7. **Will a language other than English be used to obtain consent?**
   ○ Yes ◉ **No**

   If yes, complete the following:

   a. **Please indicate which form will be used:**

      If using the short form, please provide justification for why a full, translated consent document will not be used:

   b. **Describe whether translation services will be used for the consent process and how the consent process will be conducted?**

8. **Are you requesting that documentation of informed consent be waived by the IRB (a consent process in place, but no documentation of consent, e.g. questionnaire cover letter, web-based consent, consent without signature, etc.)?**
   ○ Yes ◉ **No**

   If yes, complete the following:

   a. **Explain why the waiver of consent documentation is being requested.**

   b. **Justification for the waiver is one of the following:**
      There are no items to display

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5. Data Monitoring Plan

1. **Privacy Protections:** Privacy refers to persons and to their interest in controlling access of others to themselves. Privacy can be defined in terms of having control over the extent, timing and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. **What precautions will be used to ensure subject privacy is protected?**

   Select all that apply:

   The research intervention is conducted in a private place

   Discussing the study with participants individually instead of in front of a group

   The collection of information about participants is limited to the amount necessary to achieve the aims of the research, so that no unneeded information is being collected

   Other or additional details (specify):

2. **Confidentiality Precautions:** Confidentiality is an extension of the concept of privacy; it refers to the subject's understanding of, and agreement to, the ways identifiable information will be stored and shared. Identifiable information can be printed information, electronic information or visual information such as photographs. **What precautions will be used to maintain the confidentiality of identifiable information?**

   Select all that apply:

   Storing research data on password protected computers or in locked cabinets or offices

   Other or additional details (specify):

3. **Will photos, audio recordings, or video recordings, or medical images of participants be made during the study?**

   ○ Yes ◉ **No**

   If yes, describe the recording/images and what will become of them after creation (e.g., shown at scientific meetings, stored in the medical/research record, transcribed, erased, etc.):

4. **How will study data and documentation be monitored throughout the study?**

   Select all that apply:

   Periodic review and confirmation of participant eligibility

   Periodic review of informed consent documentation

   Periodic review of the transfer/transcription of data from the original source to the research record

   Confirmation that all appropriate information has been reported to the sponsor, oversight agencies (such as the FDA), and/or IRB

   Other or additional details (specify):

   Other additional details (specify):
   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 and the data monitoring site in the Pediatric Clinical Trials Office at the University of Utah. Investigative teams at each site have full access to data collected from participants enrolled through their respective site. There is limited access to data collected from other centers. Only the data monitor, Dr. Spigarelli, and database manager, Mr. LaSalle, have full access to data collected from this study.

   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.

5. **Who will be the primary monitor of the study data and documentation?**

   Select all that apply:

   Principal Investigator

   Study Coordinator or Research Nurse

   Study Monitor or Contract Research Organization (CRO)

   Data (and safety) Monitoring Board or Committee

   Other or additional details (specify):
   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 in the Informatics Core in the CCTS in the University of Utah is 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.

6. How often is study data and documentation monitoring planned (e.g., monthly, twice a year, annually, after N participants are enrolled, etc.)?

The study monitor will be assessing enrollment and data flow on a weekly basis. As data accumulates it will be documented on a weekly basis. Data analysis will not begin until after exit bone densitomitry scans have been completed on 50 participants. The purpose for interim review is to determine if the higher dose of vitamin D is less safe than the lower dose.

IRB_00055719 **Created:** 2/24/2012 4:00 PM

PI: David Viskochil M.D., Ph.D. **Submitted:** 2/5/2013

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)

Safety Monitoring Plan

1. **Describe the safety monitoring entity for this study:**

   a. **Select all that apply:**

   Principal Investigator

   Safety Monitor

   Other (specify):

   Please specify:
   The medical monitor will also play a role in safety monitoring by receiving and reviewing all adverse events from each of the 4 sites. The medical monitoring team will provide a list to the safety monitor for review every 6 months. Serious adverse events are communicated from the medical monitor (Pediatric Clinical Trials Office) directly to the PI, David Viskochil, and the study coordinators and PIs at the other 3 sites in addition to notifying the safety monitor in the CCTS, the Department of Defense human subjects research committee, and the FDA.

   b. **Describe the expertise and affiliation of the individual(s) selected above who will monitor the study:**

   David Viskochil is the PI of the study from the University of Utah. He is familiar with potential medical complications of NF1 that may arise as part of the natural history of the disease rather than as result of the vitamin D supplementation. He will work with the safety monitor in assessing if an event is study related versus NF1 related.

   CCTS-approved studies have access to a safety monitor for minimal to low risk studies. This individual will serve as the external medical safety monitor to review adverse events at the University of Utah. He will also review adverse event forms collected and forwarded through the medical and data monitor in the Pediatric Clinical Trials Office under the direction of one of the co-investigators, Dr. Michael Spigarelli. Presently, Dr. Richard Kanner serves as the Research Compliance Officer of the Center for Clinical & Translational Sciences at the University of Utah, and we are requesting his services in the CCTS application form attached to this IRB submission.

   The Medical Monitor is provided under the Pediatric Clinical Trials Office under the directorship of Dr. Michael Spigarelli, who is one of the co-investigators of the study. His role is to oversee data collection, compliance of the 4 sites with timely submission of CRFs, and randomization and distribution of the vitamin D in the form of Ddrops. This office will monitor the data collection, serum collection, and adverse events. The office will not analyze the data, but will communicate with the PIs and study coordinators at each site, the safety monitor, and the FDA regarding serious adverse events and other safety issues.

2. **Describe the data and events that will be monitored and reviewed (e.g., vital signs, safety blood labs, depression scales, neurological exams, types of adverse events, etc.):**

   The PI from each participating institution will provide the Medical Monitor at the University of Utah Pediatric Clinical Trials Office with a copy of the initial IRB protocol approval and the yearly IRB continuing reviews. The Medical Monitor will also submit these to the USAMRMC ORP HRPO human subjects research oversight committee. Registration will be halted at a participating institution if a current continuing approval is not on file at the Medical Monitor office. 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. As an IND study, communication from the Medical Monitor will, by way of annual report and serious adverse event reporting, be transmitted to the FDA.

   Data collected from each participating site includes multiple CRFs with vital signs, growth parameters, physical examination with a focus on NF1-related features, labs (25-OH vitamin D, calcium, iPTH), DXA scans, surveys, documentation of diary review for study drug ingestion, and adverse events. These CRFs collections will be documented and study coordinators notified of lack of compliance in timely submission of CRFs for each participant over the duration of the 2 year study.

   A safety analysis will be performed at the time of the initial serum vit D, calcium and iPTH, DXA scan, and the individual diary and clinical assessments. 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 a BMD in the osteoporosis category warrants notification of the participant's self-identified primary care provider via the study coordinator or PI at the respective enrollment site. The Medical Monitoring team will review the entry serum 25(OH) vitamin D levels. He will notify the participating center within 1 month of enrollment of any serum vitamin D levels below 8 ng/mL, and these subjects will not initiate the study protocol. They will be referred for evaluation and treatment of vitamin D deficiency. The intial DXA scans will be reviewed by the study monitor team before the initiation of vitamin D (Ddrops), and those deemed to have osteoporosis will be notified and referred to their primary care provider for initiation of clinical intervention. Such participants will not receive vitamin D supplementation, and they will be followed locally through the remainder of the 2-year study. A second safety analysis will be performed on serum samples provided at the 12 month assessment visit to ensure that calcium, phosporus, and/or iPTH levels are maintained in the normal range. The final safety analysis will be conducted on the final visit, at which time participants are notified of all the values of data collected over the duration of the 2-year study.

   Participants will be clinically monitored for signs and symptoms of hypercalcemia throughout the trial period by diary review, medical history, review of systems, and serum calcium levels 1 year after the onset of vitamin D therapy.

   All observed or volunteered adverse events, regardless of suspected causal relationship to study drug, will be recorded as Adverse Events in the 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 would disallow continued participation in the protocol, and participant would be unblinded. Unblinding will be accomplished by having the site principal investigator contact Dr. Spigarelli who will provide the study arm assignment (low or high dose) for the withdrawn participant. For participants that have not been withdrawn from the protocol, determination regarding unblinding will be decided by Dr. Spigarelli based upon the specifics of the request.

   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 in accordance with the Common Terminology Criteria for Adverse Event (CTCAE) version 3.0

(http://ctep.info.nih.gov).

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

3. Describe the types of reports that will be produced by the monitoring entity (e.g., safety, study progress, interim analysis, etc.):

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

Adverse event forms will be collected by the study monitor and reviewed every 6 months by the safety monitor. Serious adverse event forms will be collected by the study monitor and the safety monitor will be alerted to review on a case by case basis. A report by the safety monitor will allert the investigators of each of the 4 sites that a serious adverse event occured and a formal report stating if it is related to study drug and if it is either an expected or unexpected event. The safety monitor will make a written recommendation to each site PI on how best to proceed with the study. An annual report of all adverse events will be compiled by the safety monitor, and this will be incorporated into an annual report for the FDA and Department of Defense.

4. Describe the specific triggers or stopping rules for the study:

a. Under what conditions will a participant be withdrawn from the study?

Severe Adverse Event (SAE) with sufficient severity to require that the subject should be removed from treatment and or a subject who voluntarily withdraws.

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. 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.

There are 3 instances where participants will receive information based on their enrollment in the study:

1) 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.

2) There is an assessment of the DXA scan to identify those who have clinically treatable osteoporosis. If so, their primary care provider may need to intervene.

3) An interim serum calcium level at 1 year may indicate hypercalcemia, regardless of dosing. Without breaking the double blind dosing, the study sites will be notified to assess for signs and symptoms of hypercalcemia and the primary care provider notified that additional surveillance for hypercalcemia may be indicated. These 3 results may determine long-term care management for some participants.

b. Under what conditions will the study be modified or stopped?

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 their 2-year assessment and again when 100 participants have completed their 2-year 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 ($p<0.01$) at either of these points. This report will be provided each of the participating sites, the FDA for IND monitoring purposes, and the Department of Defense as the funding agency with oversight of the study.

5. How often will the data and events be reviewed by the monitoring entity (e.g., after every 5 submits, monthly, quarterly, twice a year, etc.)?

The safety monitor will review non-severe adverse events semi-annually and SAEs as they arise.

Data accummulation will be monitored weekly and reviewed monthly for a timely report to the PIs at each site regarding patient accrual, number of adverse events, and data acquisition. The study monitor will be responsible for these functions and perform the interim data analysis. The risk of this study is relatively low, but tracking of enrollment, randomization and data acquisition from 4 sites will require consistent monitoring.

IRB_00055719 **Created:** 2/24/2012 4:00 PM

PI: David Viskochil M.D., Ph.D. **Submitted:** 2/5/2013

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)

6. Risks and Benefits

1. Describe the reasonable foreseeable risks or discomforts to the participants:

There is a risk for vitamin D toxicity with over-supplementation; however, it is highly unlikely that treating with 4000IU vitamin D_3/day (the higher dose in this clinical trial) will cause toxicity. In comparison to the amount of vitamin D manufactured in the skin of a young adult, the treatment dose is small. For example, the equivalent dose 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.

Vitamin D_3 overdose can be detected by signs and symptoms of hypercalcemia. Study participants will be counseled 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 D_3 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.

Side affects from use of vitamin D in this trial are not anticipated; however, 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 counseled to keep the vitamin D_3 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. Calcitonin promotes calcium uptake in bone, and is could be used in those patients with severe hyperparathyroidism. Corticosteroids may also be given.

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. Pregnancy tests will be obtained on all women prior to DXA and participants who are pregnant will be excluded.

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

2. Describe the potential benefits to society AND to participants (do not include compensation):

Potential Benefits

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

Participants may benefit from improved bone mineral density (BMD), awareness of their BMD status, and documentation of a baseline BMD. We anticipate that some subjects may have improved BMD after treatment with vitamin D_3 and the anticipated rate of decline in BMD may be diminished or reversed in other participants. 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.

3. Are there any costs to the participants from participation in research?

○ Yes ◉ **No**

If yes, specify:

4. Is there any compensation to the participants?

◉ **Yes** ○ No

a. If yes, answer the following:
Specify overall amount:
enrollment: Initial enrollment = $25
study visit 1: DXA scan/surveys = $50
study visit 2: surveys/safety assessment = $70
exit visit: DXA scan/surveys/safety assessment = $70
total = $215

b. Specify when participants will be paid (e.g. at each visit, at end of study, etc.):

Payment will be mailed after visit.

c. If applicable, please specify payment by visit or other time interval (e.g. $10 per visit, etc.):
enrollment: Initial enrollment = $25
study visit 1: DXA scan/surveys = $50
study visit 2: surveys/safety assessment = $70
exit visit: DXA scan/surveys/safety assessment = $70

d. If applicable, explain plan for prorating payments if participant does not complete the study:
Payment per visit, no prorating of payments.

IRB_00055719 **Created:** 2/24/2012 4:00 PM

PI: David Viskochil M.D., Ph.D. **Submitted:** 2/5/2013

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)

7. HIPAA and the Covered Entity

1. **Does this study involve Protected Health Information (PHI) or de-identified health information?**

   (●) **Yes** ( ) No

   a. **If yes, select the method(s) of authorization that will be used:**
   (Consent and) Authorization Document

   If needed, select De-Identification Form:

   b. **If yes, will PHI be disclosed outside the Covered Entity?**
   (●) **Yes** ( ) No

   If so, to whom? Army Medical Research and Materiel Command; Food and Drug Administration

   And for what purposes?
   Army Medical Research and Materiel Command- as funding agency with human subjects research oversight this agency may request specific information on subject(s) for issues related to conduct of the trial and safety issues.

   FDA - may request to review PHI specifically for issues related to the investigational drug and safety monitoring

2. **Does this study involve any of the following:**

   a. **The investigational use of a drug?**
   (●) **Yes** ( ) No

   b. **The investigational use of a medical device?**
   ( ) Yes (●) **No**

   c. **Is this an investigator-initiated drug or device trial lead by the Principal Investigator?**
   (●) **Yes** ( ) No

   d. **Exposure to radioisotopes or ionizing radiation?**
   (●) **Yes** ( ) No

   e. **Does the study involve cancer patients and address a cancer question?**
   ( ) Yes (●) **No**

   f. **Obtaining data or information from the UUHSC Enterprise Data Warehouse (EDW) in a query outside of the Utah Population Database (UPDB)?**
   ( ) Yes (●) **No**

   g. **Any component of the Center for Clinical and Translational Science (CCTS)?**
   (●) **Yes** ( ) No

   The Clinical Services Core (CSC)?
   (●) **Yes** ( ) No

   h. **A Humanitarian Device Exemption (HDE)?**
   ( ) Yes (●) **No**

   i. **Creating or sending samples to a tissue bank/repository?**
   ( ) Yes (●) **No**

   j. **The use of human subjects and biological agents (e.g., staphylococcus aureus, adenovirus), or the deliberate transfer of recombinant DNA vectors/plasmids (recombinant DNA, or DNA or RNA derived from recombinant DNA) into human research participants?**
   ( ) Yes (●) **No**

IRB_00055719 **Created:** 2/24/2012 4:00 PM

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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)

Investigational Use of a Drug

#1: Complete this column if an investigational new drug (IND) number is required.

A. Provide IND Number(s):

IND #	Drug name	IND Holder
119135	Cholecalciferol	David Viskochil M.D.,PhD.

B. Attach verification of the IND number to the documents and attachments page. Please check the method by which you choose to verify the IND number:

FDA letter (this is the actual letter sent to the holder of the IND with the number)

You must:

- *Attach a copy of the Investigator Brochure or product insert to the documents and attachments page under the respective section.*
- *Attach a copy of the FDA Form 1572 to the documents and attachments page under Other Documents.*
- *Agree to the statement of compliance below.*

#2: Complete this column if you believe an IND is not required.

A: Drug name:

B. Select one:

C. Check all of the following that that apply:

There are no items to display

If all six of the above criteria are checked:

- *Attach a copy of the product insert to the documents and attachments page.*
- *Agree to the statement of compliance below.*
- *Please note: The convened board may still require an IND.*

Statement of Compliance

The use of investigational drugs in facilities covered by the University of Utah IRB must follow the policies and procedures of the facility in which the drug(s) will be administered and/or dispensed.

University of Utah Hospitals

If you are conducting inpatient research at the University Health Center or Huntsman Cancer Hospital, please review the Department of Pharmacy Policies and Procedures and contact the appropriate investigational pharmacist listed below.
University Health Center - **(801)585-2185**
Huntsman Cancer Hospital, **(801)585-0272**

Primary Children's Hospital

If you are conducting inpatient or outpatient research at Primary Children's Hospital, please contact the investigational pharmacist at the number listed below:
Primary Children's Hospital - **(801)662-2655**

Veteran Affairs Medical Center

If you are conducting inpatient or outpatient research at the VA, please contact the investigational pharmacist at the number listed below:
Veteran Affairs Medical Center - **(801)582-1565 ext. 1454**

The PI must agree to the Statement of Assurance when the PI uses the "Submit" activity to submit the application for IRB review. In the "Submit" activity window, a checkbox to accept this Statement of Assurance will be available. By checking the box, the PI agrees to the following:

- I have read and I understand the above information provided.
- I have reviewed the appropriate policies and procedures and/or have contacted the appropriate investigational pharmacist for my research involving an investigational agent.
- I understand the requirements regarding the distribution, storage, and control of investigational agent(s) for research purposes.

IRB_00055719 **Created:** 2/24/2012 4:00 PM

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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)

Investigational Drug Data Form

	Drug Name	Drug Accountability	Drug Supply Location
View	Cholecalciferol	Cholecalciferol in vials will be shipped from the D-drops Company to the medical monitor at the Pediatric Clinical Trials Office. The vials will have equal volume and come in a concentration of either 600IU per drop or 4,000IU per drop. The vial labels will be removed and identified by a random number that blinds the participant and local study team as to which dose each participant is designated to receive. The study vials will be shipped to the respective sites directly from the medical monitor to the study coordinator/PI of that site. The coordinator will distribute the appropire vial to the participant accoring to a randomization process.	D-drops Company -501 Rowntree Dairy Road, Unit 3, Woodbridge, ON L4L 8H1 - phone: 905 851-8889. Received by the medical monitor at the University of Utah Pediatric Clinical Trials Office then shipped to each of the 4 sites; UBC, UC, UHamburg, and U of Utah study coordination sites.

Investigational Drug Data Form

1. **Name of Investigational Drug:** Cholecalciferol

2. **Synonyms:**
Vitamin D- liquid

3. **Manufacturer or Other Source:** TUMS

4. **Other Study Drugs:**
A calcium supplement like TUMS at 1,000 mg per day (400 mg elemental calcium), but this is not a study drug, only a supplement. Calcium is routinely given in clinical practice to those who are insufficient in serum 25(OH) vitamin D.

5. **Type of Study (Blinding Information):**
Blinded

6. **Strength(s) and Dosage Form(s):**
600 IU and 4000 IU

7. **Indications for Use and Pharmacology:**
Anabolic bone remodeling by increasing absorption of calcium and phosphorus, decreasing excretion of calcium and phosphorus, and enhancing bone remodeling. 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. 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.

8. **Possible Side-Effects / Adverse Reactions:**
None expected. However, if there was an overdose symptoms may include:

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.

9. **Drug Administration Information**

   a. **Usual Therapeutic Dose:**
   Variable; usually between 400IU and 4,000IU per day; or 50,000IU one time dose.

   b. **Dosage Range:**
   Usual and routine dosage range is recommended between 400IU to 4,000IU per day. However, no recommendations are available for individuals with NF1.

   c. **Therapeutic Blood Levels:**
   >29ng/ml serum 25(OH) vitamin D

   d. **Route of Administration:**
   Oral or sunlight. Vitamin supplementation is provided by oral route, but subcutaneous injection is used if an individual is found to be deficient in thier level of 25(OH)vitamin D.

   e. **Rate of Administration for IV Infusion or Push:**
   N/A

   f. **Reconstitution Directions (include stability info):**
   Stable as a liquid.

   g. **Precautions and Special Instructions for Administration:**
   None- take as prescribed 2 drops a day. Subjects will be instructed that if they forget a day, they may take the dose on the next day (4 drops in total, instead of two).

   h. **Toxicology and Antidote:**
   N/A

10. **Describe the plan to control, store, and dispense the investigational drug. This plan should ensure that the drug is only used by qualified investigator(s) for the participants enrolled in this research project.**
Cholecalciferol in vials will be shipped from the D-drops Company to the medical monitor at the Pediatric Clinical Trials Office. The vials will have equal volume and come in a concentration of either 600IU per drop or 4,000IU per drop. The vial labels will be removed and identified by a random number that blinds the participant and local study team as to which dose each participant is designated to receive. The study vials will be

shipped to the respective sites directly from the medical monitor to the study coordinator/PI of that site. The coordinator will distribute the appropire vial to the participant accoring to a randomization process.

11. **Location of Drug Supply:**
D-drops Company -501 Rowntree Dairy Road, Unit 3, Woodbridge, ON L4L 8H1 -phone: 905 851-8889. Received by the medical monitor at the University of Utah Pediatric Clinical Trials Office then shipped to each of the 4 sites; UBC, UC, UHamburg, and U of Utah study coordination sites.

12. **Storage Requirements:**

Room Temperature

Protect from Light

Do Not Freeze

If Other, Please Explain:

13. **Emergency Drug Information (include name and phone number):**
Emergency Department at the University of Utah 801-581-2121 or Dr. David Viskochil at 801-581-8943

IRB_00055719 **Created:** 2/24/2012 4:00 PM

PI: David Viskochil M.D., Ph.D. **Submitted:** 2/5/2013

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)

8. Resources and Responsibilities

1. **State and justify the qualifications of the study staff:**

   Dr. Viskochil or a Co-I of this study will identify potential study particiapnts and refer to a clinical coordinator for enrollment. Coordinators will review the study in it's entirty with potential participants, consent and process samples.

   Dr. Michael Spigarelli is the designated study monitor, and he and his team at the University of Utah are well-qualified to monitor patient acruel, randomization, data acquisition, and recognize safety issues related to serum 25(OH) vitamin D deficiency, osteoporosis on DXA scan, and hypercalcemia.

2. **Describe the training that study staff and investigators will receive in order to be informed about the protocol and understand their research-related duties and functions:**

   No special training sessions for patients or clinicl personnel are required for this straightforward protcol. Training by conference call will take place after all IRB notifications of approval are obtained from each of the 4 sites. Regular conference calls will held to discuss the study, progress and any concerns. Dr. Viskochil and the lead coordinator will ensure through emails and training that each staff member at each center is ready to consent or enroll any participants.

3. **Describe the facilities to be used for the research activities (e.g. hospitals, clinics, laboratories, classrooms/schools, offices, tissue banks, etc.):**
   CCTS (Center for Clinical and Translational Science)
   ARUP
   PCTO (Pediatrics Clinical Trials Office)

4. **Describe the medical or psychological resources available at this site (and other participating sites, if applicable) that participants might require as a consequence of the research. If not applicable, please state.**
   N/A

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Documents and Attachments

If any of your documents (such as investigational brochures, sponsor protocols, advertisements, etc.) are not available in an electronic format, please scan and save them as PDF files or contact our office for assistance.

Naming Documents: Please use the title field to clearly indicate the content of each form. The name you enter will be listed on your approval letter. Use names that will differentiate from earlier versions.

Examples:
Consent Document Control Group 04/14/05
Consent Document Treatment Group 4/14/05
Sponsor Protocol 04/14/05 Version 2
Assent Document (Highlighted Changes)

Apple/Macintosh Users: MS Word documents must have a .doc file extension. See ERICA home page for instructions.

Print View: IRB Draft Protocol Summary

eProtocol Summary:

Name	Version	Date Created	Date Modified
There are no items to display			

Consent Documents, Consent Cover Letters, Consent Information Sheets, Consent Scripts, etc.:

Name	Version	Date Created	Date Modified
There are no items to display			

Parental Permission Documents:

Name	Version	Date Created	Date Modified
There are no items to display			

Assent Documents:

Name	Version	Date Created	Date Modified
There are no items to display			

VA Consent Documents:

Name	Version	Date Created	Date Modified
There are no items to display			

Surveys, Questionnaires, Interview Scripts, etc.:

Name	Version	Date Created	Date Modified
There are no items to display			

Full Protocol (company protocol, sponsor protocol, investigator-initiated protocol, etc.):

Name	Version	Date Created	Date Modified
There are no items to display			

Investigational Brochure (IB) for Investigational Drug or Drug/Device Package Insert:

Name	Version	Date Created	Date Modified
There are no items to display			

Grant Application:

Name	Version	Date Created	Date Modified
There are no items to display			

Literature Cited/References:

Name	Version	Date Created	Date Modified
There are no items to display			

Principal Investigator's Scholarly Record (CV/Resume):

Name	Version	Date Created	Date Modified
D. VIskochil Biosketch 2013	0.01	9/20/2013 1:18 PM	9/20/2013 1:18 PM

Faculty Sponsor's Scholarly Record (CV/Resume):

Name	Version	Date Created	Date Modified
There are no items to display			

Other Stamped Documents:

Only attach documents here as directed by the IRB, such as the Data/Information Request Form for UUHSC EDW.

