Parkview Institutional Review Board
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TITLE: Treatment of Vitamin D deficiency with large bolus cholecalciferol in the outpatient setting

PROTOCOL VERSION DATE: 1/2/19
VERSION: 3

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Role in project: co-investigator

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Role in project: co-investigator

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Role in project: faculty advisor/study coordinator

I. OBJECTIVES

The primary purpose of our study will be to evaluate the efficacy of large, single bolus vitamin D supplementation for the treatment of vitamin D deficiency when compared to standard treatment regimens. The null hypothesis will be that large single bolus administration of vitamin D will be non-inferior in efficacy of the standard vitamin D replacement. Secondary objectives will include evaluation of the duration of sufficient serum levels after the large bolus of cholecalciferol and evaluation of compliance with single dose regimens compared with standard daily regimens. We hypothesize that large bolus vitamin D replacement will have a duration of sufficient serum levels of at least one year.

II. BACKGROUND AND SIGNIFICANCE

Vitamin D deficiency has been recognized as a worldwide health concern for many years. Vitamin D is a fat-soluble steroid hormone with known effects on the absorption of calcium, magnesium and phosphorus from bone and the gastrointestinal tract, as well as other, less well understood effects on multiple body systems. Vitamin D deficiency is seen more in elderly patients, patients with autoimmune disorders (2), chronic kidney disease (3), chronic liver disease (4), hypertension (5), and malabsorptive conditions such as inflammatory bowel disease (6). Vitamin D deficiency is more common at far north and south latitudes and in climates with decreased sun exposure.

Vitamin D deficiency is associated with increased calcium resorption from bone leading to osteomalacia and increased risks of osteoporosis (7,8). Treatment of vitamin D deficiency has been

shown to slow progression of osteoporosis in elderly women. In recent years, vitamin D deficiency has been shown to be associated with other health conditions including cardiovascular disease (9), hypertension, type 2 diabetes mellitus (10), thyroid dysfunction, colon cancer, and neuropsychiatric disorders such as depression and dementia. These conditions are simply associated with vitamin D deficiency and there is a paucity of data regarding the effect of treatment of vitamin D deficiency on the overall disease state. Interestingly, vitamin D supplementation had been associated with a decrease in overall mortality (11)

In humans, vitamin D is predominantly obtained via exposure to sunlight. Solar ultraviolet B (UVB) radiation penetrates into the skin and starts the synthesis of vitamin D3 from pre-vitamin D. This is then hydroxylated to 25-hydroxyvitamin D in the liver. Serum 25-hydroxyvitamin D is the vitamin D level that is checked on routine laboratory testing because it is the best measure for total body stores. The 25-hydroxyvitamin D is hydroxylated again in the kidney to the biologically active form, 1,25-dihydroxyvitamin D (2). The biologically active form has a short half-life in plasma.

Pharmacologic preparations of vitamin D are available as both enteral and parenteral depot formulations. Cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) are the two calciferols available in the United States. Vitamin D2 is a plant-derived form while vitamin D3 is the form naturally produced in humans. When administered, both forms enter the metabolism cascade at the first hydroxylation step. Large bolus doses of ergocalciferol have been available in the United States for decades while large dose cholecalciferol became readily available in the last 15 years. There is limited data but some small studies have shown Vitamin D3 to be more effective for treatment in humans (12).

High dose Vitamin D therapy in children and adolescents, also known as Stoss therapy, was initiated in late 1930's Germany in the study of treatment and prevention of rickets (13). Since that time several studies have been performed to investigate Vitamin D supplementation in many different areas, patient populations and disease states. Current Endocrine Society guidelines define vitamin D deficiency at levels <20 ng/mL and insufficiency of Vitamin D at levels <30 ng/ml. Those guidelines recommend daily supplementation equivalent to 5,000-6,000 IU to achieve levels above this range (2). There are not guidelines regarding the frequency of checking Vitamin D levels while on treatment.

The significance of this research will aim to help guide treatment guidelines in terms of routine laboratory testing for follow-up, which will then potentially aid in guidance of when repeat dosing will occur. Upon review of the literature, many articles looked at serum levels immediately after large dose administration and with follow up as far as 9 months, but in the longer follow up studies laboratory testing from initial dose to last check was sparse. While many studies had short term follow up after initial dose, whether this was due to initial serum Vitamin D levels or dosage administered was not clearly defined. This study will aim to provide closer follow-up after a researched dose of 300,000IU that has been shown to have minimal adverse effects and multiple benefits beyond serum Vitamin D levels.

III. PRELIMINARY STUDIES

The pharmacodynamics of cholecalciferol allow for the potential of infrequent, large bolus administration. Once absorbed, cholecalciferol is either metabolized into 25(OH)-D or can be redistributed into fat. 25(OH)-D has a prolonged circulating half-life of approximately 2-3 weeks prior to being further hydroxylated in the kidney to the active metabolite (14). Cholecalciferol that is redistributed into fat is released slowly overtime to sustain circulating levels of 25(OH)-D for prolonged periods of time between dosing (13, 15, 16).

To this point, there has been inconclusive research on the efficacy of high dose vitamin D supplementation for vitamin D deficiency. Studies have shown that doses of 300,000IU are typically most efficacious for normalizing vitamin D levels while minimizing adverse effects (16). Dosage of 250,000IU or less have been ineffective for long-term improvement of vitamin D status (17, 18, 16).

Doses greater than 300,000IU have shown similar efficacy in raising serum vitamin D levels but increase the risk of adverse effects (19). No studies have identified a standard duration of efficacy for large bolus vitamin D supplementation.

Of the studies that were reviewed, none showed significant adverse effects related to hypervitaminosis D. This was even with cholecalciferol doses greater than 300,000IU (13, 15, 16). Two case series that evaluated patients with vitamin D toxicity in India showed toxicity resulting from repeated cholecalciferol administration totaling greater than 1,000,000IU over a minimum of three months. All case reports of hypervitaminosis D reviewed had a significantly higher dose of cholecalciferol than our proposed dose.

IV. RESEARCH STUDY DESIGN

- Study will be a prospective, unblinded, randomized controlled study.
- There will be two study arms:
  - Large-bolus group that will get one-time, 300,000IU cholecalciferol.
  - Standard treatment group that will take 5,000IU cholecalciferol daily.
- Participants will be randomized based on the order they join the study. *Randomizer.org* was used to create at randomly organized set of 20 including 10 ones (large bolus) and 10 twos (standard treatment).

	A	B	C	D
1	Research Randomizer Results:			
2	2 Sets of 10 No Numbers Per Set			
3	Range: From 1 to 2 -- No			
4	Set 1	Set 2		
5	2	2		
6	1	1		
7	2	1		
8	1	2		
9	2	1		
10	2	2		
11	1	1		
12	1	2		
13	1	1		
14	2	2		

1.	Bolus	11.	Standard
2.