Name	Version	Date Created	Date Modified
There are no items to display			

Recruitment Materials, Advertisements, etc.:

Name	Version	Date Created	Date Modified
There are no items to display			

Other Documents:

Name	Version	Date Created	Date Modified
There are no items to display			

IRB_00055719 **Created:** 2/24/2012 4:00 PM

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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)

Ancillary Application

This page should be used for submitting human research applications to the following ancillary committees:

Resource for Genetic Epidemiology (RGE) for the use of the Utah Population Database (UPDB)
Phone: 801-581-6351
Website: http://www.research.utah.edu/rge/index.html

Radiological Drug Research Committee Human Use Subcommittee (RDRC-HUS)
Phone: 801-581-6141
Website: http://www.rso.utah.edu/policies/RDRC.pdf

ID	Name	Date Submitted	Status
HUS_00003374	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)		Approved

The University of Utah
Center for Clinical and Translational Science

Center for Clinical and Translational Science (CCTS) Clinical Services Core Application Questions

The Clinical Services Core, located on the fifth floor of the University of Utah Medical Center, serves as the CCTS venue for inpatient and outpatient human subjects studies. You have indicated plans for use of the Clinical Services Core (CSC). Your application will be reviewed by, and must be approved by both the IRB and the CCTS before you may begin the study. In addition to human subject safety and risk, the CCTS will evaluate and score your protocol on scientific merit, feasibility, statistical rigor, likely academic benefit to the institution and investigator, and utilization of CCTS resources. Please assure that your protocol description adequately addresses these aspects, and provides sufficient background to allow reviewers to understand the research question to be studied. We encourage you to consult with the CCTS Biostatistician, Dr. Richard Holubkov (801-587-3326) regarding the statistical methods and data analysis for this study.

For detailed information regarding this application and the process for review and approval of CSC protocols, please refer to the CCTS website. In addition, you may contact the CCTS:

University of Utah Center for Clinical and Translational Science
Phone: (801) 581-6736
Fax: (801) 585-1461
Website: http://www.ccts.utah.edu/
Administrative Contact: Lynette Holman

Principal Investigator: David Viskochil

Department: PEDIATRICS

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)

The CCTS review committee will evaluate each of the components of the IRB application. In addition to these application elements, please complete the following questions to apply for use of the CSC.

Study Information Required by NIH

1. **Provide the NIH eRA Commons User Name for the PI.**

   Principal Investigator's eRA Commons User Name: David Viskochil

   Sub-Investigator(s):

Name	eRA Commons User Name
Heather Hanson	
Bernie LaSalle	
Michael Spigarelli	MICHAELSPIGARELLI
David Stevenson	
David Viskochil	David Viskochil

2. **Will subjects in your study require overnight admission to the Clinical Services Core nursing unit?**
   ○ Yes ◉ **No**

3. *The NIH has established formal policies concerning the inclusion of women, minorities and children in research study populations. A copy of the NIH publication addressing this topic is available in the CCTS office and on the CCTS website (www.ccts.utah.edu/interact). These guidelines are to be applied to all CCTS supported research protocols.*

   Are women and minorities included in the proposed research?
   ◉ **Yes** ○ No

   If no, provide justification for the exclusion of women and minorities.

   Will your research include children?
   ○ Yes ◉ **No**

   If no, provide justification for the exclusion of children.
   Recruitment age range is 25-40 years. The selected population has the most consistent levels of bone mineral density loss.

Services and Support Offered by the CCTS

NIH and University support to the Utah CCTS allows the CSC to partially subsidize services provided to CSC Investigators, including inpatient and outpatient room time, access to specialized facilities such as endoscopy, electro-diagnostic studies, body composition measurement, nutritional support and preparation of DNA and protein samples. Pharmaceutical trials pay the full cost of CSC services, while subsidies to other studies are provided based on a CCTS review process that takes into account the source of study funding and institutional goals of the CCTS. As a preliminary step to determining this subsidy, the CCTS staff will meet with each applicant to assess the time and nursing effort necessary for their protocol. **This face-to-face needs assessment must be completed before the protocol can be considered by the CCTS.** Please contact the CSC Nurse Manager, Deanna Palma, at 801-581-2224 to schedule this effort assessment meeting.

Investigators seeking grant support from extramural funding agencies (e.g. NIH, American Heart Association) will need to meet prior to submitting their grant proposal. CCTS staff will write a letter of support, to be included with the proposal, which will outline expected CSC effort and subsidy to the protocol should funding be secured and the protocol accepted for CSC performance.

4. **The following funding sources or sponsor(s) is/are indicated in the IRB application:**

Sponsor	Sponsor Type	Sponsor Contact Information
ARMY MEDICAL RESEARCH & MATERIEL COMMAND	Federal Government	MCMR- AAA-R US Dept of Defense Office of Navel Research Seattle regional office of reserach 300 5th ave st 710 Seattle WA- 98104

Select any *additional funding* you intend to seek, other than the funding already indicated in the IRB application. If no secured funding is indicated in the IRB application, select any funding you intend to seek:

Select all that apply:

No funding source

If Other:

5. **Please provide a brief (2 or 3 sentence) description of CSC evaluation space, nursing effort and procedural services your protocol will require. Please refer to www.ccts.utah.edu/interact for a list of Nursing and Procedural Services available through the CSC.**
   1-No nursing effort needed.
   2-Will require evaluation space for 2 hours per visit and DXA room for scanning at inital and close out visits.
   3-Saftey monitor - Richard Kanner
   4-Database support- Bernie Lasallie

6. **Will your protocol require nursing services outside of the CSC space (for example, scattered nursing at Primary Children's Medical Center)?**
   ○ Yes ◉ **No**

   If so, please briefly describe.

7. **Will nutritional support or body composition measurements be needed?**
   ○ Yes ◉ **No**

   If yes, please describe the needs:

   Please contact the CSC research Nutritionist, Kitiya Suvannasankha with any questions, 801-581-7665.

8. **Will any of the following services or support be requested from the CCTS Translational Technology Resources Core? (you may check one or more options)**

   There are no items to display

   If Other:

   If you indicated yes for one or more services, please answer the following questions for each services:

   a. **For how many subjects will this service be required?**
      N/A

   b. **What is the estimated number of samples that will be collected for this purpose?**
      N/A

   c. **Where will the resulting DNA be stored?**
      N/A

   d. **If multiple Investigators or entities may claim these samples, how will their ownership be determined?**
      N/A

   e. **What is the justification for the requested services/support?** (Note that under rare circumstances, DNA samples absolutely require lymphocyte transformation as opposed to simple DNA isolation; e.g. patients with terminal cancer, from whom additional blood samples could not subsequently be obtained in the event that isolated DNA samples was exhausted).
      N/A

   Please contact the Translational Technology Resources Core Director, Dr. Sayed Ahmed at 801-581-6736 with questions or concerns regarding DNA or protein isolation.

Additional required components of the CSC application

- As a PDF attachment to the IRB application, provide a brief "Executive Summary" of the consent document, summarizing the study and highlighting primary risks to be shared with subjects during the consent process. An Executive Summary template and examples are provided on the CCTS website.
- Please assure that your consent document includes the NIH "Reporting Race and Ethnicity Data" page. This form is required by NIH for all protocols performed on the CSC online at http://grants.nih.gov/grants/funding/women_min/race_ethnicity_qa.htm.
- **If your study involves the use of an investigational drug**, you must contact the Investigation Drug Services Pharmacist, Winter Reed (801-585-2185 or UIDS@hsc.utah.edu) to schedule an appointment to review your research pharmacy needs. An agreement with Investigational Pharmacy will be necessary before your study can be performed on the CSC.

IRB_00055719 **Created:** 2/24/2012 4:00 PM

PI: David Viskochil M.D., Ph.D. **Submitted:** 2/5/2013

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)

Finish Instructions

Finish Instructions

1. **To view errors, select the "Hide/Show Errors" option at the top or bottom of the page. If you have errors on your application, you won't be able to submit it to the IRB.**
2. **Selecting the Finish button will NOT submit the application to the IRB.**
   You MUST select the "Submit" option on the workspace once you've selected the "Finish" button.
3. **If your study has a faculty sponsor: Once the PI submits the application, it will be sent to the faculty sponsor for final approval. The IRB cannot review the study until the faculty sponsor submits the application to the IRB.**

IRB_00055719 **Created:** 2/24/2012 4:00 PM

PI: David Viskochil M.D., Ph.D. **Submitted:** 2/5/2013

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)

uTRAC

University TRAcking of Clinical research (uTRAC)

All prospective clinical research studies conducted at the University of Utah must complete a uTRAC application prior to IRB approval and the initiation of research procedures. Based on the responses provided in your IRB application, a uTRAC application is necessary for this study.

For more information about uTRAC and the requirements, please contact the Clinical Research Compliance and Education (CRCE) Office at:
Phone: 801-213-3601
Email: utrac-support@umail.utah.edu
Website: http://healthsciences.utah.edu/crce

If you do not have a uTRAC account, please have your department's account requestor request one. If you are unable to locate an account requestor please contact uTRAC support utrac-support@umail.utah.edu.

Instructions:

1. **If you have already created a uTRAC application, click the Select button below to link the trial to the ERICA application.**
2. **If your study has been given an exemption from the CRCE office, please attach it where indicated below.**

Clinical Trials:

Link	PI	Title	uTRAC Status
FP00002709	Viskochil	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)	Draft

CRCE Exemption Attachments:

Name	Version	Date Created	Date Modified
There are no items to display			

Consent and Authorization Document

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)

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.

- Your initial blood test will be drawn by a trained technologist. If you live more than 100 kilometers (60 miles) from the study center then your blood draw will be arranged by the study coordinator. Otherwise, you will come to your respective study center for the blood draw. The amount of blood required is about 3 teaspoons (15ml). The initial blood sample is to test your serum vitamin D level. Other serum studies will be performed if you are eligible for the second part of the study, and these include parathyroid hormone (a measure of bone metabolism) and calcium. You need to be fasting for 4 hours before the blood draw.

- 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 ($\geq$30ng/ml), 2) deficient (<8ng/ml), or 3) insufficient ($\geq$8 but <30 ng/ml). If you are in the insufficient range you will be invited to participate in the vitamin D/bone densitometry part of the study. We expect that about two-thirds of people will have insufficient vitamin D levels and thus be eligible for the full study. If you are in the sufficient range of vitamin D you will be offered ongoing follow-up in this study for fractures and quality of life for at least 2 years. If you are in the deficient range of vitamin D you will be referred to your personal physician for management and you will be offered follow-up in this study for fractures and quality of life for at least 2 years.

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.

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

CLINICAL TRIAL

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. You will take one measured drop every day. 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 6 months. At the end of that time, we will provide a new bottle with the same dose 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 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.

RISKS
WHAT ARE THE POSSIBLE HARMS AND SIDE EFFECTS OF PARTICIPATING?

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

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. 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

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.

CONFIDENTIALITY

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

Your confidentiality will be respected. No information that discloses your identity will be released or published. 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.

PERSON TO CONTACT

WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY?

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 clinical research coordinator, Heather Hanson, at 801-587-9017. The principal I 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

WHAT HAPPENS IF SOMETHING GOES WRONG?

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.

UNFORESEEEABLE 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 is this research from a DXA scan.

COSTS AND COMPENSATION TO PARTICIPANTS

WHAT WILL THE STUDY COST ME?

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

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.

NUMBER OF PARTICIPANTS

We plan to enroll approximately 200 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 information about your health for this research study. You can choose whether or not you will participate in this research study. However, in order to participate you have to sign this consent and authorization form.
This is the information we will use:

- <<Name>>
- <<Address>>
- <<Telephone number>>
- <<Family medical history>>
- <<Allergies>>
- <<Current and past medications or therapies>>
- *<<Information from a physical examination, such as blood pressure reading, heart rate, breathing rate, and temperature>>*
- *<<All other tests and procedures that will be performed in the study>>*
- *<<Any other personal health information that will be obtained from other sources to be used in the research record, including prior medical history, tests or records from other sites>>*

Others who will have access to your information for this research project are the University's Institutional Review Board (the committee that oversees research studying people) and authorized members of the University of Utah who need the information to perform their duties (for example: to provide treatment, to ensure integrity of the research and for accounting or billing matters).

In conducting this study, we may share your information with groups outside the University of Utah Health Sciences Center. The information we share may include information that directly identifies you. These are the groups:

- 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;

Information disclosed to groups outside the University of Utah Health Sciences Center may no longer be covered by the federal privacy protections.

You may revoke this authorization. **This must be done in writing.** You must either give your revocation in person to the Principal Investigator or the Principal Investigator's staff, or mail it to Dr. David Viskochil, 50 N. Mario Capecchi Drive, Room 2C412 S.O.M., SLC, UT, 84132. If you revoke this authorization, 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.

CONSENT
By signing this form, you are consenting to participate.

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
Date of Birth: _____

Race: _____American Indian or Alaskan Native
_____Asian or Pacific Islander
_____Black
_____Hispanic

_____White

Ethnicity: _____Hispanic or Latino
_____Not Hispanic or Latino

_____ Respectfully decline to provide demographic information

INSTITUTIONAL REVIEW BOARD
THE UNIVERSITY OF UTAH
75 South 2000 East Salt Lake City, UT 84112 | 801.581.3655 | IRB@utah.edu

IRB: IRB_00055719

PI: David Viskochil

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)

This New Study Application has been reviewed and approved by a University of Utah IRB convened board. The convened board approved your study as a Greater Than Minimal risk study on 11/20/2013. The approval is effective as of 11/22/2013. Federal regulations and University of Utah IRB policy require this research protocol to be re-reviewed and re-approved prior to the expiration date, as determined by the convened board.

Your study will expire on 11/19/2014.
Any changes to this study must be submitted to the IRB prior to initiation via an amendment form.

Submission of final IRB approval from University of British Columbia, University of Hamburg, and University of Cincinnati is required. You must submit these approvals to the University of Utah IRB by way of Amendment. The approvals must be signed to be considered valid. Please note that no research-related procedures may be conducted at those sites until the Amendment is approved.

APPROVED DOCUMENTS

Informed Consent Document
DV Vit D Consent -Clean 2013

Surveys, etc.
CTCAE v3.0
Activity Questionnaire
NF Exam Form
Check List
SF-36 v2 survey
Calcium intake
Phone assessment

Company Protocol
NF1 vitamin D BMD protocol 10-2013

Investigational Brochure
IB - cholecalciferol
cholecalciferol-DDrop label

Grant Application
Grant Application Intervention Protocol
Grant application Human Subjects Procedures
Grant Application Project Narrative
Grant Application Data Management

Literature Cited/References
Vit D References

Recruitment Materials, Advertisements, etc.
Vit D Subject Letter

Other Documents
FDA-IND Viskochil Vit D
DV VIt D 1572
CCTS IRB consent exec summary vit D study

Click IRB_00055719 to view the application and access the approved documents.

Please take a moment to complete our customer service survey. We appreciate your opinions and feedback.

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).

NF1 - Telephone Assessment

The purpose of this form is to assist the coordinator to screen people who may not be eligible due to medical conditions or medications.

Ask about general categories of medications and list them down by name and dosage. This list will be verified by the appropriate co-investigator, who will be ultimately responsible for inclusion or exclusion on medical grounds.

Name of potential study participant: _____
(This will be replaced by a study number if the person is enrolled)

Does the potential study participant have (or ever been told they have) the following conditions:

□ osteoporosis ?
Treatment with bisphosphonates or calcitonin? _____
Other treatment?

□ treatment with glucocorticoids for over 3 months?
Name of glucocorticoids _____

□ current treatment for epilepsy / seizures?
Name of drug _____

□ current treatment with blood thinners (anticoagulants)?
Name of drug _____

□ current or past treatment for thyroid or parathyroid problems?
Name of drug or treatment (when?)_____

□ Paget's disease

□ kidney failure

□ kidney stone in the last 5 years?

□ pregnant, or planning a pregnancy within time frame of study

□ any hip or spine prostheses? Scoliosis treatment, hip replacement?

Any other chronic health concerns /comments_____
_____
_____

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).

NF1 - Telephone Assessment

The purpose of this form is to assist the coordinator to screen people by telephone to ensure there is a reasonable probability that they have NF1. If there is doubt, potential participants can be offered a physical examination to confirm NF1 by study clinicians. Medical records can also be consulted, with the appropriate written permission.

Name of potential study participant: _____
(This will be replaced by a study number if the person is enrolled)

Does the potential study participant have (or ever been told they have):

□ café au lait macules? How many over 15mm (approx finger width)_____

□ intertriginous freckling? Where _____

□ any neurofibromas?

□ optic glioma?

□ Lisch nodules?

□ scoliosis?

□ long bone dysplasia / pseudarthrosis?

□ an affected family member?

Date_____

To Whom It May Concern:

The researchers at the University of Utah would like invite you to participate in a Vitamin D clinical trial. We are asking if you would like to participate in this study because you are an adult between 25-40 years of age with neurofibromatosis type 1 (NF1). This research study is evaluating vitamin D as a possible treatment for adult NF1 individuals with low Vitamin D levels as adults with NF1 have a higher risk of osteopenia and osteoporosis, a condition of low bone density that can lead to fragile bones and bone breakage.

If you are interested in this clinical trial or have questions, please feel free to contact me at 801-587-9017 (toll-free at (877) 942-6600).

Thank you for your interest in our research.

Sincerely,

Heather Hanson

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
David H. Viskochil	Professor, Pediatrics
eRA COMMONS USER NAME	
DVISKOCH	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Arizona	B.S.	1977	Biology
University of North Carolina	Ph.D.	1983	Biochemistry
University of North Carolina	M.D.	1985	Medicine
University of Utah Affiliated Hospitals	Residency	1988	Pediatrics
University of Utah	Fellowship	1988 - 1991	Clinical Genetics

A. Personal Statement: I have been involved in research related to neurofibromatosis type 1 (NF1) since my fellowship in Clinical Genetics when I was a key member of the lab that cloned and characterized the *NF1* gene. About 5 years ago, I transitioned from benchwork to an emphasis on clinical trials. I now oversee multiple clinical trials for NF1 and lysosomal storage disorders (LSDs). I presently serve as chair of the Clinical Care Advisory Board of the Children's Tumor Foundation (CTF), a national support group for the neurofibromatoses. I am the site principal investigator of 5 clinical trials and I am conducting a natural history study for progressive scoliosis in pre-pubertal individuals with NF1 (R01 NS050509). The focus for the remainder of my career is the development of novel therapies to treat patients with genetic disorders, specifically NF1 and LSDs. As co-director of the NF Clinic at the University of Utah, I follow over 200 NF patients, and almost all have enrolled in our NF Registry with over 150 participating in at least one clinical study. Our NF Clinic is a member of the NFCN (Neurofibromatosis Clinic Network supported by the CTF). I serve as the site PI for the University of Utah collaborative effort within the Lysosomal Disorder Network (operation center at University of Minnesota – U54 NS065768, Whitley (PI)). I participate as the local PI for 2 LSD trials supported by industry; immunotolerance therapy in Pompe disease (Genzyme, AGLU03707) and intrathecal administration of idursulfase in MPS II (Shire, HGT-HIT-045, Muenzer (PI)). I am a co-director of the Clinical Genetics Research Program (Phenotype Core), which is embedded in the Center for Clinical and Translational Sciences (CCTS) at the University of Utah.

A. Positions and Honors

Positions and Employment

1991-1997 Assistant Professor, Pediatrics, U of Utah, Salt Lake City, UT
1997-2003 Associate Professor, Pediatrics, University of Utah
2003-present Professor, Pediatrics, University of Utah
2000-2008 Director, Division of Medical Genetics
2002-present Medical Director, University of Utah Graduate Program in Genetic Counseling
2008-present Director of Clinical Genetics Services, Division of Medical Genetics

Honors

1988-1990 Young Investigator Award, National Neurofibromatosis Foundation
1991-1994 Clinical Investigator Award (K08), Institute of Neurological Disorders and Stroke
2005-present Chair, Clinical Care Advisory Board of the Children's Tumor Foundation
2002-present Chair, Genetic Advisory Committee for the Utah State Department of Health

B. Selected peer-reviewed publications (in chronological order)

1. **Viskochil D**, Buchberg A, Xu G, Cawthon R, Stevens J, Wolff R, Culver M, Carey J, Copeland N, Jenkins N, White R and O'Connell P: Deletions and a translocation interrupt a cloned gene at the neurofibromatosis type 1 locus, 1990, Cell, 62:187-192

2. Martin G, **Viskochil D**, Bollag G, McCabe P, Crosier W, Haubruck H, Conroy L, Clark R, O'Connell P, Cawthon R, Innis M and McCormick F: The GAP-Related Domain of the Neurofibromatosis Type 1 Gene Product Interacts with ras p21. Cell, 1990, 63:843-849
3. Xu G, O'Connell P, **Viskochil D**, Cawthon R, Robertson M, Culver M, Dunn D, Stevens J, et al.: The neurofibromatosis type 1 gene encodes a protein related to GAP. Cell, 1990, 62:599-608
4. Cawthon R, Weiss R, Xu G, **Viskochil D**, Culver M, Stevens J, Robertson M, Dunn D, Gesteland R, O'Connell P and White R: A major segment of the neurofibromatosis type 1 gene: cDNA sequence, genomic structure, and point mutations. Cell, 1990, 62:193-201
5. **Viskochil D**, Cawthon R, O'Connell P, Xu G, Stevens J, Culver M, Carey J, White R: The gene encoding the oligodendrocyte-myelin glycoprotein is embedded within the neurofibromatosis type 1 gene. Mol. Cell. Biol, 1991, 11:906-912
6. Jorde L, Watkins WS, **Viskochil D**, O'Connell P, and Ward K: Linkage Disequilibrium in the Neurofibromatosis 1 Region: Implications for Gene Mapping. Am J Hum Genet, 1993, 53:1038-1050
7. Li Y, O'Connell P, Breidenbach Huntsman H, Cawthon R, Stevens J, Gangfeng X, Neil S, Robertson M, White R and **Viskochil D**. Genomic Organization of the Neurofibromatosis 1 Gene (*NF1*). Genomics, 1995, 25:9-18
8. Sawada S, Florell S, Purandare S, Ota M, Stephens K and **Viskochil D**. Identification of *NF1* Mutations in Both Alleles of a Dermal Neurofibroma. Nature Genet, 1996, 14:110-112
9. Purandare S, Cawthon R, Nelson L. Sawada S, Watkins S, Ward K, Jorde L and **Viskochil D**. Genotyping of PCR-based Polymorphisms and Linkage-Disequilibrium Analysis at the NF1 Locus. Am J Hum Genet, 59:159-166, 1996.
10. Gutmann D, Aylsworth A, Carey J, Korf B, Marks J, Pyeritz R, Rubenstein A, **Viskochil D**. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA 278:51-57, 1997.
11. DeClue JE, Heffelfinger S, Benvenuto G, Ling B, Li S, Rui W, Vass WC, **Viskochil D**, Ratner N. Epidermal growth factor receptor expression in neurofibromatosis type 1-related tumors and NF1 animal models. J Clin Invest. 105:1233-41, 2000.
12. Liew MA, Coffin CM, Fletcher JA, Hang MT, Tanito K, Niimura M, **Viskochil D**. Peripheral nerve sheath tumors from patients with neurofibromatosis type 1 do not have the chromosome translocation t(X:18). Pediatr Dev Pathol. 5:165-169. 2002.
13. **Viskochil D**. Genetics of Neurofibromatosis 1 and the *NF1* Gene. J Child Neurology 17:562-570, 2002.
14. Zhou H, Coffin C, Perkins SL, Tripp SR, Liew M, **Viskochil DH**. Malignant Peripheral Nerve Sheath Tumor (MPNST):A comparison of grade, immunophenotype, and cell cycle/growth activation marker expression in sporadic and neurofibromatosis 1 (NF1)-related lesions. Am J Surg Pathol 27:1337-45, 2003.
17. Stevenson DA, Zhou H, Ashrafi S, Messiaen LM, Carey JC, D'Astous JL, Santora SD, **Viskochil DH**. Double-inactivation of NF1 in tibial pseudarthrosis. Am J Hum Genet 79:143-148, 2006.
18. Stevenson DA, Moyer-Mileur LJ, Murray M, Slater H, Sheng X, Carey JC, Dube B, **Viskochil DH**. Bone mineral density in children and adolescents with neurofibromatosis type 1. J Pediatr 150:83-88, 2007.
19. Stevenson D, **Viskochil D**, Schorry E, Crawford A, D'Astous J, Murray K, Friedman J, Armstrong L, Carey J. The use of anterolateral bowing of the lower leg in the diagnostic criteria for neurofibromatosis type 1. Genet Med 9:409-412, 2007.
20. Elefteriou F, Kolanczyk M, Schindeler A, **Viskochil D**, Hock J, Schorry E, Crawford A, Friedman J, Little D, Peltonen J, Carey J, Feldman D, Yu X, Armstrong L, Birch P, Kendler D, Mundlos S, Yang FC, Agiostratidou G, Hunter-Schaedle K, Stevenson D. 2009. Skeletal abnormalities in neurofibromatosis type 1: Approaches to therapeutic options. Am J Med Genet 149A:2327-2338.
21. Stevenson D, Carey J, **Viskochil D**, Moyer-Mileur L, Slater H, Murray M, D'Astous J, Murray K. 2009. Analysis of radiographic characteristics of anterolateral bowing of the leg before fracture in neurofibromatosis type 1. J Pediatr Othop 29;385-392.
22. Stevenson D, **Viskochil**. 2009. Pigmentary findings in neurofibromatosis type 1-like syndrome (Legius syndrome): potential diagnostic dilemmas. JAMA 302:2150-1.
23. Muram-Zborovski T, Stevenson D, **Viskochil D**, Dries D, Wilson A, Mao R. 2010. *SPRED1* mutations in a Neurofibromatosis Clinic. J Child Neurol 25, 1203-1209.
24. Thompson H, **Viskochil D**, Stevenson D, Chapman K. 2010. Speech-language characteristics of children with neurofibromatosis type 1. Am J Med Genet 152A,284-290.

25. Muram-Zborovski T, Vaughn C, **Viskochil D**, Hanson H, Mao R, Stevenson D. 2010. *NF1* exon 22 analysis of individuals with the clinical diagnosis of neurofibromatosis type 1. Am J Med Genet 152A, 1973-1978.
26. Stevenson D, Schwarz E, Carey J, **Viskochil D**, Hanson H, Bauer S, Weng H, Green T, Reinker K, Swensen J, Chan R, Yang F, Senbanjo L, Yang Z, Mao R, Pasquali M. 2011. Bone resorption in syndromes of the Ras/MAPK pathway. Clin Genet 80, 566-573.
27. Rieley M, Stevenson D, **Viskochil D**, Tinkle B, Martin L, Schorry E. 2011. Variable expression of Neurofibromatosis 1 in monzygotic twins. Am J Med Genet A 155A,478-485.
28. Rauen K, Banerjee A, Bishop W, Lauchle J, McCormick F, McMahon M, Melese T, Munster P, Nadaf S, packer R, Sebolt-Leopold J, **Viskochil D**. 2011. Costello and cardio-facio-cutaneous syndromes: moving toward clinical trials in RASopathies. Am J Med Genet C Semin Med Genet, 157, 136-146.
29. Furtado L, Putnam A, **Viskochil D**, Lowichick A, Erickson L, Dries D, Opitz J. 2011. Unilateral sclerocornea and tracheal stenosis: unusual findings in a patient with Goldenhar anomaly. Fetal Pediatr Pathol, 30, 397-404.
30. Johnson K, Fisher M, Listernick R, North K, Schorry E, **Viskochil D**, Weinstein M, Rubin J, Gutmann D. 2012. Parent-of-origin in individuals with familial neurofibromatosis type 1 and optic pathway gliomas. Fam Cancer, 11, 653-656.
31. Banugaria S, Prater S, McGann J, Feldman J, Tannenbaum J, Bailey C, Gera R, Conway R, **Viskochil D**, Kobori J, Rosenberg A, Kishnani P. 2013. Bortezomib in the rapid reduction of high sustained antibody titers in disorders treated with therapeutic protein: lessons learned from Pompe disease. Genet Med 15,123-131.
32. Polgreen L, Thomas W, Fung E, **Viskochil D**, Stevenson D, Steinberger J, Orchard P, Whitley C, Ensrud K. 2013. Low bone mineral content and chanllenges in interpretation of dual-energy x-ray absorptiometry in chidren with mucopolysaccharidosis types I, II, and VI. J Clin Densitom

C. Research Support

Ongoing Research Support

DAMD-W81XWH-11-NFRP-CTA Viskochil (PI) 09/30/12-09/29/16
Title: A phase II trial on the effect of low-dose verus high-dose vitamin D supplementation on bone mass in adults with neurofibromatosis 1 (NF1)
Specific aim: compare effects of daily supplementation of 600 IU vitamin D versus 4,000 IU vitamin D on maintenance of bone mineral density in young adults with NF1 initially insufficient for serum 25-OH vitamin D.
Role: Principal Investigator

U54 NS065768 Whitley (PI) 09/30/09-08/31/14
Lysosomal Disease Network (Multicenter Project)
Specific aims are to characterize bone disease in MPS I, MPS II, and MPS VI by measurements of bone architecture, density, strength, metabolism and mobility.
Role: Co-Investigator and PI at the University of Utah site.

Protocol Number: AGLU03707 Viskochil (PI) 02/01/09-09/30/13
Genzyme contract for Clinical Trial
Title: An Exploratory Study of the Safety and Efficacy of Immune Tolerance Induction (ITI) in Patients with Pompe Disease who have Previously Received Myozyme
The specific aim of this study is to evaluate the Myozyme antibody response with immune modulation.
Role: PI at the University of Utah site.

Protocol Number: HGT-HIT-045 Muenzer (PI) 01/01/10-06/30/13
Shire subcontract for Clinical Trial with University of North Carolina
Title: A Phase I/II Randomized Safety and Ascending Dose Ranging Study of Idursulfase (Intrathecal) Administration via an Intrathecal Drug Delivery Device in Pediatric Patients with Hunter Syndrome who Demonstrate Evidence of Central Nervous System Involvement and who are Receiving Elaprase.
Role: PI of subcontract at the University of Utah

Completed Research Support (last 5 years)

R01 NS050509 Viskochil (PI) 7/01/06-9/30/12
NIH/NINDS
Title: Spinal Abnormalities in Neurofibromatosis Type 1
Specific aims are to prospectively identify associations of spinal cord anomalies and spinal neurofibromas, with dysplastic osseous abnormalities and the development of dystrophic scoliosis in individuals with NF1.
Role: Principal Investigator

DAMD- W81XWH-05-1-0615 Korf (PI) 4/01/07-3/31/12
Department of the Army - NF Research Program
DAMD Subcontracts with University of Alabama, Birmingham Operations Center
Specific aims of these projects are to conduct 2 clinical trials with the NF Clinical Trials Consortium. The University of Utah site is one of 10 NF Clinical Trials Consortium Sites, and these clinical trials are for plexiform neurofibroma (sirolimus) and cognitivie impairment (lovastatin) in patients with NF1.
Role: Co-Investigator of NF Clinical Trials Consortium; Viskochil is PI of the University of Utah Site

K23 NS052500-01 Stevenson (PI) 8/15/05-3/31/10
NIH/NINDS
Title: Osseous Abnormalities in Neurofibromatosis Type 1
Specific aims were to determine bone-health variables in NF1, to determine bone-related genotype-phenotype correlations in NF1, and to assess health-related quality of life (HRQL) in NF1 with scoliosis.
Role: Co-Mentor

Shriners Research Grant #8510 Roach (PI) 01/01/09-12/31/10
Title: Phenotypic Variability and Genetic Mapping of Developmental Dysplasia of the Hip (DDH)
Specific aims are to elucidate the phenotypic variability of DDH and its contribution to the development of osteoarthritis, and identify genetic factors that predispose individuals to the development of DDH.
Role: Co-Investigator

Shriner Grant 9198 D'Astous (PI) 1/01/06-12/31/09
Shriners Research Foundation
Title: Spinal abnormalities in neurofibromatosis 1 (NF1) Patients
Specific aims are to assess health-related quality of life (HRQL) in NF1 patients with scoliosis and to assess biochemical markers of bone metabolism in NF1 individuals.
Role: Co-Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Richard E. Kanner	Professor of Internal Medicine, School of Medicine
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Michigan, Ann Arbor, MI	B.A.	1952-58	Premedical Sciences
SUNY at Brooklyn, Brooklyn, NY	M.D.	1958-62	Medicine
University of Utah School of Medicine, Salt Lake City, UT	Intern	1962-63	
University of Utah School of Medicine, Salt Lake City, UT	Resident	1963-65	Internal Medicine
Columbia - Presbyterian Medical Center of New York, New York, NY	Fellow	1965-66	Pulmonary Medicine
University of Utah School of Medicine, Salt Lake City, UT	Fellow	1968-70	

A. Personal Statement

B. Positions and Honors

Positions and Employment

1966 - 1967 Lieutenant, United States Naval Reserve, Portsmouth, Va and Danang, RVN
1966 - 1967 Internist, Naval Hospital, Portsmouth, VA
1967 - 1968 Internist, Assistant Chief of Medicine, Station Hospital, Naval Support Activity, Da nang, RVN
1968 - 1973 LCDR, United States Naval Reserve-R,
1970 - 1973 Executive Medical Director, Respiratory Disease Section, Intermountain Regional Medical Program,
1970 - 1989 Director, Medical Chest Clinic, University of Utah Hospital, Salt Lake City, UT
1970 - 1971 Instructor of Medicine, University of Utah School of Medicine, Salt Lake City, UT
1971 - 1977 Assistant Professor of Medicine, University of Utah, School of Medicine, Salt Lake City, UT
1972 - 1980 Medical Director, Respiratory Therapy Department, University of Utah Hospital, Salt Lake City, UT
1974 - 1977 CDR, United States Naval Reserve,
1975 - 1980 Clinical Associate Professor of Health Occupations, School of Allied Health Services, Weber State College, Ogden, UT
1977 - 1991 Associate Professor of Medicine, University of Utah School of Medicine, Salt Lake City, UT
1978 - 1985 "B" Reader, Medical Examination Program of NIOSH, University of Utah, Salt Lake City, UT
1980 - 1981 Visiting Associate Professor of Medicine, Harvard Medical School,
1988 - Present Director, Pulmonary Function Lab, University of Utah Hospital,
1991 - Present Professor of Medicine, University of Utah School of Medicine, Salt Lake City, UT

Honors

1961	Alpha Omega Alpha
1965 - 1966	New York Heart Association, Fellow
1968 - 1970	NIH Training Fellow
1970 - 1974	Edward Livingston Trudeau Fellowship of the American Lung Association in Pulmonary Diseases
1980 - 1981	National Research Service Award from the National Institute of Environmental Health Sciences of the NIH

Federal Government Public Advisory Committee(s)

1975 - 1988	Editorial Board, Editorial Advisory Board for Respiratory Therapy, The Journal of Inhalation Technology (name changed to Respiratory Management)
1988 - Present	Editorial Board, Editorial Advisory Board for RT, the Journal for Respiratory Care Practitioners
1989 - Present	Editorial Board, Editorial Advisory Board for Choices in Respiratory Management
2001 - 2006	Editorial Board, Editorial Board for CHEST
2004 - Present	Editor, Editorial Consultant for Asthma module for the Physicians' nformation and Education Resource (PIER). American College of Physicians

C. Selected peer-reviewed publications (In chronological order. Selected from 58 peer-reviewed publications.)

1. Rom WN, **Kanner RE**, Renzetti AD Jr, Shigeoka JW, Barkman HW, Nichols M, Turner WA, Coleman M, Wright WE. (1981). Respiratory disease in Utah coal miners. *Am Rev Respir Dis*, *123*(4 Pt 1), 372-7.
2. Rom WN, Turner WG, **Kanner RE**, Renzetti AD Jr, Peebles C, Tan E, Olsen DM. (1983). Antinuclear antibodies in Utah coal miners. *Chest*, *83*(3), 515-9.
3. **Kanner RE**, Schenker MB, Munoz A, Speizer FE. (1983). Spirometry in children. Methodology for obtaining optimal results for clinical and epidemiologic studies. *Am Rev Respir Dis*, *127*(6), 720-4.
4. **Kanner RE**. (1983). Bilateral vocal cord paralysis for 26 years with respiratory failure. Timing of restoration of tidal volume and serum electrolytes after tracheostomy. *Chest*, *84*(3), 304-6.
5. **Kanner RE**, Renzetti AD Jr. (1984). Predictors of spirometric changes and mortality in the obstructive airway disorders. *Chest*, *85*, 15S-17S.
6. **Kanner RE**. (1984). The role of the pulmonary function laboratory in patients with bronchial asthma. *Asthma Series*, *9*, 2-9.
7. **Kanner RE**. (1984). The relationship between airways responsiveness and chronic airflow limitation. *Chest*, *86*(1), 54-7.
8. **Kanner RE**, Barkman HW Jr, Rom WN, Taylor AT Jr. (1985). Gallium-67 citrate imaging in underground coal miners. *Am J Ind Med*, *8*(1), 49-55.
9. **ATS Committee on Impairment/Disability (Kanner RE)**. (1986). Evaluation for impairment/disability secondary to respiratory disease. *Am Rev Respir Dis*, *133*, 1205-1209.
10. Collins DV, Cutillo AG, Armstrong JD, Crapo RO, **Kanner RE**, Tocino I, Renzetti AD Jr. (1986). Large airway size, lung size, and maximal expiratory flow in healthy nonsmokers. *Am Rev Respir Dis*, *134*(5), 951-5.
11. Crapo RO, **Kanner RE**, Jensen RL, Elliott CG. (1988). Variability of the single-breath carbon monoxide transfer factor as a function of inspired oxygen pressure. *Eur Respir J*, *1*(6), 573-4.
12. Watanabe S, **Kanner RE**, Cutillo AG, Menlove RL, Bachand RT Jr, Szalkowski MB, Renzetti AD Jr. (1989). Long-term effect of almitrine bismesylate in patients with hypoxemic chronic obstructive pulmonary disease. *Am Rev Respir Dis*, *140*(5), 1269-73.
13. Frey TM, Crapo RO, Jensen RL, **Kanner RE**, Kass JE, Castriotta RJ, Mohsenifar Z. (1990). Adjustment of DLCO for varying COHb, and alveolar PO2 using a theoretical adjustment equation. *Respir*

Physiol, *81*(3), 303-11.

14. Kadunce DP, Burr R, Gress R, **Kanner RE**, Lyon JL, Zone JJ. (1991). Cigarette smoking as a risk factor for facial wrinkling. *Ann Intern Med*, *114*, 840-844.
15. Tashkin DP, Altose MD, Bleecker ER, Connett JE, **Kanner RE**, Lee WW, Wise R. (1992). The lung health study: airway responsiveness to inhaled methacholine in smokers with mild to moderate airflow limitation. The Lung Health Study Research Group. *Am Rev Respir Dis*, *145*(2 Pt 1), 301-10.
16. Pope CA 3rd, **Kanner RE**. (1993). Acute effects of PM10 pollution on pulmonary function of smokers with mild to moderate chronic obstructive pulmonary disease. *Am Rev Respir Dis*, *147*(6 Pt 1), 1336-40.
17. Buist AS, Connett JE, Miller RD, **Kanner RE**, Owens GR, Voelker HT. (1993). Chronic Obstructive Pulmonary Disease Early Intervention Trial (Lung Health Study). Baseline characteristics of randomized participants. *Chest*, *103*(6), 1863-72.
18. **Kanner RE**, Connett JE, Altose MD, Buist AS, Lee WW, Tashkin DP, Wise RA. (1994). Gender difference in airway hyperresponsiveness in smokers with mild COPD. The Lung Health Study. *Am J Respir Crit Care Med*, *150*(4), 956-61.
19. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, Conway WA Jr, Enright PL, **Kanner RE**, O'Hara P, et al. (1994). Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA*, *272*(19), 1497-505.
20. Wise RA, Connett J, Kurnow K, Grill J, Johnson L, **Kanner RE**, Enright P. (1995). Selection of spirometric measurments in a clinical trial, the Lung Health Study. *Am J Respir Crit Care Med*, *151*, 675-681.
21. Enright PL, Connett JE, **Kanner RE**, Johnson LR, Lee WW. (1995). Spirometry in the Lung Health Study: II. Determinants of short-term intraindividual variability. *Am J Respir Crit Care Med*, *151*(2 Pt 1), 406-11.
22. Alexander GJ, **Kanner RE**. (1996). Air Pollution. Pulmonary and Critical Care Update. *Chest*, *11*, (Lesson 13) 1-8.
23. **Kanner RE**. (1996). Early intervention in chronic obstructive pulmonary disease. A review of the Lung Health Study results. *Med Clin North Am*, *80*(3), 523-47.
24. Tashkin DP, Altose MD, Connett JE, **Kanner RE**, Lee WW, Wise RA. (1996). Methacholine reactivity predicts changes in lung function over time in smokers with early chronic obstructive pulmonary disease. The Lung Health Study Research Group. *Am J Respir Crit Care Med*, *153*(6 Pt 1), 1802-11.
25. Carveth HJ, **Kanner RE**. (1997). Early intervention in COPD. *Compr Ther*, *23*(1), 31-7.
26. **Kanner RE**, Kanter LJ, Dwork P. (1997). A comparison of drug delivery from a metered-dose inhaler plus an inspiratory flow control device with a metered-dose inhaler plus a spacer device. *J Allergy Clin Immunol*, *99*(6 Pt 1), 853-4.
27. Wise RA, Enright PL, Connett JE, Anthonisen NR, **Kanner RE**, Lindgren P, O'Hara P, Owens GR, Rand CS, Tashkin DP. (1998). Effect of weight gain on pulmonary function after smoking cessation in the Lung Health Study. *Am J Respir Crit Care Med*, *157*(3 Pt 1), 866-72.
28. Dockery DW, Pope CA 3rd, **Kanner RE**, Martin Villegas G, Schwartz J. (1999). Daily changes in oxygen saturation and pulse rate associated with particulate air pollution and barometric pressure. *Res Rep Health Eff Inst*, (83), 1-19; discussion 21-8.
29. Pope CA3rd, Dockery DW, **Kanner RE**, Villegas GM, Schwartz J. (1999). Oxygen saturation, pulse rate, and particulate air pollution: A daily time-series panel study. *Am J Respir Crit Care Med*, *159*(2), 365-72.
30. **Kanner RE**, Connett JE, Williams DE, Buist AS. (1999). Effects of randomized assignment to a smoking cessation intervention and changes in smoking habits on respiratory symptoms in smokers with early chronic obstructive pulmonary disease: the Lung Health Study. *Am J Med*, *106*(4), 410-6.
31. Pope CA 3rd, Verrier RL, Lovett EG, Larson AC, Raizenne ME, **Kanner RE**, Schwartz J, Villegas GM, Gold DR, Dockery DW. (1999). Heart rate variability associated with particulate air pollution. *Am Heart J*, *138*(5 Pt 1), 890-9.
32. **The Lung Health Study Research Group (Kanner RE)**. (2000). Effect of inhaled triamcinolone on the

decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med*, *343*, 1902-1909.

33. Tashkin D, **Kanner R**, Bailey W, Buist S, Anderson P, Nides M, Gonzales D, Dozier G, Patel MK, Jamerson B. (2001). Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet*, *357*(9268), 1571-5.
34. Pope CA 3rd, Eatough DJ, Gold DR, Pang Y, Nielsen KR, Nath P, Verrier RL, **Kanner RE**. (2001). Acute exposure to environmental tobacco smoke and heart rate variability. *Environ Health Perspect*, *109*(7), 711-6. PMCID: PMC1240375
35. **Kanner RE**, Anthonisen NR, Connett JE. (2001). Lower respiratory illnesses promote FEV(1) decline in current smokers but not ex-smokers with mild chronic obstructive pulmonary disease: results from the lung health study. *Am J Respir Crit Care Med*, *164*(3), 358-64.
36. Wise RA, **Kanner RE**, Lindgren P, Connett JE, Altose MD, Enright PL, Tashkin DP. (2003). The effect of smoking intervention and an inhaled bronchodilator on airways reactivity in COPD: the Lung Health Study. *Chest*, *124*(2), 449-58.
37. Malhotra A, Peiffer AP, Ryujin DT, Elsner T, **Kanner RE**, Leppert MF, Hasstedt SJ. (2003). Further evidence for the role of genes on chromosome 2 and chromosome 5 in the inheritance of pulmonary function. *Am J Respir Crit Care Med*, *168*(5), 556-61.
38. Scanlon PD, Connett JE, Wise RA, Tashkin DP, Madhok T, Skeans M, Carpenter PC, Bailey WC, Buist AS, Eichenhorn M, **Kanner RE**, Weinmann G. (2004). Loss of bone density with inhaled triamcinolone in Lung Health Study II. *Am J Respir Crit Care Med*, *170*(12), 1302-9.
39. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, **Kanner RE**, Connett JE. (2005). The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med*, *142*(4), 233-9.
40. Anthonisen NR, Lindgren PG, Tashkin DP, **Kanner RE**, Scanlon PD, Connett JE. (2005). Bronchodilator response in the lung health study over 11 yrs. *Eur Respir J*, *26*(1), 45-51.
41. Herpel LB, **Kanner RE**, Lee SM, Fessler HE, Sciurba FC, Connett JE, Wise RA. (2006). Variability of spirometry in chronic obstructive pulmonary disease: results from two clinical trials. *Am J Respir Crit Care Med*, *173*(10), 1106-13.
42. Reddy CB, **Kanner RE**. (2007). Is Combination Therapy with Inhaled Anticholinergics and b2-Adrenoceptor Agonists Justified for Chronic Obstructive Pulmonary Disease? *Drugs Aging*, *24*, 615-628.
43. Weiss RB, Baker TB, Cannon DS, Von Nieder Hausern A, Dunn DM, Matsunami N, Singh NA, Coon H, McMahon WM, Piper ME, Flore M, Scholand MB, Lonnett JE, **Kanner RE**, Gahring LC, Rogers SW, Hoidal JR Leppert MF. (2008). Association of Human NACHR Variants with Nicotine Dependence; Evidence for a Gene x Environmental Interaction. *PLoS Genet*.

D. Research Support

Current Support

Kanner (PI) 09/30/1984 - 07/31/1993
National Heart, Lung and Blood Institute
Early Intervention Of Chronic Obstructive Pulmonary Disease.
Role: Principal Investigator

Kanner (PI) 04/01/2002 - 12/31/2007
Boehringer Ingelheim Pharmaceuticals
A randomized, double-blind, placebo controlled, parallel group trial assessing the rate of decline of lung function with Tiotropium 18 mcg inhalation capsule once daily in patients with chronic obstructive pulmonary disease
Role: Principal Investigator

HHSN268200736194C Scholand; Kanner (PIs) 10/31/2006 - 10/31/2013

National Institutes of Health
LOTT
Role: Principal Investigator

Kanner (PI) 04/30/2008 - 12/31/2009
Mds Pharma
Chf 4226
Role: Principal Investigator

HHSN268200900018C Hoidal; Scholand; Kanner (PIs) 02/01/2009 - 01/31/2016
National Heart Lung & Blood Institute
Spiromics
Role: Principal Investigator

Completed Support

NIH National Heart, Lung and Blood Institute (NHLBI) 01/01/1970 - 01/01/1975
Emphysema Study
Role: Co-Investigator

Kanner (PI) 09/04/1993 - 01/31/2003
National Heart, Lung and Blood Institute
The Efficiency Of Inhaled Corticosteroids In Copd. Cfda 93.838/Research Project Cooperative Agreement (U01).
Role: Principal Investigator

Kanner (PI) 09/01/1995 - 12/17/1996
Harvard University
Does Particulate Air Pollution Induce Hypoxemia?
Role: Principal Investigator

Kanner (PI) 02/01/1998 - 01/31/2003
National Heart, Lung and Blood Institute
Lung Health Study -- Long Term Follow-Up. Cfda 93.838/U10.
Role: Principal Investigator

Kanner (PI) 03/09/1998 - 07/03/2001
GLAXO WELLCOME INC
A Milticenter Evaluation Of The Effects Of Zyban (Bupropion Hydrochloride Sustained Release Tablets) Versus Placebo...Fixed Price.
Role: Principal Investigator

Kanner (PI) 04/01/1999 - 04/05/2001
MERCK & CO INC
Randomized 3 Period Crossover Study To Investigate The Safety & Tolerability Of L-753099 In Patients With COPD. Fixed Price.
Role: Principal Investigator

Kanner (PI) 02/01/2000 - 01/31/2003
US Environmental Protection Agency (EPA)
Relationship Retween Pms.5 Semi-Volatile Organic Material. Cost Reimbursable.
Role: Principal Investigator

Kanner (PI) 02/21/2000 - 01/31/2001
GLAXO WELLCOME INC
Group Trial Assessing...Fluticasone Proprionate Inhalation Powder (250 Mcg Qd) & Placebo In Subject >12

Yrs. With Chronic Asthma. Protocol Fpd 400010. Fixed Pr.
Role: Principal Investigator

Kanner (PI) 01/31/2001 - 11/30/2002
Smithkline Beecham Pharmaceuticals, Co.
A 24-week, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety and tolerability of Ariflo (15mg bid) in patients with COPD
Role: Principal Investigator

Kanner (PI) 06/01/2001 - 06/30/2003
Schering-Plough Research Institute (SPRI)
Efficacy...Mometasone Furoate Dry Powder Inhaler In The Treatment Of Patients With Chronic Obstructive Pulmonary Disease. Fixed Price.
Role: Principal Investigator

CITI Collaborative Institutional Training Initiative

Human Research Curriculum Completion Report
Printed on Monday, June 14, 2010

Learner: Richard Kanner (username: rkanner)
Institution: University of Utah
Contact Information: 26 N. 1900 E
Salt Lake City, Utah 84132-4701 USA
Department: Internal Medicine
Phone: 801 581 7806
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Group 1.Biomedical Research Investigators and Key Personnel.:

Stage 3. Refresher Course Passed on 06/12/10 (Ref # 4217107)

Required Modules	Date completed	Score
History and Ethical Principles.	06/12/10	0
Regulations and Process, Part 1	06/12/10	100
Regulations and Process, Part 2	06/12/10	100
Informed Consent.	06/12/10	100
Social & Behavioral Research (SBR)	06/12/10	50
Genetics Research, Part 1	06/12/10	100
Genetics Research, Part 2	06/12/10	100
Records-Based Research, Part 1	06/12/10	100
Records-Based Research, Part 2	06/12/10	100
Records-Based Research, Part 3	06/12/10	100
Research with Protected Populations - Vulnerable Subjects: A Definition.	06/12/10	100
Vulnerable Subjects - Prisoners, Part 1	06/12/10	100
Vulnerable Subjects - Prisoners, Part 2	06/12/10	100
Studies With Minors, Part 1	06/12/10	100
Studies With Minors, Part 2	06/12/10	100
Studies With Minors, Part 3	06/12/10	0
Studies with Pregnant Women and Fetuses, Part 1	06/12/10	100
Studies with Pregnant Women and Fetuses, Part 2	06/12/10	0
Group Harms: Research with Culturally or Medically Vulnerable Groups.	06/12/10	100
FDA-Regulated Research, Part 1	06/12/10	100
FDA-Regulated Research, Part 2	06/12/10	50
Human Subjects Protections at the VA, Part 1	06/12/10	100
Human Subjects Protections at the VA, Part 2	06/12/10	100
HIPAA and Human Subjects Research.	06/12/10	100
Conflicts of Interest in Research Involving Human Subjects.	06/12/10	50

How to Complete the CITI Refresher Course and Receive a Completion Report	06/12/10	0

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Paul Braunschweiger Ph.D.
Professor, University of Miami
Director Office of Research Education
CITI Course Coordinator

CITI Collaborative Institutional Training Initiative

Good Clinical Practice Course Curriculum Completion Report
Printed on 3/11/2013

Learner: David Stevenson (username: 00067526)
Institution: University of Utah
Contact Information
University of Utah
Division of Medical Genetics
2C412 SOM
SLC, UT 84132 USA
Department: Pediatrics
Phone: (801) 581-4296
Email: david.stevenson@hsc.utah.edu

Good Clinical Practice Course (US FDA focus):

Stage 1. Stage 1 Passed on 03/11/13 (Ref # 9917204)

Elective Modules	Date Completed	Score
GCP Introduction	03/11/13	3/3 (100%)
Overview of New Drug Development	03/11/13	4/5 (80%)
ICH Overview	03/11/13	3/4 (75%)
ICH - Comparison Between ICH GCP E6 and U.S. FDA Regulations	03/11/13	4/4 (100%)
Conducting Investigator-Initiated Studies According to FDA Regulations and Good Clinical Practices	03/11/13	3/3 (100%)
Investigator Obligations in FDA-Regulated Clinical Research	03/11/13	5/5 (100%)
Managing Investigational Agents According to GCP Requirements	03/11/13	5/5 (100%)
Conducting Clinical Trials of Medical Devices	03/11/13	3/3 (100%)
Informed Consent	03/11/13	3/4 (75%)
Detection and Evaluation of Adverse Events	03/11/13	4/4 (100%)
Reporting Serious Adverse Events	03/11/13	3/4 (75%)
Audits and Inspections in Clinical Trials	03/11/13	4/5 (80%)
Monitoring of Clinical Trials by Industry Sponsors	03/11/13	7/8 (88%)
Completing the CITI GCP Course	03/11/13	no quiz

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Paul Braunschweiger Ph.D.
Professor, University of Miami
Director Office of Research Education
CITI Course Coordinator

Return

3/11/13

CITI Collaborative Institutional Training Initiative

Human Research Curriculum Completion Report
Printed on 1/28/2013

Learner: HEATHER HANSON (username: heather4)
Institution: University of Utah
Contact Information Department: Pediatric Admin
Phone: 801-587-9017
Email: HEATHER.HANSON@HSC.UTAH.EDU

Group 1.Biomedical Research Investigators and Key Personnel.:

Stage 3. Refresher Course Passed on 01/28/13 (Ref # 9091831)

Required Modules	Date Completed	Score
Biomedical 200 Refresher Course - History and Ethical Principles	01/28/13	3/3 (100%)
Biomedical 200 Refresher Course - Regulations and Process, Part 1	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - Regulations and Process, Part 2	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - Informed Consent	01/28/13	3/3 (100%)
Biomedical 200 Refresher Course - Social & Behavioral Research (SBR)	01/28/13	3/3 (100%)
Biomedical 200 Refresher Course - Genetics Research, Part 1	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - Genetics Research, Part 2	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - Records-Based Research, Part 1	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - Records-Based Research, Part 2	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - Records-Based Research, Part 3	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - Research Involving Vulnerable Subjects	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - Vulnerable Subjects - Research Involving Prisoners, Part 1	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - Vulnerable Subjects - Research Involving Prisoners, Part 2	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - Vulnerable Subjects - Research Involving Children, Part 1	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - Vulnerable Subjects - Research Involving Children, Part 2	01/28/13	1/1 (100%)

Biomedical 200 Refresher Course -Vulnerable Subjects - Research Involving Children, Part 3	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - Vulnerable Subjects - Research Involving Pregnant Women, Human Fetuses, and Neonates, Part 1	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - Vulnerable Subjects - Research Involving Pregnant Women, Human Fetuses, and Neonates, Part 2	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - Avoiding Group Harms	01/28/13	3/3 (100%)
Biomedical 200 Refresher Course - FDA-Regulated Research, Part 1	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - FDA-Regulated Research, Part 2	01/28/13	2/2 (100%)
Biomedical 200 Refresher Course - Human Subjects Protections at the VA, Part 1	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - Human Subjects Protections at the VA, Part 2	01/28/13	1/1 (100%)
Biomedical 200 Refresher Course - HIPAA and Human Subjects Research	01/28/13	4/5 (80%)
Biomedical 200 Refresher Course - Financial Conflicts of Interest in Research Involving Human Subjects	01/28/13	3/3 (100%)
How to Complete the CITI Refresher Course and Receive a Completion Report	01/28/13	no quiz

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Paul Braunschweiger Ph.D.
Professor, University of Miami
Director Office of Research Education
CITI Course Coordinator

Return

CITI Collaborative Institutional Training Initiative

Good Clinical Practice Course Curriculum Completion Report
Printed on 1/28/2013

Learner: HEATHER HANSON (username: heather4)
Institution: University of Utah
Contact Information Department: Pediatric Admin
Phone: 801-587-9017
Email: HEATHER.HANSON@HSC.UTAH.EDU

Good Clinical Practice Course (US FDA focus):

Stage 1. Stage 1 Passed on 01/28/13 (Ref # 9523151)

Elective Modules	Date Completed	Score
GCP Introduction	01/18/13	3/3 (100%)
Overview of New Drug Development	01/18/13	5/5 (100%)
ICH Overview	01/18/13	4/4 (100%)
ICH - Comparison Between ICH GCP E6 and U.S. FDA Regulations	01/18/13	4/4 (100%)
Conducting Investigator-Initiated Studies According to FDA Regulations and Good Clinical Practices	01/28/13	3/3 (100%)
Investigator Obligations in FDA-Regulated Clinical Research	01/28/13	5/5 (100%)
Managing Investigational Agents According to GCP Requirements	01/28/13	4/5 (80%)
Conducting Clinical Trials of Medical Devices	01/28/13	3/3 (100%)
Informed Consent	01/28/13	4/4 (100%)
Detection and Evaluation of Adverse Events	01/28/13	4/4 (100%)
Reporting Serious Adverse Events	01/28/13	4/4 (100%)
Audits and Inspections in Clinical Trials	01/28/13	5/5 (100%)
Monitoring of Clinical Trials by Industry Sponsors	01/28/13	7/8 (88%)
Completing the CITI GCP Course	01/28/13	no quiz

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Paul Braunschweiger Ph.D.
Professor, University of Miami
Director Office of Research Education
CITI Course Coordinator

Return

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
LaSalle, Bernard A.	Adjunct Instructor Medicine Center for Clinical and Translational Science (CCTS) Informatics Core Director
eRA COMMONS USER NAME	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Utah, Salt Lake City, UT	BS	1982	Biology

A. Positions and Honors

Positions and Employment

1979-1982	Research Specialist, Department of Internal Medicine, University of Utah, Salt Lake City, UT
1982-1986	Clinical Research Coordinator, Department of Internal Medicine, University of Utah, Salt Lake City, UT
1986-1998	Systems Manager, GCRC Computerized Data Management Analysis System, Salt Lake City, UT
1998-2006	Director, GCRC Informatics Core, University of Utah, Salt Lake City, UT
1999-2003	Chairperson, NCRR Bioinformatics Conference
2002-2005	IRB Technology Project Manager, University of Utah, Salt Lake City, UT
2010-present	Instructor, Department of Biomedical Informatics, University of Utah, Salt Lake City, UT
2010-present	Director of Operations, CCTS Biomedical Research Informatics Service Core, University of Utah, Salt Lake City, UT
2010-2012	Project Director, Utah Biohealth Initiative, University of Utah, Salt Lake City, UT

Other Experience and Professional Membership

1988-1998	Association of GCRC Systems Managers conference. Provided networked systems and training seminars
1988-2006	Association of GCRC Systems Managers
1990-1998	National Institutes of Health, Prophet Advisory Panel. Development of clinical research data acquisition and analysis software
1992-1994	Developed data acquisition/reporting system for multi-center clinical trial
1993-1996	Belmont Research, Cambridge, MA, Development of innovative object-oriented displays for clinical research data
1998-2006	Association of Clinical Research Professionals
1998-1999	Directed workgroup in the task of rewriting NIH guidelines for GCRC Informatics Cores
1999-2006	Conducted sites visits for National Center for Research Resources to evaluate bioinformatics projects.
2000-2006	NIH/NCRR Study section
2000-2005	Director, Data Coordinator Center, Pediatric Clinical Trial
2001-present	Faculty on Masters in Clinical Research Program
2002-2004	NIH Special Emphasis Panel – Biomedical Informatics Research Network
2002-2005	Committee co-chairperson Data and Safety Monitoring, University of Utah
2003-2005	Project Director – IRB Data management development project
2005-2010	Director, Data Coordinating Center, Project Cure SMA
2006-2007	Biomedical Research Informatics Association
2007-present	AMIA

2010-present Member, CTSA Informatics Key Function Committee

B. Selected Peer-Reviewed Publications

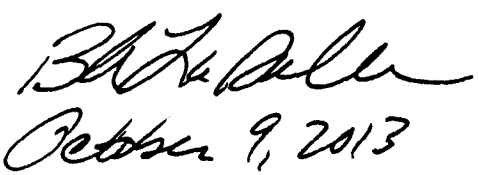
1. Kissel JT, Scott CB, Reyna SP, Crawford TO, Simard LR, Krosschell KJ, Acsadi G, Elsheik B, Schroth MK, D'Anjou G, LaSalle B, Prior TW, Sorenson S, Maczulski JA, Bromberg MB, Chan GM, Swoboda KJ; Project Cure Spinal Muscular Atrophy Investigators' Network.
2. Swoboda KJ, Scott CB, Crawford TO, Simard LR, Reyna SP, Krosschell KJ, Acsadi G, Elsheik B, Schroth MK, D'Anjou G, **LaSalle B**, Prior TW, Sorenson SL, Maczulski JA, Bromberg MB, Chan GM, Kissel JT; Project Cure Spinal Muscular Atrophy Investigators Network.PLoS One. 2010 Aug 19;5(8):e12140.
3. Swoboda KJ, Scott CB, Reyna SP, Prior TW, LaSalle B, Sorenson SL, Wood J, Acsadi G, Crawford TO, Kissel JT, Krosschell KJ, D'Anjou G, Bromberg MB, Schroth MK, Chan GM, Elsheikh B, Simard LR. Phase II open label study of valproic acid in spinal muscular atrophy. PLoS One. 2009;4(5):e5268. Epub 2009 May 14.
4. Rocha R, Hurdle J, Matney SA, Narus S, Meystre S, Lasalle B, Deshmukh V, Hunter C, Mineau G, Facelli JC, Joyce M. AMIA Annu Symp Proc. 2008 Nov 6:1114.
5. Shaddy RE, Curtin EL, Sower B, Tani LY, Burr J, LaSalle B, Boucek MM, Mahony L, Hsu DT, Pahl E, Burch GH, Schlencker-Herceg R. The Pediatric Randomized Carvedilol Trial in Children with Heart Failure: rationale and design. Am Heart J. 2002 Sep;144(3):383-9.
6. Shaddy RE, Burr J, LaSalle BA. Initiation and Mangement of Pediatric Multicenter Drug Trial by an Academic Center. Current Therapeutic Res. 2002 August; 68 (3) : 514-25
7. Bulaj ZJ, Ajioka RS, Phillips JD, LaSalle BA, Jorde LB, Griffen LM, Edwards CQ, Kushner JP. Disease-related conditions in relatives of patients with hemochromatosis. N Engl J Med. 2000 Nov 23;343(21):1529-35.
8. Zone JJ, LaSalle BA, Provost TT. Induction of IgA circulating immune complexes after wheat feeding in dermatitis herpetiformis patients. J Invest Dermatol. 1982 May;78(5):375-80.
9. Zone JJ, LaSalle BA, Provost TT. Circulating immune complexes of IgA type in dermatitis herpetiformis. J Invest Dermatol. 1980 Aug;75(2):152-5.
10. Olmstead AD, Zone JJ, LaSalle B, Krueger GG. Immune complexes in the pathogenesis of hypergammaglobulinemic purpura. J Am Acad Dermatol. 1980 Aug;3(2):174-9.

Abstracts

1. LaSalle BA, Brashaw RL, Matney SA. Maximizing Project Cure SMA Data Value From Multiple Clinical Trials, 14th Annual International SMA Research Group Meeting, Santa Clara, CA June 2010
2. LaSalle BA. Overview of the Bioinformatics Initiative Within the GCRC Program of the National Center for Research Resources. Atlanta, GA, Joint Statistical Meeting, August 2001
3. Enriquez FR, Kuhn R, Peiffer A, Leppert M, Filloux FM, LaSalle B. PEDS: A Pediatric Epilepsy Database System for Genetic and Clinical Studies. Washington DC: General Clinical Research Center National Conference, March 2001.

Presentations

1. NIH Informatics Integration workshop October 2003 *Developing Common Technology and Research Funding: The Key to Integration and Collaboration,* Joint Statistical Meeting, Atlanta, GA, August 2001. *Bioinformatics, Genomics and Clinical Research.*



October 9, 2013

COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI)

HUMAN RESEARCH CURRICULUM COMPLETION REPORT

Printed on 10/09/2013

LEARNER	Bernard LaSalle (ID: 1244618) 26 South 2000 East 5700 HSEB Salt Lake City UT 84112 United States
DEPARTMENT	Biomedical Informatics
PHONE	801-581-4080
EMAIL	bernie.lasalle@hsc.utah.edu
INSTITUTION	University of Utah
EXPIRATION DATE	10/09/2015

GROUP 1.BIOMEDICAL RESEARCH INVESTIGATORS AND KEY PERSONNEL.

COURSE/STAGE:	Refresher Course/4
PASSED ON:	10/09/2013
REFERENCE ID:	9197043

REQUIRED MODULES	DATE COMPLETED	SCORE
Biomed Refresher 2 – History and Ethical Principles	10/08/13	3/3 (100%)
Biomed Refresher 2 – Regulations and Process	10/08/13	2/2 (100%)
Biomed Refresher 2 – Informed Consent	10/08/13	3/3 (100%)
Biomed Refresher 2 – SBR Methodologies in Biomedical Research	10/08/13	3/4 (75%)
Biomed Refresher 2 – Genetics Research	10/08/13	2/2 (100%)
Biomed Refresher 2 – Records-Based Research	10/08/13	3/3 (100%)
Biomed Refresher 2 – Research Involving Vulnerable Subjects	10/08/13	1/1 (100%)
Biomed Refresher 2 – Vulnerable Subjects – Prisoners	10/08/13	2/2 (100%)
Biomed Refresher 2 – Vulnerable Subjects – Children	10/09/13	3/3 (100%)
Biomed Refresher 2 – Vulnerable Subjects – Pregnant Women, Human Fetuses, Neonates	10/09/13	2/2 (100%)
Biomed Refresher 2 – FDA-Regulated Research	10/09/13	3/3 (100%)
Biomed Refresher 2 – HIPAA and Human Subjects Research	10/09/13	9/9 (100%)
Biomed Refresher 2 – Conflicts of Interest in Research Involving Human Subjects	10/09/13	3/3 (100%)
How to Complete the CITI Refresher Course and Receive a Completion Report	10/09/13	No Quiz

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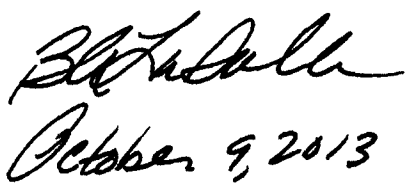
Paul Braunschweiger Ph.D.
Professor, University of Miami
Director Office of Research Education
CITI Program Course Coordinator



Health Canada Santé Canada

VITAMIN D

Date: August 16, 2007

Proper name(s): Vitamin D (Sweetman 2007; IOM 2003; O'Neil et al. 2001)

Common name(s): Vitamin D, vitamin D_2, vitamin D_3 (Sweetman 2007; IOM 2003; O'Neil et al. 2001)

Source material(s):

- Vitamin D_2/Ergocalciferol
  (Sweetman 2007; IOM 2003 O'Neil et al. 2001)
- Vitamin D_3/Cholecalciferol)
  (Sweetman 2007; IOM 2003; O'Neil et al. 2001)

Note: The slash (/) indicates that the terms are synonyms. Either term may be selected by the applicant.

Route(s) of administration: Oral

Dosage form(s): Those pharmaceutical dosage forms suited to oral administration, including but not limited to chewable tablets, caplets, capsules, strips, lozenges, powders or liquids where the dose is measured in drops, teaspoons or tablespoons, are acceptable. This monograph is not intended to include food-like dosage forms such as bars, gums or beverages.

Use(s) or Purpose(s): Statement(s) to the effect of:

General: A factor in the maintenance of good health (IOM 2006; IOM 1997).

Specific:

For all products:

- Helps in the development and maintenance of bones (IOM 2006; Shils et al. 2006; Groff and Gropper 2000; IOM 1997).

Canada

- Helps in the development and maintenance of teeth (Shils et al. 2006).
- Helps in the absorption and use of calcium and phosphorus (IOM 2006; Shils et al. 2006; Groff and Gropper 2000; IOM 1997).
- For products providing calcium as a medicinal ingredient, if the following statement is used it must be verbatim:
"Calcium intake, when combined with sufficient vitamin D, a healthy diet, and regular exercise, may reduce the risk of developing osteoporosis" (Shils et al. 2006; Groff and Gropper 2000; NIH 2000).

Dose-specific: For products providing daily doses of vitamin D at or above the Adequate Intake (AI) (adjusted for the life stage groups), the following use or purpose is acceptable:
Helps to prevent vitamin D deficiency (IOM 2006; Shils et al. 2006; Groff and Gropper 2000; IOM 1997).

See Appendix 1 for definitions and Table 2 in Appendix 2 for AI values.

Dose(s):

Table 1: Dose information for vitamin D presented as dose per day

Life stage group		Vitamin D (µg/day) Minimum[1]	Maximum[2]
Infants	0-12 mo	0.2	25
Children	1-3 y	0.2	25
	4-8 y	0.2	25
Adolescents	9-13 y	0.2	25
	14-18 y	0.8	25
Adults[3]	≥ 19 y	0.8	25

[1] Based on approximately 5% of the highest AI (IOM 2006). See Appendix 1 for definitions and Table 2 in Appendix 2 for AI values.
[2] These values are based on the *Food and Drug Regulations* Schedule F limit (HC 2007).
[3] Includes pregnant and breastfeeding women.

Conversion Factors:

1 IU of vitamin D activity per:
= 0.025 µg cholecalciferol (IOM 2006)
= 0.025 µg ergocalciferol

Duration of use: No statement required.

Risk information: Statement(s) to the effect of:

Caution(s) and warning(s): No statement required.

Contraindication(s): No statement required.

Known adverse reaction(s): No statement required.

Non-medicinal ingredients: Must be chosen from the current NHPD *List of Acceptable Non-medicinal Ingredients* and must meet the limitations outlined in the list.

Specifications: Must comply with the minimum specifications outlined in the current NHPD *Compendium of Monographs.*

References:

Groff J, Gropper S. Advanced Nutrition and Human Metabolism, 3rd edition. Belmont (CA): Wadsworth/Thomson Learning; 2000.

HC 2007: Health Canada. *Food and Drug Regulations* (F-27 – C.R.C., c.870). Ottawa (ON): Health Canada; 2007. [Accessed 2007-06-05]. Available at: http://laws.justice.gc.ca/en/F-27/C.R.C.-c.870/text.html

IOM 2006: Institute of Medicine. Otten JJ, Pitzi Hellwig J, Meyers LD, editors. Institute of Medicine. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Washington (DC): National Academies Press; 2006.

IOM 2003: Institute of Medicine. Committee on Food Chemicals Codex, Food and Nutrition Board, Institute of Medicine. Food Chemicals Codex, 5th edition. Washington (DC): National Academies Press; 2003.

IOM 1997: Institute of Medicine. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride. Washington (DC): National Academies Press; 1997.

NIH 2000: National Institute of Health. Osteoporosis Prevention, Diagnosis, and Therapy. NIH Consensus Statement Online 2000;17(1):1-36. Bethesda (MD): National Institute of Health; March 27-29, 2000. [Accessed 2007-03-21]. Available from: http://www.consensus.nih.gov/2000/2000Osteoporosis111html.htm

O'Neil MJ, Smith A, Heckelman PE, Budavari S, editors. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 13th edition. Whitehouse Station (NJ): Merck & Co., Inc.; 2001.

Shils ME, Olson JA, Shike M, Ross AC, editors. Modern Nutrition in Health and Disease, 10th edition. Philadelphia (PA): Lippincott Williams and Wilkins; 2006.

Sweetman SC, editor. Martindale: The Complete Drug Reference, 35th edition. London (UK): Pharmaceutical Press; 2007.

Canada

Appendix 1: Definitions

Adequate Intake (AI): The recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate; used when a Recommended Dietary Allowance (RDA) cannot be determined (IOM 2006).

Recommended Dietary Allowances (RDA): The average daily dietary nutrient intake level sufficient to meet the nutrient requirements of nearly all (97-98%) healthy individuals in a particular life stage and gender group (IOM 2006).

Appendix 2: AI Values

The AI values for vitamin D are provided below. For the purpose of this monograph, these values are intended to:

- provide targets for setting appropriate supplement dosage levels;
- provide the minimum dose for the use of the dose-specific use or purpose: "Helps to prevent vitamin D deficiency";
- facilitate the optional labelling of % AI values.

Table 2: Adequate Intake values based on life stage group (IOM 2006)

Life stage group		Vitamin D (µg/day)
Infants	0-12 mo	5
Children	1-3 y	5
	4-8 y	5
Adolescents	9-13 y	5
	14-18 y	5
Adults	19-50 y	5
	51-70 y	10
	>70 y	15
Pregnancy	14-50 y	5
Breastfeeding	14-50 y	5

CITI Collaborative Institutional Training Initiative

Human Research Curriculum Completion Report
Printed on Wednesday, March 30, 2011

Learner: Michael Spigarelli (username: spibf6)
Institution: University of Utah
Contact Information: Department: Pediatrics
Phone: 801 587-7513
Email: spig@umich.edu

Group 1.Biomedical Research Investigators and Key Personnel.:

Stage 2. Refresher Course Passed on 03/29/11 (Ref # 5831458)

Required Modules	Date completed	Score
History and Ethical Principles.	03/29/11	0
Regulations and Process, Part 1	03/29/11	100
Regulations and Process, Part 2	03/29/11	100
Informed Consent.	03/29/11	100
Social & Behavioral Research (SBR)	03/29/11	100
Genetics Research, Part 1	03/29/11	100
Genetics Research, Part 2	03/29/11	100
Records-Based Research, Part 1	03/29/11	100
Records-Based Research, Part 2	03/29/11	100
Records-Based Research, Part 3	03/29/11	100
Research with Protected Populations - Vulnerable Subjects: A Definition.	03/29/11	100
Vulnerable Subjects - Prisoners, Part 1	03/29/11	100
Vulnerable Subjects - Prisoners, Part 2	03/29/11	100
Studies With Minors, Part 1	03/29/11	100
Studies With Minors, Part 2	03/29/11	100
Studies With Minors, Part 3	03/29/11	100
Studies with Pregnant Women and Fetuses, Part 1	03/29/11	100
Studies with Pregnant Women and Fetuses, Part 2	03/29/11	100
Group Harms: Research with Culturally or Medically Vulnerable Groups.	03/29/11	100
FDA-Regulated Research, Part 1	03/29/11	100
FDA-Regulated Research, Part 2	03/29/11	100
Human Subjects Protections at the VA, Part 1	03/29/11	0
Human Subjects Protections at the VA, Part 2	03/29/11	100
HIPAA and Human Subjects Research.	03/29/11	50
Conflicts of Interest in Research Involving Human Subjects.	03/29/11	100
How to Complete the CITI Refresher Course and Receive a Completion Report	03/29/11	0

For this Completion Report to be valid, the learner listed above must be affiliated with a CITI participating institution. Falsified information and unauthorized use of the CITI course site is unethical, and may be considered scientific misconduct by your institution.

Paul Braunschweiger Ph.D.
Professor, University of Miami
Director Office of Research Education
CITI Course Coordinator

CITI Collaborative Institutional Training Initiative

Good Clinical Practice Course Curriculum Completion Report
Printed on Friday, September 7, 2012

Learner: Michael Spigarelli (username: spibf6)
Institution: University of Utah
Contact Information: Department: Pediatrics
Phone: 801 587-7513
Email: spig@umich.edu

Good Clinical Practice Course (US FDA focus):

Stage 1. Stage 1 Passed on 09/06/12 (Ref # 8658815)

Elective Modules	Date Completed	Score
GCP Introduction	09/06/12	3/3 (100%)
Overview of New Drug Development	04/17/09	5/6 (83%)
ICH Overview	04/17/09	5/5 (100%)
ICH - Comparison Between ICH GCP E6 and U.S. FDA Regulations	09/06/12	3/4 (75%)
Conducting Investigator-Initiated Studies According to FDA Regulations and Good Clinical Practices	04/17/09	2/4 (50%)
Investigator Obligations in FDA-Regulated Clinical Research	04/17/09	5/5 (100%)
Managing Investigational Agents According to GCP Requirements	04/17/09	5/5 (100%)
Conducting Clinical Trials of Medical Devices	04/17/09	5/6 (83%)
Informed Consent	04/17/09	4/4 (100%)
Detection and Evaluation of Adverse Events	04/17/09	5/5 (100%)
Reporting Serious Adverse Events	04/17/09	3/6 (50%)
Audits and Inspections in Clinical Trials	04/17/09	5/8 (63%)
Monitoring of Clinical Trials by Industry Sponsors	04/17/09	10/10 (100%)
Completing the CITI GCP Course	04/17/09	no quiz

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Paul Braunschweiger Ph.D.
Professor, University of Miami
Director Office of Research Education
CITI Course Coordinator

CITI Collaborative Institutional Training Initiative

Good Clinical Practice Course Curriculum Completion Report
Printed on 3/18/2013

Learner: David Viskochil (username: dviskoch)
Institution: University of Utah
Contact Information
2C412 S.O.M.
50 N. Medical Dr.
Salt Lake City, Utah 84132 USA
Department: Pediatrics
Phone: 801 581-8943
Email: dave.viskochil@hsc.utah.edu

Good Clinical Practice Course (US FDA focus):

Stage 1. Stage 1 Passed on 03/18/13 (Ref # 9917054)

Elective Modules	Date Completed	Score
GCP Introduction	03/08/13	3/3 (100%)
Overview of New Drug Development	03/08/13	5/5 (100%)
ICH Overview	03/08/13	4/4 (100%)
ICH - Comparison Between ICH GCP E6 and U.S. FDA Regulations	03/11/13	4/4 (100%)
Conducting Investigator-Initiated Studies According to FDA Regulations and Good Clinical Practices	03/11/13	3/3 (100%)
Investigator Obligations in FDA-Regulated Clinical Research	03/17/13	4/5 (80%)
Managing Investigational Agents According to GCP Requirements	03/17/13	5/5 (100%)
Conducting Clinical Trials of Medical Devices	03/17/13	3/3 (100%)
Informed Consent	03/08/13	4/4 (100%)
Detection and Evaluation of Adverse Events	03/17/13	4/4 (100%)
Reporting Serious Adverse Events	03/11/13	4/4 (100%)
Audits and Inspections in Clinical Trials	03/17/13	5/5 (100%)
Monitoring of Clinical Trials by Industry Sponsors	03/17/13	8/8 (100%)
Completing the CITI GCP Course	03/18/13	no quiz

For this Completion Report to be valid, the learner listed above must be affiliated with a CITI participating institution. Falsified information and unauthorized use of the CITI course site is unethical, and may be considered scientific misconduct by your institution.

Paul Braunschweiger Ph.D.
Professor, University of Miami
Director Office of Research Education
CITI Course Coordinator

3/18/13

Return

CITI Collaborative Institutional Training Initiative

Human Research Curriculum Completion Report
Printed on Monday, April 13, 2009

Learner: David Viskochil (username: dviskoch)
Institution: University of Utah
Contact Information: 2C412 S.O.M.
50 N. Medical Dr.
Salt Lake City, Utah 84132 USA
Department: Pediatrics
Phone: 801 581-8943
Email: dave.viskochil@hsc.utah.edu
Group 1.: Biomedical Research Investigators and Key Personnel.

Stage 3. Refresher 3 Course Passed on 04/13/09 (Ref # 2416426)

Required Modules	Date completed	Score
History and Ethical Principles.	04/13/09	0
Regulations and Process, Part 1	04/13/09	100
Regulations and Process, Part 2	04/13/09	100
Informed Consent.	04/13/09	100
Social & Behavioral Research (SBR)	04/13/09	100
Genetics Research, Part 1	04/13/09	100
Genetics Research, Part 2	04/13/09	100
Records-Based Research, Part 1	04/13/09	100
Records-Based Research, Part 2	04/13/09	100
Records-Based Research, Part 3	04/13/09	100
Research with Protected Populations - Vulnerable Subjects: A Definition.	04/13/09	100
Vulnerable Subjects - Prisoners, Part 1	04/13/09	100
Vulnerable Subjects - Prisoners, Part 2	04/13/09	100
Studies With Minors, Part 1	04/13/09	100
Studies With Minors, Part 2	04/13/09	0
Studies With Minors, Part 3	04/13/09	100
Studies with Pregnant Women and Fetuses, Part 1	04/13/09	100
Studies with Pregnant Women and Fetuses, Part 2	04/13/09	0
Group Harms: Research with Culturally or Medically Vulnerable Groups.	04/13/09	100
FDA Regulated Research, Part 1	04/13/09	100
FDA Regulated Research, Part 2	04/13/09	50
Human Subjects Protections at the VA, Part 1	04/13/09	100
Human Subjects Protections at the VA, Part 2	04/13/09	100
HIPAA and Human Subjects Research.	04/13/09	100
Conflicts of Interest in Research Involving Human Subjects.	04/13/09	50

How to Complete the CITI Refresher Course and Receive a Completion Report	04/13/09	0

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Paul Braunschweiger Ph.D.
Professor, University of Miami
Director Office of Research Education
CITI Course Coordinator

Death Form Source Doument

Participant ID	1. Report Date	2. Staff ID
101-☐☐☐-☐☐☐☐☐☐	☐☐/☐☐/☐☐☐☐	☐☐☐
Protocol # Site # Screen #	Month Day Year	

1. Date of death: ☐☐/☐☐/☐☐☐☐
   mm dd yyyy

3. Status in study at time of death: ☐
   1-On protocol treatment
   2-Within 30 days of the last dose of protocol treatment
   3-More than 30 days from the last dose of protocol treatment
   9-Before protocol treatment started

4. Choose one of the following reasons for primary cause of death ☐
   1-Neurofibromatosis
   2-Concomitant condition
   3-Treatment toxicity
   9-Other: (Provide stated cause of death.)
   _____

   _____

   _____

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

Death Form Source Doument

Participant ID	1. Report Date	2. Staff ID
101-☐☐☐-☐☐☐☐☐☐	☐☐/☐☐/☐☐☐☐	☐☐☐
Protocol # Site # Screen #	Month Day Year	

2. Date of death: ☐☐/☐☐/☐☐☐☐
   mm dd yyyy

3. Status in study at time of death: ☐
   1-On protocol treatment
   2-Within 30 days of the last dose of protocol treatment
   3-More than 30 days from the last dose of protocol treatment
   9-Before protocol treatment started

4. Choose one of the following reasons for primary cause of death ☐
   1-Neurofibromatosis
   2-Concomitant condition
   3-Treatment toxicity
   9-Other: (Provide stated cause of death.)
   _____

   _____

   _____

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

Personal Health History

Personal Information:

Date: _____

Date of Birth _____

Zip Code: _____

Ethnicity: ☐ White ☐ Hispanic ☐ Asian ☐ Black
☐ Native American ☐ Pacific Islander ☐ Other: _____

Height_____

Weight_____

Medications:
Please list all medications, vitamins, calcium or herbal supplements that you have taken during the past year (indicate starting dates for new medications):

Medication	Amount	How Often	Reason

Do you have any allergies to food or medication? ☐ Yes ☐ No

If yes, what are they? _____

What was your birth weight? _____ lbs. _____ oz.

Were you born: ☐ Early ☐ Full term

If you were born early, how many weeks before your due date? _____

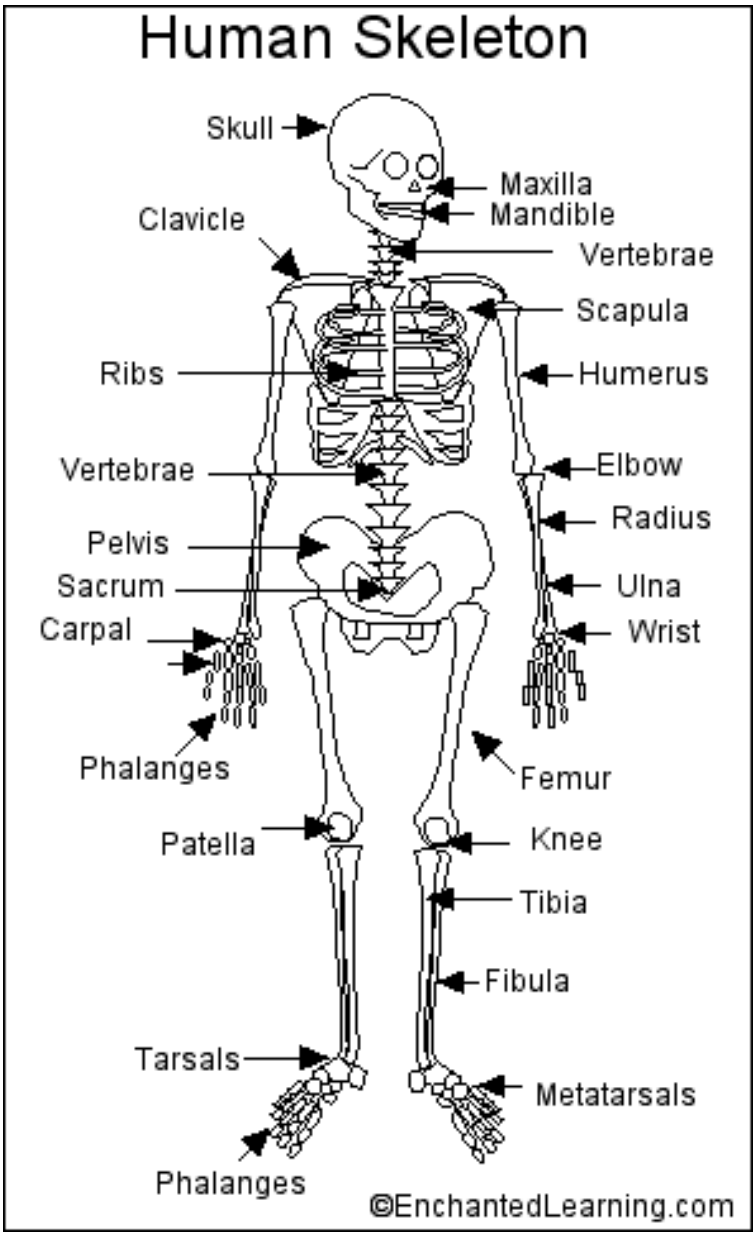
Have you been diagnosed with ADHD (attention déficit hyperactivity disorder)?
☐ Yes ☐ No

Have you ever broken a bone?

☐ No (skip the rest of this page)

☐ Yes

If yes, please look at the skeleton below; circle the bone(s) and mark on the table which bone(s) fractured. Then, the study physician will complete Page 4 with you (additional questions about each broken bone).



For Females:

Have you started to have a period? ☐ Yes ☐ No
If yes, please answer the following question:

How old were you when you had your first period? _____

For Males:

Have you started shaving? ☐ Yes ☐ No
If yes, please answer the following questions:

How old were you when you first started shaving?_____

How old were you when you first noticed pubic and armpit hair? _____

To Be Completed with Study Physician:

Event	Age at Fracture	Location Code (use multiple codes for multiple simultaneous fractures)	Fracture Type Code	Trauma description code
1.				
2.				
3.				
4.				
5.				

Event	Treatment Code	Complications Code	Where was treatment and where were X-rays taken?
1.			
2.			
3.			
4.			
5.			

For Study Physician Use:

Fracture Location Code	
a = toes/foot	j = shoulder
b = ankle	k = humerus
c = tibia	l = radius
d = fibula	m = ulna
e = lower leg unspec	n = lower arm unspec
f = hips/pelvis	o = wrist
g = spine/neck	p = hand/fingers
h = ribs	q = other
i = skull/face	r = uncertain which

Fracture Type Code (use as many as apply)
s = simple
t = compound (through the skin)
u = complete
v = incomplete
w = stress/fatigue
x = pathologic (due to disease)
y = multiple
z = unknown

Treatment Code (use as many as apply)
a = casting
b = pins/plates
c = graft
d = surgery unspec.
e = other (specify)
f = unknown

Complications Code (use as many as apply)
k = none (bone set, no sequelae)
l = infection
m = won't heal
n = pain in area of fracture
o = limited motion/functional impairment
p = other (specify)

Trauma Code	
Yes	Certain trauma (e.g. MVA, fall)
No	No trauma (apparently minimal reason for break)
Unknown	Unknown level of trauma

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).

NF1 - Telephone Assessment

The purpose of this form is to assist the coordinator to screen people who may not be eligible due to medical conditions or medications.

Ask about general categories of medications and list them down by name and dosage. This list will be verified by the appropriate co-investigator, who will be ultimately responsible for inclusion or exclusion on medical grounds.

Name of potential study participant: _____
(This will be replaced by a study number if the person is enrolled)

Does the potential study participant have (or ever been told they have) the following conditions:

□ osteoporosis ?
Treatment with bisphosphonates or calcitonin? _____
Other treatment?

□ treatment with glucocorticoids for over 3 months?
Name of glucocorticoids _____

□ current treatment for epilepsy / seizures?
Name of drug _____

□ current treatment with blood thinners (anticoagulants)?
Name of drug _____

□ current or past treatment for thyroid or parathyroid problems?
Name of drug or treatment (when?)_____

□ Paget's disease

□ kidney failure

□ kidney stone in the last 5 years?

□ pregnant, or planning a pregnancy within time frame of study

□ any hip or spine prostheses? Scoliosis treatment, hip replacement?

Any other chronic health concerns /comments_____
_____
_____

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).

NF1 - Telephone Assessment

The purpose of this form is to assist the coordinator to screen people by telephone to ensure there is a reasonable probability that they have NF1. If there is doubt, potential participants can be offered a physical examination to confirm NF1 by study clinicians. Medical records can also be consulted, with the appropriate written permission.

Name of potential study participant: _____
(This will be replaced by a study number if the person is enrolled)

Does the potential study participant have (or ever been told they have):

□ café au lait macules? How many over 15mm (approx finger width)_____

□ intertriginous freckling? Where _____

□ any neurofibromas?

□ optic glioma?

□ Lisch nodules?

□ scoliosis?

□ long bone dysplasia / pseudarthrosis?

□ an affected family member?

Physician: _____ **NF 1 EXAMINATION FORM** Registry #_____

Name (Subject): _____DOB: _____Date of Exam: _____Age at Exam:____

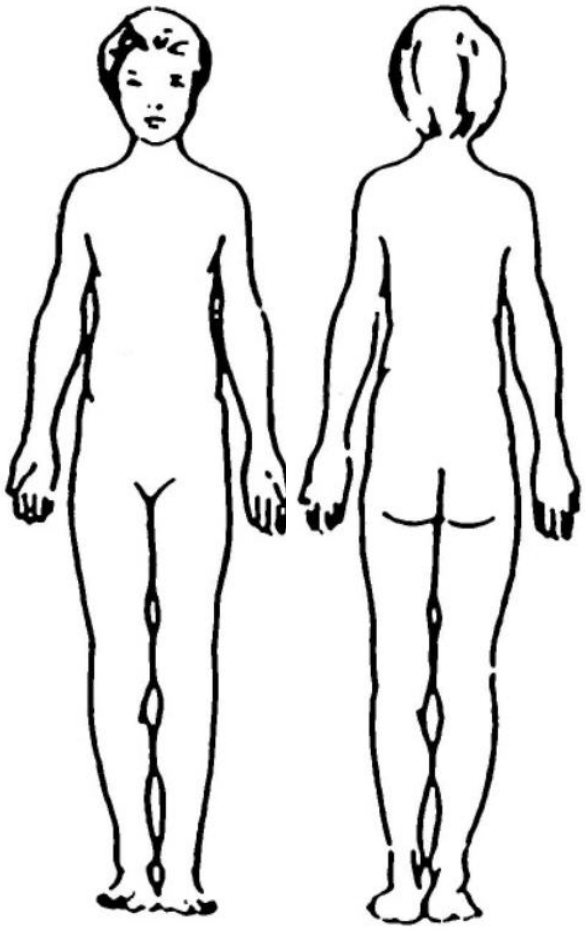
Proband: Y N Name of Proband: _____Relation to Examinee: _____
(if other than patient)

Gender: M F Ethnicity: American Indian/Alaska Native Asian Black/African America Native Hawaiian/Pacific Islander White More Than One Race Unknown/ Unreported

NF Inheritance: Sporadic Familial: Mother Father Unknown Sib(s)_____			
Ascertainment: Primary Care Dr.	Specialist	Self Referral	NF Support Group
Ht: _____(%) NF1_____(%)	Wt:_____(%) NF1_____(%)		
Head Circum: _____(%) NF1: _____(%)	Blood Pressure: /	Age at Dx:	
Dominant Hand: R L Ambidextrous			

DERMATOLOGY

Cafe au Lait Spots:	0.5-1.5 cm	>1.5 cm		
Number:				
Freckling/Location:	-	+	Groin: R L	
Ax: R L	Atypical:		Other:	



NEUROFIBROMAS

Paraspinal:	-	+	u	cerv	thor	lumb	Bx: Y N
Cutaneous/Pendulous:	-	+	u	<10	10-100	>100	Bx: Y N
Subcutaneous:	-	+	u	<10	10-100	>100	Bx: Y N
Plexiforms:	-	+	u	<10	10-100	>100	Bx: Y N
1 Location: Face/ Head/ Neck/ Leg: R L/ Eyes: R L /Trunk/Arms: R L							Bx: Y N
2 Location: Face/ Head/ Neck/ Leg: R L/ Eyes: R L /Trunk/Arms: R L							Bx: Y N
3 Location: Face/ Head/ Neck/ Leg: R L/ Eyes: R L/Trunk /Arms: R L							Bx: Y N

OTHER SKIN FINDINGS (Circle all that apply)

Hemangiomas:	- +	mild/mod/sev	Head Neck Trunk Leg Arm
HypopigmentedAreas:	- +	mild/mod/sev	Head Neck Trunk Leg Arm
Hyperpigmentation:	- +	mild/mod/sev	Head Neck Trunk Leg Arm
Xanthogranulomas:	- +	mild/mod/sev	Head Neck Trunk Leg Arm
Troublesome Itch:	- +	mild/mod/sev	Head Neck Trunk Leg Arm
Other/Comments			

OCULAR ABNORMALITIES

Cataract/Opacity:	- + Unk R L Bil Unknown
Lisch Nodules:	- + Unk On Slit Lamp: - R L
Proptosis:	- + Unk R L Bilateral Unknown
Strabismus:	- + Unk R L Bilateral Unknown
Optic Glioma:	Abs:Scan/Clinical Presentation Asmp/Symp Unknown
Location	Unilateral: R L Bilateral
Optic Glioma TX:	NA No Tx Chemo Surg Combo Rad Unknown
Other/Comment:	

PSYCHOLOGY/INTELLECTUAL DEVELOPMENT

Behavior:	ADHD Autism Behavior Problems Comments:_____
Cognition:	Normal Mild Delay Signi. Delay Unknown IQ (age ___) Full____ Verbal ____ Perform____ Testing: Yes No Type:_____ Edu. Completed:_____
Learning Problems:	None Unknown Present Type: Coordination Prob Y / N Speech Prob Y / N

CARDIOVASCULAR

Congenital Heart Disease:	-: clin | echo +: clin | card Unk Aortic Stenosis ASD Patent Ductus Arteriosus VSD Pulmonic Stenosis Tetralogy of Fallot Unknown Other: _____
Hypertension:	- + Treatment:_____
Vascular Anomalies:	- + Unk Renal Artery Stenosis Arterial Stenosis Moya Moya Other

NEUROLOGY

Headaches(#/Month):	- + Migraines # ___ Other #___ Multiple Types #____ Unknown Type _____
Hydrocephalus:	- Unk + Clinical| Scan: Non-communicating Communicating Aqueductal Stenosis Other: _____
Seizures:	None Febrile Only Hypsarrhymia Generalized Partial Multiple Present-type Unknown
Age of OnsetSeizures:	NA Congenital Infantile Onset Unknown Unknown EEG
SN Hearing Loss:	Abs / Present: Clinically/Audiometry Age@Onset:_____ Partial: R L B Unknown

IMAGING

Brain:	CT or MRI: Nl Abnl T2HI Unknown Age of Imaging ____ Comments:_____
Spine:	CT or MRI: Nl Abnl Unknown Age of Imaging ____ Comments:_____
Other Areas:	- + Unknown

DYSMORPHIC FEATURES

Photo:	Age:_____ Yes No
Noonan Phenotype:	Yes No Possible Unknown
Facial Asymmerty:	Yes No Possible Unknown
Soft Tissue Asymmety:	Yes No Possible Unknown
Orbit Shading:	Yes No Possible Unknown
Other/Comments	

ENDOCRINOLOGY

Puberty:	Age:_____ NA Unknown
	Tanner Stage: PH___ Br ____ Gen___
Menarche:	Age: _____ NA Unknown
Other Problems:	Yes No Unknown
Stature:	<5 5-10 10-50 50-90 90-95 >95
Growth Hormone:	- + Comments:_____

ORTHOPEDIC ABNORMALITIES

Abnormality	-/+ Clinical	-/+ Rad	Unk	Age
Long Bone Bowing (bone____)				
Long Bone Thinning:				
Long Bone Cortical Atrophy:				
Pseudarthrosis (bone_____)				
Dysplastic Sphenoid Wing:				
Bone Cysts				
Bony Asymmetry:				
Bony Overgrowth:				
Dysplastic Vertebrae:				
Spinal Compression:				
Scoliosis/Kyphosis:				

Curve/Degree Present:	NA		Degrees:		Unk
Level of Major Curve: # of Vert _____	NA	Cerv	Thor	Lum	Unk
Fracture(s) Location_____	-	+	Unk	Age: _____	
Pectus Deformity	-	+	Exc	Car	Mix
Other Orthopedic Anomaly:					

GENETICS:___

Mutation:	-	+	Not tested	Unk
Type of Mutation:	Deletion	SSV	MisS	NonS
Exact Mutation:				

ADDITIONAL PROBLEMS

Problem	-	+	Unk	Age
GI Problems				
Neoplasm:				
Dentition Abn:				

Pain Issue:

Comments:

FAMILY HX:

Cancer NF1 Type_____

Cancer NON NF1 Type_____

Other comments:_____

Pseudarthrosis Short Stature Scoliosis

Vasuclopathy Dev. Delay Optic Pathway Tumor

MEDICATIONS:

IMPRESSIONS:

RECOMMENDATIONS:

Vitamin Diary Name/ID _____Next Clinic Visit _____
Medication Log start date: _____ _____end date: _____
Please record your study vitamin administration. Remember to bring this diary and vitamin bottles (empty or with drops) with you to each study visit.

Date	Ddrops Yes/No	Calcium Yes/No	Other meds	Comments (Please log reason for missed dose(s) or any signs or symptoms- cold, headache etc.)
/ / 14				
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Study coordinator name_____
Study coordinator's phone number _____
Signature of Subject-verified log is accurate_____ Date_____
Signature of Coordinator- verified study log with subject _____Date_____

Vitamin Diary Name/ID _____Next Clinic Visit _____
Medication Log start date: _____ _____end date: _____
Please record your study vitamin administration. Remember to bring this diary and vitamin bottles (empty or with drops) with you to each study visit.

Date	Ddrops Yes/No	Calcium Yes/No	Other meds	Comments (Please log reason for missed dose(s) or any signs or symptoms- cold, headache etc.)
/ / 15				
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Study coordinator name_____
Study coordinator's phone number _____
Signature of Subject-verified log is accurate_____ Date_____
Signature of Coordinator- verified study log with subject _____Date_____

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

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

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

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

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

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

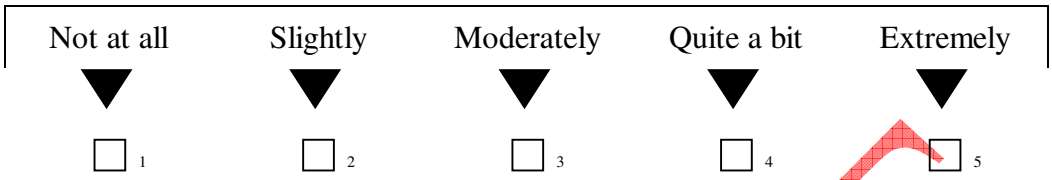
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b Accomplished less than you would like	1	2	3	4	5
c Were limited in the kind of work or other activities	1	2	3	4	5
d Had difficulty performing the work or other activities (for example, it took extra effort)	1	2	3	4	5

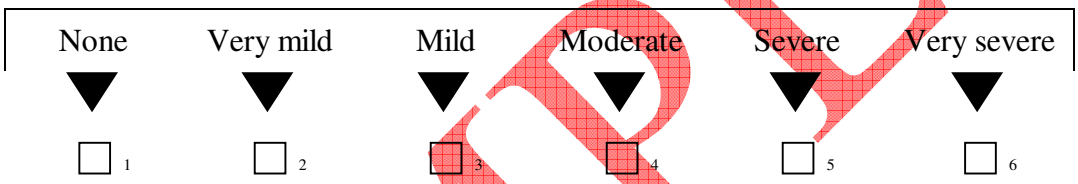
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b Accomplished less than you would like	1	2	3	4	5
c Did work or other activities less carefully than usual	1	2	3	4	5

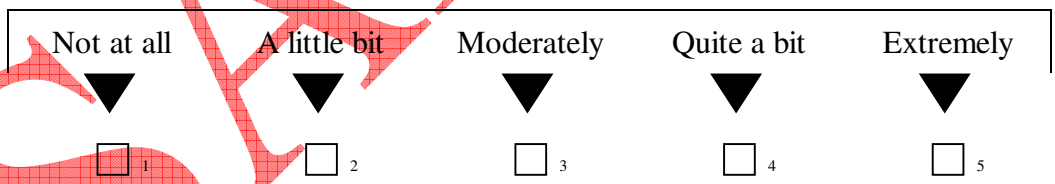
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?



7. How much bodily pain have you had during the past 4 weeks?



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



9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. 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 <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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

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

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Date_____

To Whom It May Concern:

The researchers at the University of Utah would like invite you to participate in a Vitamin D clinical trial. We are asking if you would like to participate in this study because you are an adult between 25-40 years of age with neurofibromatosis type 1 (NF1). This research study is evaluating vitamin D as a possible treatment for adult NF1 individuals with low Vitamin D levels as adults with NF1 have a higher risk of osteopenia and osteoporosis, a condition of low bone density that can lead to fragile bones and bone breakage.

If you are interested in this clinical trial or have questions, please feel free to contact me at 801-587-9017 (toll-free at (877) 942-6600).

Thank you for your interest in our research.

Sincerely,

Heather Hanson

VIT D STUDY

Scan and email or Fax
COVER SHEET

Email to Heather.hanson@hsc.utah.,edu
Or
FAX to: 1-801-587-9166

Site # :(circle one) _UT, UBC, CIN or UH_ Staff Name_____

Telephone #:_____

Date: _____

Participant ID: _____ _____

Total # of pages (including cover):_____ _____

Please check which CRFs you're submitting for this participant:
Visit #-baseline and assessment visit numbers identifiers- 00, 6, 12, 18 and 24,

FORM #	VISIT #	FORM #	VISIT #
☐ 100	_____	☐ 114	_____
☐ 101	_____	☐ 115	_____
☐ 102	_____	☐ 116	_____
☐ 103	_____	☐ 117	_____
☐ 104	_____	☐ 118	_____
☐ 105	_____	☐ 119	_____
☐ 106	_____	☐ 120	_____
☐ 107	_____	☐ 121	_____
☐ 108	_____	☐ 122	_____
☐ 109	_____	☐ 123	_____
☐ 110	_____	☐ 124	_____
☐ 111	_____	☐ 125	_____
☐ 112	_____	☐ 126	_____
☐ 113	_____	☐ 127	_____

_____ I have reviewed the data, and no PHI is being sent in this transmission.

Vitamin D Clinical Trial Source Document
Off Study Form

Subject ID#_____ Date of Report_____ Date aware of SAE_____ Visit #_____

1. Date of last contact: ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)

2. Visit # completed ☐☐ or Follow up year ☐☐

3. Reason why patient off study (check one of the following items)

   ☐ Completed all follow up visits per protocol

   ☐ Death—complete death form

   ☐ Lost to follow-up

   ☐ Withdrawal of consent for any further data submission

   ☐ Other (specify) _____

Vitamin D Clinical Trial Source Document
Serious Adverse Event Form

Subject ID#_____ Date of Report_____ Date aware of SAE_____ Visit #_____

5. Event term (CTCAE v. 3) _____

6. Severity -check one:
   - ☐ Grade 2 – Moderate
   - ☐ Grade 3 – Severe
   - ☐ Grade 4 – Life threatening
   - ☐ Grade 5 - Death

7. Date of onset: ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)

8. Relationship to study drug (check one):
   ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite

9. If unrelated to study drug, specify cause: _____

10. Action taken/ corrective therapy (check all that apply)
    - ☐ Inpatient visit or hospital admission
    - ☐ Prescription medication
    - ☐ ER or out-patient visit
    - ☐ Procedure performed
    - ☐ Other _____

11. Action taken regarding study drug (check one):
    ☐ Reduced ☐ Interrupted ☐ Discontinued ☐ None

12. Outcome
    - ☐ Resolved and date of resolution ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)
    - ☐ Continuing (at this report date)
    - ☐ Recovered with residual effect ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)
    - ☐ Required or prolonged hospitalization
    - ☐ Resulted in permanent or severe disability ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)
    - ☐ Required intervention to prevent permanent damage or disability
    - ☐ Died—Complete Death Form ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)

13. Is the event an expected side effect of Vitamin D? Yes ☐ No ☐

14. Med Watch form was completed and sent to University of Utah Yes ☐ No ☐
    (University of Utah fax # 1-801-587-9166 or E-mail)

15. Completed SAE Report and sent to University of Utah. Yes ☐ No ☐
    (University of Utah fax # 1-801-587-9166 or E-mail)

_____ _____
PI Signature date

Vitamin D Clinical Trial Source Document
Adverse Event Form

Subject ID#_____ Date of Report_____ Date aware of AE_____ Visit #_____

4. Did the patient have any new, continuing, or resolved adverse events since the last visit?
   - ☐ Yes--If yes, record below.
   - ☐ No--If no, stop here.

5. AE term (CTCAE v 3): _____

6. Date of Onset: ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)

7. Continuing ☐ Yes or Date Resolved: ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)

8. Grade/Severity*: ☐

9. Relationship to Study Drug*: ☐

10. Outcome*: ☐

11. Effect on Study Drug dosage*: ☐

12. Action Taken Regarding Adverse Event*: ☐

13. Is the event an expected side effect of Vitamin D? ☐ Yes ☐ No

14. Is the event considered Serious? ☐ Yes ☐ No If yes, complete SAE Report, SAE Form, and Med-Watch Forms and send to University Hospital (fax # 1-801-587-9166 or E-mail))

Severity*	Relationship*	Outcome*	Effect on study drug*	Action*
G1-Mild	1-Unrelated	1-Complete recovery w/o residual effect	1- None Continue dose	1-None
G2-Moderate	2-Unlikely	2-Recovered with residual effect	2-Interrupted On hold	2-Prescription
G3-Severe	3-Possibly	3-Recovered with persistent effect	3-Reduced Cut back on dose	3-OTC/non-RX
G4-Life Threatening	4-Probably	4-Not yet recovered	4-Discontinued	4-Hospitalization
G5-Death	5-Definitely	5-Died		5. Other – complete Comment Form

Vitamin D Clinical Trial
Inclusion Criteria Form (page 1 of 2)

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

Inclusion Criteria **All inclusion criteria must be checked "YES" or NA in order for a participant to be eligible.**			
	YES	**NO**	**N/A**
1. Signed informed consent/assent statements by parent or legal guardian. a. Date consent/assent and HIPAA signed:☐☐/☐☐/☐☐☐☐ mm dd yyyy NOTE: Consent date example: 04/21/2012	☐	☐	
2. Is the patient ≥ 24 years 12 months and ≤ 40 years at time of study enrollment? a. Date of birth:☐☐/☐☐/☐☐☐☐ mm dd yyyy	☐	☐	
3. Does the subject meet all diagnostic criteria of individuals with NF1 on physical examination?	☐	☐	
3. The subject has not taken bisphosphonates, calcitonin (treatment for osteoporosis) or glucocorticoids for over 3 months?	☐	☐	
4 The subject is not taking some types of seizure medications, blood thinners, and or thyroid treatments?	☐	☐	
5. The female subject is not pregnant? a. Date urine pregnancy test done :☐☐/☐☐/☐☐☐☐ mm dd yyyy	☐	☐	
6. Does the subject's current vitamin D, level fall below 30ng/ml (75nmol/L) and above 8ng/ml? a. Date of last Vitamin D serum level:☐☐/☐☐/☐☐☐☐ mm dd yyyy	☐	☐	
7. Subject willing to comply with the two-year study protocol?	☐	☐	☐
8. Subject willing to obtain blood samples on routine venipuncture	☐	☐	☐
9.. Subject has not had calcium supplementation in last 6 months equal to or greater than 1000mg	☐	☐	☐
10. Subject does not have a history of kidney stones and hypercalciuria?	☐	☐	

Vitamin D Clinical Trial Source Document
Inclusion Criteria Form (page 2 of 2)

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

Inclusion Criteria **All inclusion criteria must be checked "Yes" or NA in order for a participant to be eligible.**			
	YES	**NO**	**N/A**
9. Subject does not have any metal instrumentation in spine or hip?	☐	☐	
10. Has the study investigator reviewed and confirmed that all inclusion criteria have been satisfied and eligibility checklist has been signed and dated?	☐	☐	
11. Medications taken within 30 days prior to screening have been recorded in subject research record.	☐	☐	
12. Will the study treatment start within 14 days of enrollment. (Enrollment begins when PI signs and dates eligibility checklist per Q.10 above.)	☐	☐	
13. Has the study site PI been contacted to review subject's eligibility prior to study enrollment?	☐	☐	
	☐	☐	

Study Investigator has reviewed and confirmed all inclusion criteria and has confirmed study enrollment.

PI Signature **Date**

Vitamin D Clinical Trial Source Document
Medical History
Initial

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

Was the Medical History done at this visit? ☐ Yes ☐ No

1. Allergies	1a. ☐ Yes ☐ No	4b.

Please check the appropriate box. If significant or new abnormalities are detected, please comment.

Body System	Normal	Abn	ND	Comment
2. H/E/E/N/T	2a. ☐	☐	☐	2b.
3. Neck	3a. ☐	☐	☐	3b.
4. Respiratory	4a. ☐	☐	☐	4b.
5. Cardiovascular	5a. ☐	☐	☐	5b.
6. Gastrointestinal	6a. ☐	☐	☐	6b.
7. Musculoskeletal	7a. ☐	☐	☐	7b.
8. Dermatologic	8a. ☐	☐	☐	8b.
9. Hematopoietic/Lymph	9a. ☐	☐	☐	9b.
10. Endocrine/Metabolic	10a. ☐	☐	☐	10b.
11. Urinary	11a. ☐	☐	☐	11b.
12. Genitalia	12a. ☐	☐	☐	12b.
13. Breasts	13a. ☐	☐	☐	13b.
14. Pelvis	14a. ☐	☐	☐	14b.
15. Abdomen	15a. ☐	☐	☐	15b.
16. Neurologic	16a. ☐	☐	☐	16b.
17. Psychological	17a. ☐	☐	☐	17b.
18. Other	18a. ☐	☐	☐	18b.

Vitamin D Clinical Trial Source Document
Medical History
Interim

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

Was the Medical History done at this visit? ☐ Yes ☐ No

1. Allergies	1a. ☐ Yes ☐ No	1b.
Please check the appropriate box. If significant or new abnormalities are detected, please comment.		
Body System	**Normal Abn ND**	**Specify if Abn or change from baseline:**
2. H/E/E/N/T	2a. ☐ ☐ ☐	2b.
2. Neck	6a. ☐ ☐ ☐	3b.
4. Respiratory	4a. ☐ ☐ ☐	4b.
5. Cardiovascular	5a. ☐ ☐ ☐	5b.
6. Gastrointestinal	6a. ☐ ☐ ☐	6b.
7. Musculoskeletal	7a. ☐ ☐ ☐	7b.
8. Dermatologic	8a. ☐ ☐ ☐	8b.
9. Hematopoietic/Lymph	9a. ☐ ☐ ☐	9b.
10. Endocrine/Metabolic	10a. ☐ ☐ ☐	10b.
11. Urinary	11a. ☐ ☐ ☐	11b.
12. Pelvis	12a. ☐ ☐ ☐	12b.
13. Abdomen	13a. ☐ ☐ ☐	13b.
14. Neurologic	14a. ☐ ☐ ☐	14b.
15. Psychological	15a. ☐ ☐ ☐	15b.
16. Other	16a. ☐ ☐ ☐	16b.

Vitamin D Clinical Trial Source Document
On Study Form

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

1. Participant Eligible Yes ☐ No ☐
2. Date Participant Enrolled ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)
3. Date Vitamin D started: ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)
4. Date Calcium started: ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)

Vitamin D Clinical Trial Source Document
Pregnancy Test Form

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

Was the pregnancy test done at this visit? ☐ Yes ☐ No

1. If the patient is female of child-bearing potential, was urine pregnancy test done?
☐ Yes ☐ No ☐ N/A

If yes,
1a. Date: ☐☐/☐☐/☐☐☐☐ (mm/ddy/yyyy)

1b. Result: ☐ Positive ☐ Negative ☐ Undetermined * (*conduct serum pregnancy test)

2. If patient is female of child-bearing potential, was serum pregnancy test done?
☐ Yes ☐ No ☐ N/A

If yes,
2a. Date: ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)

2b. Result: ☐ Positive ☐ Negative ☐ Undetermined – Repeat test in 3-5 days.

Vitamin D Clinical Trial Source Document
Activity Questionaire Form 1 of 2

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

INSTRUCTIONS: Circle all activities that you did **at least 10 times** in the past year.
(Do not include time spent in school physical education classes. Be sure to include any sport teams that you participated on.)

Aerobics	Hiking	Swimming
Band/Drill Team	Ice Skating	Tennis
Baseball	Roller blading	Trampoline
Basketball	Roller skating	Volleyball
Bicycling	Running for exercise	Walking
Bowling	Scootering	Water Skiing
Cheerleading	Skateboarding	Weight Training
Dance	Snow Skiing	Wrestling
Football	Soccer	Others:_____
Garden/Yard work	Softball	_____
Gymnastics	Street Hockey	_____

Write the activities you circled here

Check the months you participated in those activities here

Describe how often/how long you did it here
(use numbers only, do not use "sometimes" or "frequently")

Activity	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Months per Year	Days per Week	Minutes per day

1. How many times **in the past 14 days** have you done at least 20 minutes of exercise **hard enough to make you breathe heavily** and make your heart beat fast? (Hard exercise includes, for example, playing basketball, jogging, or fast bicycling; include time in physical education class.)
   - ☐ None
   - ☐ 1 to 2 days
   - ☐ 3 to 5 days
   - ☐ 6 to 8 days
   - ☐ 9 or more days

2. How many times **in the past 14 days** have you done at least 20 minutes of **light exercise that was not hard enough to make you breathe heavily** and make your heart beat fast? (Light exercise includes playing basketball, walking or slow bicycling; include time in physical education class.)
   - ☐ None
   - ☐ 1 to 2 days
   - ☐ 3 to 5 days
   - ☐ 6 to 8 days
   - ☐ 9 or more days

3. During a normal week, how many **hours a day** do you watch television and videos, or play computer or video games before or after school?
   - ☐ None
   - ☐ 1/2 hour a day
   - ☐ 1 hour a day
   - ☐ 2 hours a day
   - ☐ 3 hours a day
   - ☐ 4 hours a day
   - ☐ 5 or more hours a day

4. During the past 12 months, how many team or individual sports or activities did you participate in **on a competitive level**, such as varsity or junior varsity sports, intramurals, or out-of-school programs?
   - ☐ None
   - ☐ 1 activity
   - ☐ 2 activities
   - ☐ 3 activities
   - ☐ 4 or more activities

   What activities did you compete in?

   _____ _____
   _____ _____
   _____ _____
   _____ _____

Vitamin D Clinical Trial Source Document
Additional Relevant Laboratory Results Form

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

1. Reason for additional relevant laboratory results.

☐ 1a. AE/SAE 1b. CTCAE v 3 description _____

2c. AE/SAE onset date ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)

☐ 3d. Other (specify) _____

Lab Test	Lab Value	Unit	Normal Range	Normal * Abn	If Abn √NCS* √ AE*	Collection Date (mm/dd/yyyy)
4.	4a.	4b.	4c.	4d. ☐ ☐	4e. ☐ ☐	4f. ____/____/_____
5.	5a.	5b.	5c.	5d. ☐ ☐	5e. ☐ ☐	5f. ____/____/_____
6.	6a.	6b.	6c.	6d. ☐ ☐	6e. ☐ ☐	6f. ____/__/_____
7.	7a.	7b.	7c.	7d. ☐ ☐	7e. ☐ ☐	7f. ____/____/_____
8.	8a.	8b.	8c.	8d. ☐ ☐	8e. ☐ ☐	8f. ____/____/_____
9.	9a.	9b.	9c.	9d. ☐ ☐	9e. ☐ ☐	9f. ____/____/_____
10.	10a.	10b.	10c.	10d. ☐ ☐	10e. ☐ ☐	10f. ____/____/_____
11.	11a.	11b.	11c.	11d. ☐ ☐	11e. ☐ ☐	11f. ____/____/_____
12.	12a.	12b.	12c.	12d. ☐ ☐	12e. ☐ ☐	12f. ____/____/_____

***Abn = Abnormal**
***NCS= Not Clinically Significant**
***AE = Adverse Event**

Vitamin D Clinical Trial Source Document
Blood Chemistry Form

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

Was the blood chemistry done at this visit? ☐ yes ☐ no
Was lab work performed fasting? ☐ yes ☐ no

	Lab Value	Normal	Abn*	ND*	**If Abnormal** √**NCS***	√**AE***
1.. Calcium	1a. ☐☐.☐ mg/dL or ☐.☐ mmol/L	1b. ☐	☐	☐	1c. ☐	☐
2. PTH	2a. ☐☐☐ mg/dL or ☐.☐ mmol/L	2b. ☐	☐	☐	2c. ☐	☐
3. Vitamin D	3a. ☐☐.☐ mg/dL or ☐.☐ mmol/L	3a. ☐	☐	☐	3c. ☐	☐
4. HCG- only run if urine pregnancy test results are undetermined	4a. ☐☐ mg/dL or ☐.☐ mmol/L	4b. ☐	☐	☐	4c. ☐	☐

n=Abnormal *ND = Not Done *NCS= Not Clinically Significant
* Adverse Event (AE) = requires and AE form be completed

Vitamin D Clinical Trial Source Document
Study Drug Calcium Compliance and Monitoring Form

Participant Name_____ **/PID**_____ **Date** _____ **Course/Visit #**_____

Staff Person Signature_____

Calcium supplement

1. Is subject taking protocol prescribed study drug calcium dose? Yes ☐ No ☐
   If no, Check reason below:
   - ☐ _Withdrew from Study
   - ☐ _Dose Reduction (Complete AE form)
   - ☐ _Toxicity (Complete AE form)
   - ☐ _Drug Shortage (complete Protocol Deviation form)
   - ☐ _Other (Complete Comment form)

2. Participant returned the calcium bottle? Yes ☐ No ☐
3. Participant returned the completed dosing Diary? Yes ☐ No ☐
4. How many calcium doses did participant miss taking? ☐☐☐
   4a. If dosage was missed, reason_____
   _____
   _____

5. Did participant receive new calcium supplements of 400 mg/day? Yes ☐ No ☐
   Yes ☐ 5a. If yes, date given ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)
   No ☐ 5b. If no, explain _____

6. Does subject have enough calcium until the next study visit? Yes ☐ No ☐

7. Expected date of next appointment is ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy).

Vitamin D Clinical Trial Source Document
Comment Form

Subject ID#_____ Date of Report_____ Visit #_____

PLEASE PRINT Clearly on this form

Vitamin D Clinical Trial Source Document
Concomitant Medication Form

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

1. Was any medications, prescription and over the counter, being taken? Yes ☐ No ☐
If yes, list below and please capture medications started or discontinued since last clinic visit.

Medication	Dosage	Start Date (mm/dd/yyyy) or UNKNOWN	Stop Date (mm/dd/yyy) or ONGOING	Indicate why taking	AE? Yes or No
2.	2a.	2b.____/____/_____ or ☐	2d.____/____/_____ or ☐	2e.	2f. ☐ ☐
3.	3a.	3b.____/____/_____ or ☐	3d____/____/_____ or ☐	3e.	3f. ☐ ☐
4.	4a.	4b. ____/____/_____ or ☐	4d. ____/____/_____ or ☐	4e.	4f. ☐ ☐
5.	5a.	5b. ____/____/_____ or ☐	5d.____/____/_____ or ☐	5e.	5f. ☐ ☐
6.	6a.	6b. ____/____/_____ or ☐	6d.____/____/_____ or ☐	6e.	6f. ☐ ☐
7.	7a.	7b.____/____/_____ or ☐	7d. ____/____/_____ or ☐	7e.	7f. ☐ ☐

Vitamin D Clinical Trial Source Document
Death Form

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

1. Date of death: ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)

2. Status in study at time of death: ☐
   1-On protocol treatment
   2-Within 30 days of the last dose of protocol treatment
   3-More than 30 days from the last dose of protocol treatment
   4-Before protocol treatment started

3. Choose one of the following reasons for primary cause of death ☐
   1-Neurofibromatosis
   2-Concomitant condition
   3-Treatment toxicity
   4-Disease progression
   9-Other: (Provide stated cause of death.)
   _____

   _____

   _____

NOTE: If death occurred within 30 days following completion of active protocol therapy, complete a MedWatch Form and SAE Form.

Vitamin D Clinical Trial Source Document
Protocol Deviation Form

Subject ID#_____ Date of Report_____ Date aware of SAE_____ Course #_____

1. Date of deviation: ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)

2. Brief deviation description _____

_____

3. Deviation category ☐
   1-Eligibility enrollment
   2-Protocol procedure/assessment
   3-Dosing schedule/Administration
   4-Missed Visit
   5-Out of window follow-up visit schedule
   6- Other (specify) _____

4. Reason for deviation ☐
   1-Subject illness
   2-Subject unable to comply
   3-Laboratory error
   4-Investigator/study decision
   5-Other (specify) _____

5. Describe steps taken to resolve or avoid recurrence of the deviation:
_____
_____

6. Did the deviation result in an AE or SAE? ☐ Yes ☐ No
   If yes, complete the appropriate form.

7. Did the deviation result in subject termination of study follow-up? ☐ Yes ☐ No
   If yes, complete the appropriate Off Study form.

8. *Did deviation impact subject safety? ☐ Yes ☐ No

9. *Did deviation affect scientific integrity of study? ☐ Yes ☐ No

*****Notify University of Utah of safety issues and/or affect on scientific study.

Vitamin D Clinical Trial Source Document
DEXA Form

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

1. Bone densitometry completed? Yes ☐ No ☐

   Yes ☐ 1a. If yes, date performed ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)
   No ☐ 1b. If no, explain _____

2. Total BMD score_____

3. Hip density_____

4. Spine density_____

Vitamin D Clinical Trial Source Document
Diagnostic Criteria Form

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

Patient must have two or more NF1 clinical features listed in question 1 **OR** must answer **yes** to question 2. Check all that apply.

1. Participant must have two or more NF1 clinical features to be eligible and/or pathogenic NF1 gene present

	Yes	No
a. Six or more café au lait spots (≥ 0.5 cm in prepubertal individuals or ≥ 1.5 cm in postpubertal individuals)	☐	☐
b. Freckling in the axilla and/or inguinal region	☐	☐
c. An optic pathway glioma	☐	☐
d. Two or more Lisch nodules	☐	☐
e. A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia or thinning of long bone cortex)	☐	☐
f. Plexiform neurofibroma	☐	☐
g. A first degree relative with NF1	☐	☐

OR

2. Participant has a pathogenic NF1 gene mutation demonstrated in peripheral blood-derived DNA. Yes ☐ No ☐ ND ☐

Vitamin D Clinical Trial Source Document
Diet Analysis Form 1 of 2

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

INSTRUCTIONS: Indicate the **usual number of servings you eat** from each food listed below. Foods eaten less than daily should be marked under the weekly column, but **only mark one column per food**. If you do not eat the food at least monthly, leave that row blank.

DAIRY

Food Type	*Serving Size*	*Servings per Week*	*Servings per Day*
Milk	1 cup		
Chocolate Milk	1 cup		
Cheese Food	1 oz		
Cheese Sauce	¼ cup		
American Cheese	1 slice		
Cottage Cheese	1 cup		
Ricotta Cheese	1 oz		
Blue Cheese	½ cup		
Swiss Cheese	1 oz		
Cheddar, Mozzarella, Provolone	1 oz		
Buttermilk	1 cup		
Yogurt, Nonfat	1 cup		
Yogurt, Lowfat	1 cup		
Fast Food Milkshake	12 oz		
Cocoa from mix	1 packet		
Eggnog	1 cup		
Enchilada or Bean Burrito	1 cup		
Fudgesickle	1		
Custard Pie	1 slice		
Ice Cream	1 cup		
Pudding w/milk	½ cup		
Frozen Yogurt	1 cup		
Cheese Soufflet, Lasagne, Quiche, Canneloni	1 serving		
Cream Soup or Chowder	1 cup		
Cheese Pizza	1 slice		
Macaroni and Cheese	½ cup		

VEGETABLES

Food Type	*Serving Size*	*Servings per Week*	*Servings per Day*
Broccoli	1 cup		
Beet Greens	½ cup		
Bockchoy	½ cup		
Spinach	½ cup		
Summersquash	½ cup		
Iceberg Lettuce	1/8 head		
Swiss Chard	½ cup		
Peas	½ cup		
Green Beans	½ cup		
Mashed Potatoes	1 cup		
Carrots	1 medium		

Kale	1 cup		
Rhubarb	½ cup		
Scalloped Potatoes	1 cup		

FRUIT

Food Type	*Serving Size*	*Servings per Week*	*Servings per Day*
Figs	5 dried		
Orange	1 medium		
Orange Juice	½ cup		
Pear	1 medium		
Raisins	¼ cup		

PROTEIN

Food Type	*Serving Size*	*Servings per Week*	*Servings per Day*
Almonds	1/3 cup		
Beans (Baked, chili or other)	1 cup		
Creamed Fish/Meats	1 cup		
Shellfish	4 oz		
Canned Salmon	½ cup		
Canned Sardines	½ cup		
Soybeans	1 cup		
Tofu w/ Calcium Sulfate	½ cup		
Tofu w/o Calcium Sulfate	½ cup		
Perch	3 oz		
Oysters	½ cup		
Shrimp	3 oz		
Egg	1 large		
Peanuts	¼ cup		
Porkchops	3 oz		
Peanut Butter	2 Tbs		

GRAINS

Food Type	*Serving Size*	*Servings per Week*	*Servings per Day*
Bread, Bagels	1 slice		
Waffles	1 7”		
Pancakes	2 4”		
Oatmeal	½ cup		
Muffins, Biscuits, cornbread	1 medium		
Rolls, Buns	½		
Rice	½ cup		
Cereal, cold ready-to-eat	½ cup		

MISCELLANEOUS

Food Type	*Serving Size*	*Servings per Week*	*Servings per Day*
Egg McMuffin	1		
Fast Food Cheeseburger/Hamburger	1		
Taco	1		
Molasses	1 Tbs		
French fries	medium		
Soda pop (*not* diet)	1 can		
Soda pop (*diet*)	1 can		

What type of bread do you usually eat?

☐ White bread ☐ Wheat bread ☐ Half white and half wheat bread ☐ I don’t usually eat bread

Vitamin D Clinical Trial Source Document
Study Drug Dispensing Form

Participant Name_____ **/PID**_____ **Date** _____ **Course/Visit #**_____

Staff Person Signature_____

Vitamin D

1. Did participant receive the Vitamin D ("D" drops) Bottle?

Yes ☐ 1a. If yes, date given ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)

Randomized Ddrops bottle identification number _____

No ☐ 1b. If no, explain _____

2. Subject notified Ddrop bottle will last 1 year? Yes ☐ No ☐

X_____ _____
Signature of Subject Date

X_____ _____
Signature of Study Staff Date

Calcium supplement

3. Did participant receive calcium supplement of 400 mg/day? Yes ☐ No ☐

Yes ☐ 3a. If yes, date given ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)

No ☐ 3b. If no, explain _____

X_____ _____
Signature of Subject Date

X_____ _____
Signature of Study Staff Date

Vitamin D Clinical Trial
Exclusion Criteria Form (page 1 of 2)

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

Inclusion Criteria

If any of the boxes are checked "YES" the participant will be ineligible for the study.

	YES	NO	N/A
1. Lack of NF1 diagnostic criteria on physical examination?	☐	☐	
2. Potential recruit is pregnant or planning to conceive within the next two years?	☐	☐	
3. Their initial screening 25(OH)D level is <u>over</u> 29ng/ml?	☐	☐	
4. Their initial screening 25(OH)D level is <u>less than</u> 9ng/ml?	☐	☐	
5. Has had or having thyroid therapy?	☐	☐	
6. Taken vitamin D supplementation in the last 6 months equal to or greater than 600IU? a. Date of last dose :☐☐/☐☐/☐☐☐☐ mm dd yyyy	☐	☐	
7. Has he or she used high-dose steroids?	☐	☐	
8. Has he or she has had bisphosphonate therapy?	☐	☐	
9. He or she foresees that they will be unable to comply with the two-year study protocol?	☐	☐	
10. Has he or she has had calcium supplementation in last 6 months equal to or greater than 1000mg?	☐	☐	
11. He or she has a malignant peripheral nerve sheath tumor?	☐	☐	
12. Has he or she has a history of kidney stones and/or hypercalciuria?	☐	☐	
13. Has he or she has metal instrumentation in spine or hip that precludes accurate DXA interpretation?	☐	☐	
14. Has he or she had anti-epileptic therapy?	☐	☐	
15. He or she has had anticoagulant therapy?	☐	☐	
16. He or she is unable to comply for blood samples on routine venipuncture	☐	☐	
17. He or she has a diagnosis of Paget's disease, hyperthyroidism, hyperparathyroidism, or other medical conditions that affect bone health	☐	☐	

Vitamin D Clinical Trial Source Document
Exclusion Criteria Form (page 2 of 2)

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

Study Investigator has reviewed and confirmed that this person is ineligible for study enrollment.

PI Signature **Date**

Comments:_____
_____
_____
_____
_____
_____
_____
_____
_____

Vitamin D Clinical Trial Source Document
Fracture Form

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

Personal Information:

1. Date: _____
2. Date of Birth _____
3. Zip Code: _____

4. Ethnicity: ☐ White ☐ Hispanic ☐ Asian ☐ Black
   ☐ Native American ☐ Pacific Islander ☐ Other: _____

5. **Height**_____

6. **Weight**_____

7. **Medications:**

Please list all medications, vitamins, calcium or herbal supplements that you have taken during the past year (indicate starting dates for new medications):

Medication	Amount	How Often	Reason

8. Do you have any allergies to food or medication? ☐ Yes ☐ No

   8a. If yes, what are they? _____

9. What was your birth weight? _____ lbs. _____ oz.

Vitamin D Clinical Trial Source Document
Fracture Form

10. Were you born: ☐ Early ☐ Full term

10a. If you were born early, how many weeks before your due date? _____

11. Have you been diagnosed with ADHD (attention déficit hyperactivity disorder)?
☐ Yes ☐ No

For Females:

12. Have you started to have a period? ☐ Yes ☐ No
If yes, please answer the following question:

12a. How old were you when you had your first period? _____

For Males:

13. Have you started shaving? ☐ Yes ☐ No
If yes, please answer the following questions:

13a. How old were you when you first started shaving?_____

13b. How old were you when you first noticed pubic and armpit hair? _____

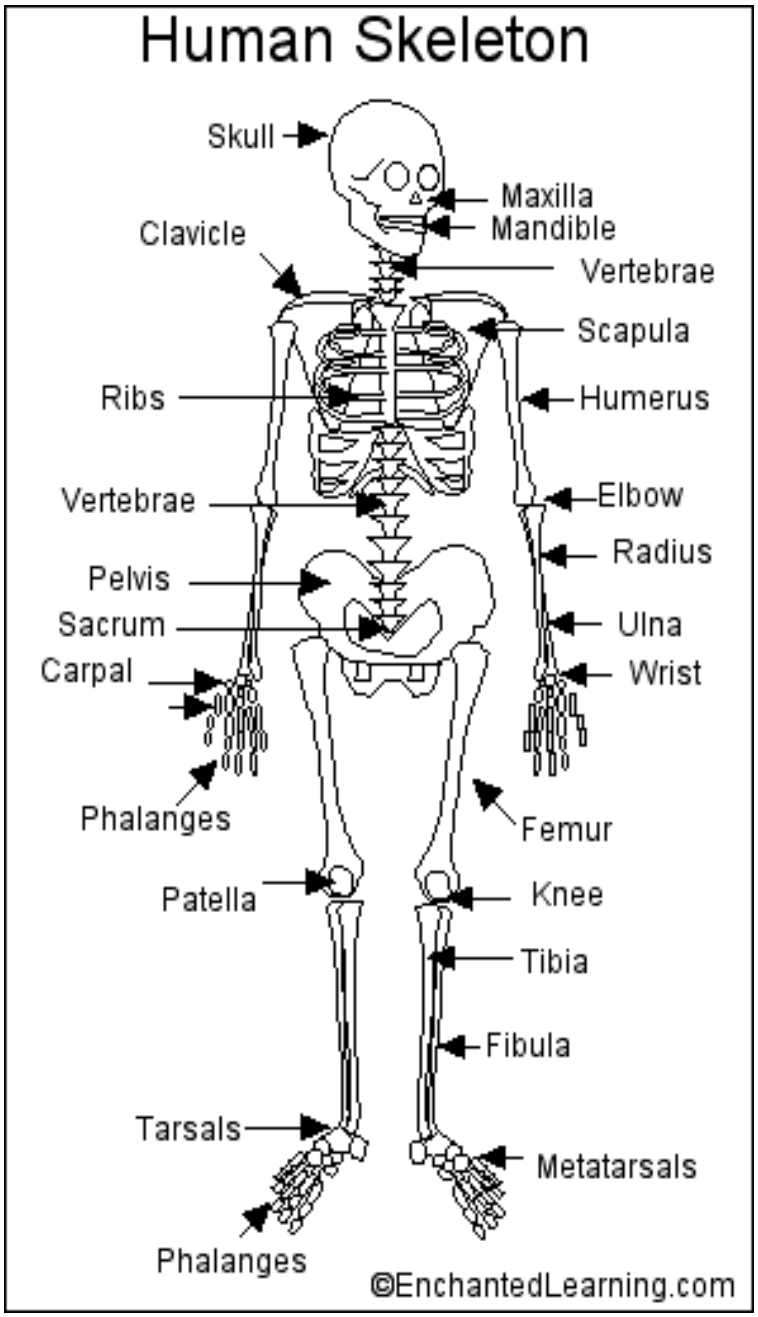
14. Have you ever broken a bone?

☐ No (skip the rest of this page)

☐ Yes

If yes, please look at the skeleton below; circle the bone(s) and mark on the table which bone(s) fractured. Then, the study physician will complete Page 4 with you (additional questions about each broken bone).

Vitamin D Clinical Trial Source Document
Fracture Form



Vitamin D Clinical Trial Source Document
Fracture Form

To Be Completed with Study Physician:

Event	Age at Fracture	Location Code (use multiple codes for multiple simultaneous fractures)	Fracture Type Code	Trauma description code
1.				
2.				
3.				
4.				
5.				

Event	Treatment Code	Complications Code	Where was treatment and where were X-rays taken?
1.			
2.			
3.			
4.			
5.			

For Study Physician Use:

Fracture Location Code	
a = toes/foot	j = shoulder
b = ankle	k = humerus
c = tibia	l = radius
d = fibula	m = ulna
e = lower leg unspec	n = lower arm unspec
f = hips/pelvis	o = wrist
g = spine/neck	p = hand/fingers
h = ribs	q = other
i = skull/face	r = uncertain which

Vitamin D Clinical Trial Source Document
Fracture Form

Fracture Type Code (use as many as apply)
s = simple t = compound (through the skin) u = complete v = incomplete w = stress/fatigue x = pathologic (due to disease) y = multiple z = unknown

Treatment Code (use as many as apply)
a = casting b = pins/plates c = graft d = surgery unspec. e = other (specify) f = unknown

Complications Code (use as many as apply)
k = none (bone set, no sequelae) l = infection m = won't heal n = pain in area of fracture o = limited motion/functional impairment p = other (specify)

Trauma Code	
Yes	Certain trauma (e.g. MVA, fall)
No	No trauma (apparently minimal reason for break)
Unknown	Unknown level of trauma

Vitamin D Clinical Trial Source Document
Medication History
Only on Screening

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

1. Has the participant taken any prescription or over the counter medication within the last 30 days? Yes ☐ No ☐
   If yes, please list below**.**

Medication	Dosage	Start Date (mm/dd/yyyy) or UNKNOWN	Stop Date (mm/dd/yyyy) or ONGOING	Indicate why taking	Allowed medication? Yes or No
2.	2a.	2b____/____/_____ or ☐	2c____/____/_____ or ☐	2d.	2e. ☐ ☐
3.	3a.	3b____/____/_____ or ☐	3c____/____/_____ or ☐	3d.	3e ☐ ☐
4.	4a.	4b____/____/_____ or ☐	4c____/____/_____ or ☐	4d.	4e. ☐ ☐
5.	5a.	5b____/____/_____ or ☐	5c____/____/_____ or ☐	5d.	5e. ☐ ☐
6.	6a.	6b____/____/_____ or ☐	6c____/____/_____ or ☐	6d.	6e. ☐ ☐
7.	7a.	7b____/____/_____ or ☐	7c____/____/_____ or ☐	7d.	7e. ☐ ☐

Vitamin D Clinical Trial Source Document
Off Study Form

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

1. Date of last contact: ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)

2. Course # completed ☐☐ or Follow up year ☐☐

3. Reason why patient is off study (check one of the following items)

   3a. ☐ Completed all follow up visits per protocol

   3b. ☐ Death—complete death form

   3c. ☐ Lost to follow-up

   3d. ☐ Withdrawal of consent for any further data submission

   3e. ☐ Other (specify) _____

Vitamin D Clinical Trial Source Document
Off Treatment Form

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____ **Staff Person Signature**_____

1. Date of last dose of study medication: ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)

2. Course number completed: ☐☐ Date of Visit ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)

Reason why the participant is off treatment: (4-12)

3. ☐ Completed the study drug, 24 month study visit.
4. ☐ Due to Side Effects (check all that apply)
   - ☐ 4a. drug-related adverse events
   - ☐ 4b. not drug-related adverse events
   - ☐ 4c. Grade 4
   - ☐ 4f. Patients who have experienced a vitamin D-associated toxicity requiring a dose modification/interruption after dose reduction.
   - ☐ 4g. Other _____
5. ☐ Patient/parent/guardian withdrawal from study
6. ☐ Non-compliance that, in the opinion of the investigator, does not allow for ongoing participation.
7. ☐ Physician determination that is not in the patient's best interest to remain on treatment.
8. ☐ Patient is prescribed a non-allowed concomitant medicine during study.
9. ☐ Death—complete death form
10. ☐ Other _____

Vitamin D Clinical Trial Source Document
Physical Exam and Vital Signs Form

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

1. Was the Physical Exam and Vital Signs done at this visit? ☐ Yes ☐ No

Physical Exam		
	Normal Abn ND	**Specify if Abnormal or change from baseline:**
2. General Appearance	2a ☐ ☐ ☐	2b.
3. Eyes, ears, nose, throat	3a. ☐ ☐ ☐	3b.
4. Neck	4a. ☐ ☐ ☐	4b.
5. Heart	5a. ☐ ☐ ☐	5b.
6. Lungs and respiration	6a. ☐ ☐ ☐	6b.
7. Abdomen	7a. ☐ ☐ ☐	7b.
8. Extremities	8a. ☐ ☐ ☐	8b.
9. Skin	9a. ☐ ☐ ☐	9b.
10. Central Nervous System	10a. ☐ ☐ ☐	12b
11. Lymph Nodes	11a. ☐ ☐ ☐	11b.
Vital Signs		
12. Height	12a. ☐☐☐.☐	12b. ☐ cm ☐ in
13. Weight	13a. ☐☐☐.☐	13b. ☐ kg ☐ lbs
14. Blood Pressure	14a. ☐☐☐ /16b. ☐☐☐ mm/Hg	
15. Performance	15a. ☐☐☐ %	15b. ☐ Karnofsky ☐ Lansky
16. Body Surface Area	16a. ☐.☐☐ m^2	
17. Heart Rate	17a. ☐☐☐ /min	
18. Temperature	18a. ☐☐☐.☐ º C or F (Circle)	
19. SaO^2	19. ☐☐☐ %	

Vitamin D Clinical Trial Source Document
Registration and Demographic Form

Participant Name_____ **Date** _____ **Course/Visit #**_____
PID_____**Staff Person Signature**_____

1. Race (choose one)
a. ☐ White (European, Middle Eastern or North American)
b. ☐ Black, African American, Haitian
c. ☐ Native Hawaiian, Other Pacific Islander (Samoan, Guamanian)
d. ☐ Asian (Cambodian, Indian, Chinese, Japanese, Korean, Malaysian, Pakistani, Filipino, Vietnamese and Thai)
e. ☐ American Indian or Alaska Native
f. ☐ Unknown
g. ☐ Other (specify)_____

2. Ethnicity
a. ☐ Hispanic/Latino
b. ☐ Non-Hispanic
c. ☐ Unknown

3. Sex
a. ☐ Male
b. ☐ Female

Vitamin D Clinical Trial Source Document
Serum sample Form

Participant Name_____ **Date** _____ **Course/Visit #**_____

PID_____**Staff Person Signature**_____

1. Serum sample obtained

   Yes ☐ 1a. If yes, date drawn ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)
   No ☐ 1b. If no, explain _____

2. Date serum was frozen? ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)

3. Date serum was shipped to the University of Utah? ☐☐/☐☐/☐☐☐☐
   (mm/dd/yyyy)

4. Mode of shipment _____

5. Shipment tracking number _____

Vitamin D Clinical Trial Source Document
Study Drug Ddrops Compliance and Monitoring Form

Participant Name_____ **/PID**_____ **Date** _____ **Course/Visit #**_____

Staff Person Signature_____

Vitamin D

1. Is subject taking protocol prescribed study drug Ddrop dose? Yes ☐ No ☐
   If no, Check reason below:
   - 1a. ☐ _Withdrew from Study
   - 1b. ☐ _Dose Reduction (Complete AE form)
   - 1c. ☐ _Toxicity (Complete AE form)
   - 1d. ☐ _Drug Shortage (complete Protocol Deviation form)
   - 1e. ☐ _Other (Complete Comment form)

2. Participant returned the "D" drop bottle? Yes ☐ No ☐
3. Participant returned the completed dosing Ddrop Diary? Yes ☐ No ☐
4. How many vitamin D drop doses did participant miss taking? ☐☐☐
   4a. If Ddrop dosage was missed, reason_____
   _____
   _____

5. Did participant receive a new Vitamin D (Ddrops) Bottle?
   Yes ☐ 1a. If yes, date given ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)
   No ☐ 1b. If no, explain _____

6. Does subject have enough Ddrops until the next study visit? Yes ☐ No ☐

7. Expected date of next appointment is ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy).

Vitamin D Clinical Trial Source Document
Study Drug Ddrops Compliance and Monitoring Form

Participant Name_____ **/PID**_____ **Date** _____ **Course/Visit #**_____

Staff Person Signature_____

Vitamin D

1. Is subject taking protocol prescribed study drug Ddrop dose? Yes ☐ No ☐
   If no, Check reason below:
   - 1a. ☐ _Withdrew from Study
   - 1b ☐ _Dose Reduction (Complete AE form)
   - 1c. ☐ _Toxicity (Complete AE form)
   - 1d. ☐ _Drug Shortage (complete Protocol Deviation form)
   - 1e. ☐ _Other (Complete Comment form)

2. Participant returned the "D" drop bottle? Yes ☐ No ☐
3. Participant returned the completed dosing Ddrop Diary? Yes ☐ No ☐
4. How many vitamin D drop doses did participant miss taking? ☐☐☐
   4a. If Ddrop dosage was missed, reason_____
   _____
   _____

5. Did participant receive an new Vitamin D (Ddrops) Bottle?
   Yes ☐ 5a. If yes, date given ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy)
   No ☐ 5b. If no, explain _____

6. Does subject have enough Ddrops until the next study visit? Yes ☐ No ☐

7. Expected date of next appointment is ☐☐/☐☐/☐☐☐☐ (mm/dd/yyyy).

Certify to None

Bernard Lasalle - November 12, 2013 - 2:10 PM

No Disclosed Relationships to Certify at this time.

From:	Conflict of Interest Office
To:	Heather Hanson
Subject:	FW: COI Outcome: No Potential Conflict
Date:	Tuesday, January 07, 2014 2:21:32 PM

From: coi@hsc.utah.edu [coi@hsc.utah.edu]
Sent: Tuesday, November 05, 2013 10:36 AM
To: David Stevenson
Subject: COI Outcome: No Potential Conflict

Conflict Review ID: CRV_00007131

Project: IRB_00055719

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)

Dear David Stevenson:

The Conflict of Interest Office has conducted an initial review of your significant financial interest(s) as certified in Business Relationship Reporting on 10/30/2013. Based on the information you provided, we have determined that none of your significant financial interest(s) present potential conflict(s) of interest that require further review by the Individual Conflict of Interest Committee for the project listed above.

The University's Individual Financial Conflict of Interest policy, UPol 1-006, Section III(D), requires investigators to update your disclosures within thirty (30) days if you acquire or discover new significant financial interests(e.g., through purchase, marriage, or inheritance) that are relevant to your professional responsibilities to the University. Please follow this link to Business Relationship Reporting if you need to update your disclosure.

Let me also remind you of other relevant University policies: Remunerative Consultation and Other Employment Activities (5-204), Patents and Inventions (7-002) and University Faculty Profit-Making Corporations (7-004). If any new intellectual property arises from your University work, please contact the Technology Commercialization Office at (801) 581-7792.

If you have questions, please contact the COI office at coi@hsc.utah.edu or by phone at (801) 581-7170 / (801) 581-6351.

Thank you for your assistance in complying with University policy.

Jahn Barlow, MPA
Conflict of Interest Officer
Research Integrity and Compliance
112 Research Administration Building (Building 512)
University of Utah

ph: 581-6351
fax: 585-9588

email: coi@hsc.utah.edu

From:	Conflict of Interest Office
To:	Heather Hanson
Subject:	FW: COI Outcome: No Potential Conflict
Date:	Tuesday, January 07, 2014 2:21:49 PM

From: coi@hsc.utah.edu [coi@hsc.utah.edu]
Sent: Tuesday, November 05, 2013 10:33 AM
To: Dave Viskochil
Subject: COI Outcome: No Potential Conflict

Conflict Review ID: CRV_00007130

Project: IRB_00055719

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)

Dear David Viskochil:

The Conflict of Interest Office has conducted an initial review of your significant financial interest(s) as certified in Business Relationship Reporting on 11/4/2013. Based on the information you provided, we have determined that none of your significant financial interest(s) present potential conflict(s) of interest that require further review by the Individual Conflict of Interest Committee for the project listed above.

The University's Individual Financial Conflict of Interest policy, UPol 1-006, Section III(D), requires investigators to update your disclosures within thirty (30) days if you acquire or discover new significant financial interests(e.g., through purchase, marriage, or inheritance) that are relevant to your professional responsibilities to the University. Please follow this link to Business Relationship Reporting if you need to update your disclosure.

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Thank you for your assistance in complying with University policy.

Jahn Barlow, MPA
Conflict of Interest Officer
Research Integrity and Compliance
112 Research Administration Building (Building 512)
University of Utah

ph: 581-6351
fax: 585-9588

email: coi@hsc.utah.edu

Certify to None

Heather Hanson - January 7, 2014 - 2:35 PM

No Disclosed Relationships to Certify at this time.

Certify to None

Mike Spigarelli - September 6, 2013 - 9:38 AM

No Disclosed Relationships to Certify at this time.

UNIVERSITY OF UTAH
SCHOOL OF MEDICINE

January 8, 2014

David Viskochil, M.D.
Department of Genetics
University of Utah

RE: CCTS Protocol 13-39

Dear Dr. Viskochil:

Your research proposal entitled "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)" was reviewed by the CCTS Internal Advisory Committee at its meeting on Wednesday, November 20, 2013. Your proposal was assigned CCTS protocol number 13-39. I am pleased to inform you that the Committee approved your proposal.

Your proposal is considered a "Category A" study. As requested in your proposal the CCTS will provide space and nursing assistance for study visits. The CCTS will not be able to subsidize laboratory testing or body composition measurements. Please contact Ms. Chris Chambreau (16736) to discuss financial arrangements for these costs.

Prior to enrollment of your first subject, please arrange to meet with the CSC nursing staff, and pharmacist or nutritionist if appropriate, to finalize operational details of your protocol. Please contact Wayne Hout (12224) to arrange these Protocol Activation meetings. All patient scheduling should be done through the CCTS Clinical Services Core, at extension 1-2224.

As a reminder, the National Center for Advancement of Translational Science (NCATS), the NIH parent organization for CTSA funding, has requested that NCATS be informed of any adverse events in clinical studies supported by NCATS resources that are "serious, unexpected and related to participation in a CCTS sponsored research protocol". If you believe that a subject in this or another of your CCTS protocols has suffered such an adverse event, it is your responsibility to bring it to the attention of the Clinical Services Core nursing supervisor so that we can fulfill this requirement, in addition to your usual responsibility to report such events to the Utah Institutional Review Board.

In addition, the NCRR and NCATS at the National Institutes of Health request that any publication resulting from studies conducted at the Center for Clinical and Translational Science carry the following footnote:

The University of Utah
School of Medicine
Center for Clinical and Translational Science
10 N. 1900 East, rm 22
Salt Lake City, Utah 84112-5890
Phone (801) 581-6736
Fax (801) 585-1461

“The project described was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant 8UL1TR000105 (formerly UL1RR025764). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.”

Please understand that in return for support of your project, *it is your responsibility to inform the CCTS staff of publications derived from CCTS support.* Inclusion of reference to these publications in our annual reports is the most important evidence of CCTS productivity, and essential for continued funding of the Utah CCTS by NCATS.

We look forward to the successful completion of your study.

With Best Regards,

J. Robinson Singleton, M.D.
Professor of Neurology
Director, CCTS Clinical Services Core

RADIOLOGICAL HEALTH DEPARTMENT
VP FOR RESEARCH | THE UNIVERSITY OF UTAH

RADIOACTIVE DRUG RESEARCH COMMITTEE AND HUMAN USE SUBCOMMITTEE OF THE RADIATION SAFETY COMMITTEE

TO: David Viskochil , M.D.

FROM: Scott C. Miller, Ph.D., RDRC-HUS Chairman

SUBJECT: Research Application HUS_00003374
IRB #IRB_00055719
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 research application 2013-07 : " 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)" has been reviewed and approved by the Radioactive Drug Research Committee and Human Use Subcommittee of the Radiation Safety Committee.

The Institutional Review Board will be notified of the RDRC-HUS approval of this application. Karen S. Langley, Radiation Safety Officer, and the Radiation Safety Committee also will be notified of this approval.

We wish you success with your continuing research efforts. We would like to remind you that all adverse effects should be reported to the RDRC-HUS. Also, we require that you inform this committee annually of the status of your study. You will be sent a brief reporting form to assist you in providing this information. Thank you for your cooperation.

Sincerely,

Scott Miller, Ph.D.
RDRC-HUS Chairman

cc: Institutional Review Board
Radiation Safety Officer

CHILD & FAMILY RESEARCH INSTITUTE
950 West 28th Avenue Vancouver BC Canada V5Z 4H4 Tel 604.875.3194 Fax 604.875.2496

August 22, 2011

David Viskochil, MD, PhD
Professor, Pediatrics
Division of Medical Genetics
University of Utah

RE: 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)

Dear Dave,

It has been exciting to plan this clinical trial, and, as the Principal Investigator at the University of British Columbia site, I am looking forward to working with you and your colleagues at the University of Utah to conduct a vitamin D clinical trial for adults with NF1. We are anxious to participate in all aspects of this multi-center trial, including participation in meetings, development and management of protocols, recruitment of patients to the trial, and data analysis.

Our neurofibromatosis clinical program has been active since the 1980's, and our research program, since 1990. We see approximately 25 adult patients with NF1 each year and, as the Provincial referral centre for medical genetics, we have a database of some 500 NF1 families to draw from. There is a close collaborative relationship between our lab and the British Columbia Neurofibromatosis Foundation patient support group, which takes a keen interest in assisting with recruitment and advertising for our studies and in promoting research amongst its members. Our research program has been studying bone mineral density in people with NF1 since 2004, and, as you know, we have successfully collaborated with your group as well as the groups in Hamburg, Manchester and Cincinnati on these studies.

Here in Vancouver, we will work with Dr. David Kendler's bone research laboratory, *Prohealth Clinical Research*. Dr. Kendler and his staff have collaborated with us on a previous study of NF1 bone health. His centre has extensive experience in clinical trials for osteoporosis and has the expertise and personnel to carry out successfully the imaging aspects of this study. As you know, Dr. Kendler has been instrumental in contributing to the design of this study and will also lend his expertise to interpretation of the results.

We very much look forward to continuing to work with all members of this multicentre team and in implementing this vitamin D clinical trial.

Sincerely,

J. M. Friedman, MD, PhD, FAAP, FABMG, FCCMG, FRCPC
Acting Executive Director, Child & Family Research Institute
Professor of Medical Genetics and Acting Associate Dean (Research)

Universitätsklinikum Hamburg-Eppendorf

Kopf- und Neurozentrum
Neurologie

Prof. Christian Gerloff
Direktor

Martinistraße 52
20246 Hamburg
Telefon: (040) 7410-53273
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v.mautner@uke.de
www.uke.de

Prof. Dr. med. V.-F. Mautner
Facharzt für Neurologie und Psychiatrie
- Leiter Bereich Phakomatosen -

Universitätsklinikum Hamburg-Eppendorf Martinistraße 52 20246 Hamburg

David Viskochil, MD, PhD
Professor, Pediatrics
Division of Medical Genetics
University of Utah

August 29, 2011

RE: 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)

Dear Dave:

As the Principal Investigator of the University Hospital Hamburg-Eppendorf I am committed to working with the University of Utah and collaborating institutions in our efforts to conduct a vitamin D clinical trial for patients with NF1 (neurofibromatosis type 1). We will be a full partner in activities of this multicenter trial, including participation in meetings, development and management of protocols, and recruitment of evaluable patients to the trial.

Our neurofibromatosis clinical program has been active since 25years. We see approximately 500 adult patients with NF1 each year and have a bone imaging center with trained personnel to carry out bone mineral density studies. We have extensive experience in conducting clinical trials, including for patients with NF1, and also for other areas as ADHS or dementia. It has been wonderful working with the group to develop a clinical trial that examines bone change while taking vitamin D3.

We look forward to continuing to work with all members of the multicenter collaboration on implementing this vitamin D study to determine efficacy in improving bone health in adults with NF1.

Sincerely,

V.-F. Mautner, M.D.

Cincinnati Children's

Elizabeth K. Schorry, M.D.
Associate Professor, Clinical Pediatrics
Division of Human Genetics
Cincinnati Children's Hospital Medical Center
Phone: 513 636-2438
Fax: 513 636-7297
elizabeth.schorry@cchmc.org

August 22, 2011

David Viskochil, MD, PhD
Professor, Pediatrics
Division of Medical Genetics
University of Utah

RE: 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)

Dear Dave:

As the Director of the Cincinnati Children's Hospital NF Clinic, I am enthusiastically committed to working as a co-investigator with the University of Utah and collaborating institutions in our efforts to conduct a clinical trial of Vitamin D for patients with NF1. We will be a full partner in activities of this multi-center trial, including participation in meetings, development and management of protocols, and recruitment of evaluable patients to the trial.

As you know, we have a very large NF program for both adults and children in Cincinnati, which has been active since 1986. We have followed over 900 patients with NF1, 380 of whom are now over age 21. Our NF clinical database lists 180 active patients between ages 25-45 years. In addition, we have contact with affected parents of NF1 children, and adult attendees of our support group meetings. Spearheaded by Dr. Alvin Crawford, one of the most renowned orthopaedic surgeons for NF1, our center has developed a major interest in bone disease in NF1. I currently serve as the chair of the Bone Committee for the DOD-funded NF Consortium, and have therefore had the opportunity to work with many other investigators interested in bone disease in NF1. Our center has significant expertise in multicenter clinical studies for NF1 bone disease, including: natural history of tibial dysplasia in NF1 (enrolled 30 patients); natural history of spinal deformities in NF1 (enrolled 33 patients); fracture survey in children with NF1 (enrolled 100 patients and 100 controls). Cincinnati Children's Hospital has a bone imaging center with trained densitometrists to carry out bone mineral density studies, and we have successfully used DEXA in previous NF1 multicenter studies. Heidi Kalkwarf, PhD, has led our DEXA-related efforts, and has been a valuable consultant on several of these studies. We are also an active member of the NF Clinical Consortium, and have participated in clinical trials of Rapamycin for plexiform neurofibromas in NF1; Lovastatin for learning disabilities in NF1; as well as several additional clinical trials which should be opening soon.

I look forward with great enthusiasm to working with all members of the multicenter group on implementing this clinical trial to determine efficacy of Vitamin D in improving bone health in adults with NF1.

Sincerely,

Elizabeth K. Schorry

Elizabeth K. Schorry, M.D.
Assoc. Professor
Division of Human Genetics
Director, NF Clinic
Cincinnati Children's Hospital

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119135

IND ACKNOWLEDGEMENT

David Viskochil, M.D., Ph.D.
Professor of Pediatrics, Division of Medical Genetics
University of Utah
50 N. Medical Drive, SOM Rm 2C412
Salt Lake City, Utah 84132

Dear Dr. Viskochil:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA). Please note the following identifying data:

IND NUMBER ASSIGNED: 119135

SPONSOR: David Viskochil, M.D., Ph.D.

PRODUCT NAME(S): cholecalciferol, 600 IU and 4000 IU

DATE OF SUBMISSION: July 11, 2013

DATE OF RECEIPT: July 12, 2013

We also acknowledge receipt of your request for IND exemption, however, we are denying your request because the product, at the doses you intend to use, is not marketed in the US [21 CFR 312.2(b)].

You may not initiate studies in humans until 30 days after the date of receipt shown above unless we notify you sooner that you may proceed. If, on or before August 11, 2013, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will immediately notify you verbally or in writing that (1) clinical studies may not be initiated under this IND ("clinical hold") or (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). If we place your human studies on clinical hold, you will be notified in writing of the reasons and the information necessary to correct the deficiencies. In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have subsequently notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **IND 119135** submitted on July 11, 2013, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

ADDITIONAL IND RESPONSIBILITIES

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

  If your IND is not in eCTD format:

  - you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;

  - if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);

  - if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as "Duplicate."

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format via the ESG. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND became active (the date clinical studies were permitted to begin) [21 CFR 312.33].

We remind you that, under 21 CFR 312.8(a)(3), you may not charge for this investigational drug without prior written authorization from FDA.

GOOD LABORATORY PRACTICE

All laboratory or animal studies intended to support the safety of this product should be conducted in compliance with the regulations for "Good Laboratory Practice for Nonclinical Laboratory Studies" (21 CFR 58). If such studies have not been conducted in compliance with these regulations, provide a statement describing in detail all differences between the practices used and those required in the regulations.

SUBMISSION REQUIREMENTS

Cite the IND number listed above at the top of the first page of any communications concerning this application. Each submission to this IND must be provided in triplicate (original plus two copies). Please include three originals of all illustrations that do not reproduce well. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to *set it up, send an email* request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see

http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/.

If you have any questions, call me at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Samantha Bell, B.S., B.A., R.A.C.
Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Why more people who choose a vitamin D supplement are choosing Ddrops™

Other Vitamin D products (chewable tablets, liquid, etc.)	Ddrops™
Contain vitamin D, but often along with artificial flavouring, colouring and other additives. (i.e. glucose syrup, sucrose, aspartame, gelatine, etc.)	Ddrops™ is the sunshine vitamin in **just one drop**. Ddrops™ is tasteless, odourless with no artificial flavours, no colouring and requires no preservatives. It is wheat-free, gluten-free, soya-free, sugar-free and peanut-free.
Flavoured chewable products are often similar to candy, and there can be concern about the potential for overdose.	Ddrops™ uses a Eurodropper format which limits the amount of vitamin D dosage that can be dispensed by accident, as it comes out one drop at a time.
Liquids can easily spill out of the bottle.	The contents cannot all spill out if the bottle tips over.
Product expiry date can vary. Chewable products can get sticky, depending on the product and storage conditions.	Ddrops™ is stable. It has a long shelf life and does not require refrigeration.
Higher potential of contamination, as people often need to use fingers and hands to get chewable products out of the container.	Very low potential of contamination, as the Eurodropper acts as a barrier, helping keep Ddrops™ pure and clean.

- **Ddrops™ has no taste and no odour.**
- **Ddrops™ is sugar-free, wheat-free, soya-free and gluten-free.**

Ddrops™ comes in a patented Eurodropper bottle. Simply turn the bottle upside down and allow a drop to come out.

Each drop of Ddrops™ contains 1000 IU of vitamin D_3.

Each drop of Ddrops™ Booster contains 600 IU of vitamin D_3.

Always read and follow the label

Ddrops™
The sunshine vitamin in just one drop®

www.ddrops.ca

From our Family to yours - The Ddrops™ Family of products

Award-winning Ddrops™ products were created as a better way to give individuals and families the vitamin D they need, in just one drop!

- **Baby Ddrops™ 400 IU** - specifically designed for breastfed babies. A mother only needs to put a single drop of Baby Ddrops™ on her nipple, where baby takes it in along with the milk.
- **Kids Ddrops™ 400 IU** - is a simple, safe, and fun way for toddlers and children to receive the recommended amount (400 IU) of vitamin D. Just one purified drop of Kids Ddrops™ contains 400 IU of vitamin D_3, without any other chemicals or additives.
- **Ddrops™ 600 IU Booster** - was developed to boost vitamin D levels to 1000 IU when complementing the 400 IU vitamin D in multivitamins and/or fixed calcium with vitamin D regimes. A welcome option for older children.
- **Ddrops™ 1000 IU** - makes it easy to take naturally sourced vitamin D_3 without pills and without additives. Each purified drop contains 1000 IU of vitamin D_3 and permits effective absorption and easy dose adjustments according to individual needs.

What could be easier?

Ddrops™ Family
Pure and simple in just one drop!
For Healthy Families

Always read and follow the label.

1. Cannell JJ, Vieth R, Umhau JC, et. al. Epidemic influenza and vitamin D. *Epidemiol Infect* 2006:134(6):1129–40.
2. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 2006;84:18-28.
3. Health Canada. www.hc-sc.gc.ca/fn-an/nutrition/child-enfant/infant-nourisson/vita_d_supp-eng.php
4. Langlois K et al. Statistics Canada: Vitamin D status of Canadians as measured in the 2007 to 2009 Canadian Health Measures Survey. March 2010. www.statcan.gc.ca/pub/82-003-x/2010001/article/11131-eng.htm
5. Canada's Food Guide: Vitamin D for people over 50: Background. www.hc-sc.gc.ca/fn-an/food-guide-aliment/context/evid-fond/vita d-eng.php
6. Canadian Cancer Society. Vitamin D. www.cancer.ca/canada-wide/prevention/vitamin d.aspx?sc_lang=en
7. Canadian Dermatology Association. Position Statement: Safe and effective way to Maintain adequate levels of vitamin D. www.dermatology.ca/media/position_statement/vitamin_d.html
8. Osteoporosis Canada. Vitamin D: A key factor in good calcium absorption. www.osteoporosis.ca/index.php/ci_id/5536/la_id/1.htm
9. International Osteoporosis Foundation. IOF position statement: vitamin D recommendations for older adults. www.iofbonehealth.org/download/osteofound/filemanager/health_professionals/pdf/endorsed-papers/vitamin-d-position-statement
10. Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx
11. American Academy of Pediatrics. Healthy Children. Summer/Back to School 2009. www.aap.org/family/healthychildren/09s_bts/Vitamin%20D.pdf - 2009-07-08

NOTE: Baby Ddrops™, Kids Ddrops™ and Ddrops™ for adults are Mom's Choice Awards® 'Gold' recipients.

The Mom's Choice Awards Honoring Excellence logo is a trademark of the Mom's Choice Awards.

www.ddrops.ca

A10HC180E-11

Ddrops™
BRAND
The sunshine vitamin in just one drop®

Who needs vitamin D?

Important information about vitamin D as part of a healthy lifestyle.

www.ddrops.ca

Why should you care about vitamin D?

Vitamin D is a natural building block for the repair and maintenance of the body. It has long been recognized as essential for the development and continued health of bones and teeth, helping prevent rickets in children and osteoporosis in adults. More and more, as medical research advances, we are seeing evidence that vitamin D plays an important part in maintaining health throughout the body, including:

- ⇨ ***the immune system***, helping prevent colds and flu, and improving resistance to many forms of cancer, rheumatoid and psoriatic arthritis, psoriasis and other dermatological conditions.[1]
- ⇨ ***the cardiovascular system***, helping reduce the incidence and severity of high blood pressure, coronary disease, congestive heart failure, heart attack and stroke.[2]
- ⇨ ***the brain and central nervous system***, where vitamin D deficiency has been associated with autism, schizophrenia, Parkinson's disease, multiple sclerosis and depression.[2]

What are the sources of vitamin D?

Sunlight is the main natural source of vitamin D. Vitamin D is made in the skin when exposed to summer sunshine. Vitamin D is not made in winter sunshine, in shade or through clothing. The use of sunscreen with a sun protection factor of eight reduces the cutaneous production of vitamin D by 97.5% in adults.[3] Vitamin D is also found in some foods – particularly in fatty fish, such as salmon, mackerel, tuna or sardines (see chart for examples) — but the amount of vitamin D per serving is highly variable and hard to determine.

Recent data shows that 1.1 million Canadians are vitamin D deficient.[4] Canada's Food Guide recognizes vitamin D as the only nutrient for which adults over 50 cannot reliably depend on diet alone to provide their recommended daily dose.[5]

How much vitamin D is recommended?

Group making recommendation	People for whom advice is intended	Recommended vitamin D_3 (IU* per day)
Canadian Cancer Society[6]	All adults	1000
Canadian Dermatology Association[7]	People concerned about not getting enough sunshine	1000
Osteoporosis Canada[8]	Adults under 50 Adults over 50	400 - 1000 800 - 2000
International Osteoporosis Foundation[9]	Older adults who are obese or have osteoporosis	Up to 2000
Canada's Food Guide[5]	Adults over 50	400
Institute of Medicine (IOM)[10]	People 1 to 70 years old	600
Institute of Medicine (IOM)[10]	Adults >71 years old	800
Institute of Medicine (IOM)[10]	Upper level intake for people over 9 years old	4000

* IU = International Unit

Note: These recommendations are for vitamin D as a supplement, in addition to the vitamin D already in a diet that includes foods like fish and vitamin D-fortified dairy products.

You may particularly benefit from taking a vitamin D supplement if:

- You avoid exposing skin to sunshine.
- You use sunscreen or sunblock to protect your skin from burning.
- Your summer clothing covers your head, arms and legs.
- You have dark skin. Skin pigment acts like a sunblock. People with dark skin need to stay in the sun for as long as 2 hours to produce the same amount of vitamin D that people with lighter skin can produce in 20 minutes of summer sun.
- You drink less than four glasses of milk or beverages fortified with vitamin D daily.
- You do not eat at least one serving (200 grams) of fish such as salmon every day.

Contraindications

- Individuals with granulomatous disease, such as tuberculosis or sarcoidosis may be hypersensitive to vitamin D.
- Vitamin D should not be taken by individuals with hypercalcemia.
- People with known medical conditions should consult with a healthcare practitioner before taking dietary supplements.

Always read and follow label.

Ddrops™
The sunshine vitamin in just one drop®

www.ddrops.ca

How much vitamin D can you get from healthy foods?

There are very few dietary sources of vitamin D. It is mainly found in fatty fish, like salmon, tuna or sardines. The chart below shows some of the more common dietary sources of vitamin D, as well as how much of each food you would need to eat in a day to receive 1000 IUs.

Dietary Source of vitamin D	Vitamin D content (approximate per serving)	Approximate amount to provide 1,000 IUs of vitamin D
Salmon, cooked	360 IU (3.5 oz, 100 g)	10 oz (300 g)
Mackerel, cooked	345 IU (3.5 oz, 100 g)	10 oz (300 g)
Tuna, canned in oil	230 IU (3.5 oz, 100 g)	15 oz (450 g)
Sardines, canned	500 IU (3.5 oz, 100 g)	8 oz (225 g)
Milk (nonfat, reduced fat or whole) Vitamin D-fortified	100 IU (8 oz, 240 ml)	80 oz (2.25 litres)
Margarine, fortified	60 IU (1 tablespoon, 15 ml)	16 tablespoons (250 ml)
Egg, whole (vitamin D is found in yolk)	20 IU	50 eggs

Adapted from reference 11

Putting just one drop of Ddrops™ into your favourite food or drink is an easy, reliable and hassle-free way to get your vitamin D_3 every day.

Health Canada Santé Canada

VITAMIN D

Date: August 16, 2007

Proper name(s): Vitamin D (Sweetman 2007; IOM 2003; O'Neil et al. 2001)

Common name(s): Vitamin D, vitamin D_2, vitamin D_3 (Sweetman 2007; IOM 2003; O'Neil et al. 2001)

Source material(s):

- Vitamin D_2 /Ergocalciferol
  (Sweetman 2007; IOM 2003 O'Neil et al. 2001)
- Vitamin D_3/Cholecalciferol)
  (Sweetman 2007; IOM 2003; O'Neil et al. 2001)

Note: The slash (/) indicates that the terms are synonyms. Either term may be selected by the applicant.

Route(s) of administration: Oral

Dosage form(s): Those pharmaceutical dosage forms suited to oral administration, including but not limited to chewable tablets, caplets, capsules, strips, lozenges, powders or liquids where the dose is measured in drops, teaspoons or tablespoons, are acceptable. This monograph is not intended to include food-like dosage forms such as bars, gums or beverages.

Use(s) or Purpose(s): Statement(s) to the effect of:

General: A factor in the maintenance of good health (IOM 2006; IOM 1997).

Specific:

For all products:

- Helps in the development and maintenance of bones (IOM 2006; Shils et al. 2006; Groff and Gropper 2000; IOM 1997).

Canada

- Helps in the development and maintenance of teeth (Shils et al. 2006).
- Helps in the absorption and use of calcium and phosphorus (IOM 2006; Shils et al. 2006; Groff and Gropper 2000; IOM 1997).
- For products providing calcium as a medicinal ingredient, if the following statement is used it must be verbatim:
"Calcium intake, when combined with sufficient vitamin D, a healthy diet, and regular exercise, may reduce the risk of developing osteoporosis" (Shils et al. 2006; Groff and Gropper 2000; NIH 2000).

Dose-specific: For products providing daily doses of vitamin D at or above the Adequate Intake (AI) (adjusted for the life stage groups), the following use or purpose is acceptable:
Helps to prevent vitamin D deficiency (IOM 2006; Shils et al. 2006; Groff and Gropper 2000; IOM 1997).

See Appendix 1 for definitions and Table 2 in Appendix 2 for AI values.

Dose(s):

Table 1: Dose information for vitamin D presented as dose per day

Life stage group		Vitamin D (µg/day) Minimum[1]	Vitamin D (µg/day) Maximum[2]
Infants	0-12 mo	0.2	25
Children	1-3 y	0.2	25
	4-8 y	0.2	25
Adolescents	9-13 y	0.2	25
	14-18 y	0.8	25
Adults[3]	≥ 19 y	0.8	25

[1] Based on approximately 5% of the highest AI (IOM 2006). See Appendix 1 for definitions and Table 2 in Appendix 2 for AI values.
[2] These values are based on the *Food and Drug Regulations* Schedule F limit (HC 2007).
[3] Includes pregnant and breastfeeding women.

Conversion Factors:

1 IU of vitamin D activity per:
= 0.025 µg cholecalciferol (IOM 2006)
= 0.025 µg ergocalciferol

Duration of use: No statement required.

Risk information: Statement(s) to the effect of:

Caution(s) and warning(s): No statement required.

Contraindication(s): No statement required.

Known adverse reaction(s): No statement required.

Non-medicinal ingredients: Must be chosen from the current NHPD *List of Acceptable Non-medicinal Ingredients* and must meet the limitations outlined in the list.

Specifications: Must comply with the minimum specifications outlined in the current NHPD *Compendium of Monographs*.

References:

Groff J, Gropper S. Advanced Nutrition and Human Metabolism, 3rd edition. Belmont (CA): Wadsworth/Thomson Learning; 2000.

HC 2007: Health Canada. *Food and Drug Regulations* (F-27 – C.R.C., c.870). Ottawa (ON): Health Canada; 2007. [Accessed 2007-06-05]. Available at: http://laws.justice.gc.ca/en/F-27/C.R.C.-c.870/text.html

IOM 2006: Institute of Medicine. Otten JJ, Pitzi Hellwig J, Meyers LD, editors. Institute of Medicine. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Washington (DC): National Academies Press; 2006.

IOM 2003: Institute of Medicine. Committee on Food Chemicals Codex, Food and Nutrition Board, Institute of Medicine. Food Chemicals Codex, 5th edition. Washington (DC): National Academies Press; 2003.

IOM 1997: Institute of Medicine. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride. Washington (DC): National Academies Press; 1997.

NIH 2000: National Institute of Health. Osteoporosis Prevention, Diagnosis, and Therapy. NIH Consensus Statement Online 2000;17(1):1-36. Bethesda (MD): National Institute of Health; March 27-29, 2000. [Accessed 2007-03-21]. Available from: http://www.consensus.nih.gov/2000/2000Osteoporosis111html.htm

O'Neil MJ, Smith A, Heckelman PE, Budavari S, editors. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 13th edition. Whitehouse Station (NJ): Merck & Co., Inc.; 2001.

Shils ME, Olson JA, Shike M, Ross AC, editors. Modern Nutrition in Health and Disease, 10th edition. Philadelphia (PA): Lippincott Williams and Wilkins; 2006.

Sweetman SC, editor. Martindale: The Complete Drug Reference, 35th edition. London (UK): Pharmaceutical Press; 2007.

Appendix 1: Definitions

Adequate Intake (AI): The recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate; used when a Recommended Dietary Allowance (RDA) cannot be determined (IOM 2006).

Recommended Dietary Allowances (RDA): The average daily dietary nutrient intake level sufficient to meet the nutrient requirements of nearly all (97-98%) healthy individuals in a particular life stage and gender group (IOM 2006).

Appendix 2: AI Values

The AI values for vitamin D are provided below. For the purpose of this monograph, these values are intended to:

- provide targets for setting appropriate supplement dosage levels;
- provide the minimum dose for the use of the dose-specific use or purpose: "Helps to prevent vitamin D deficiency";
- facilitate the optional labelling of % AI values.

Table 2: Adequate Intake values based on life stage group (IOM 2006)

Life stage group		Vitamin D (µg/day)
Infants	0-12 mo	5
Children	1-3 y 4-8 y	5 5
Adolescents	9-13 y 14-18 y	5 5
Adults	19-50 y 51-70 y >70 y	5 10 15
Pregnancy	14-50 y	5
Breastfeeding	14-50 y	5

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014.
Expiration Date: January 31, 2006.
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

David Viskochil, MD, PhD
2C412 S.O.M.
50 North Medical Dr.
Salt Lake City, UT 84132

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.

☒ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.

Center for Clinical Translational Science (CCTS)
University of Utah
Salt Lake City, UT 84132

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

Associated Regional and University Pathologists (ARUP)
500 Chipeta Way
Salt Lake City, UT 84108

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE

University of Utah Institutional Review board for Human Research
Research Administration Building
75 South 2000 East
Salt Lake City, Utah 84112

6. NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

Michael Spigarelli, MD, PhD
David Stevenson, MD
Heather Hanson, CRC

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

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 form of vitamin D that will be supplemented is cholecalciferol (vitamin D3).

8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

XX FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

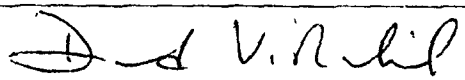
I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR
Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).

10. SIGNATURE OF INVESTIGATOR	11. DATE
	06/24/2013

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Rockville, MD 20852

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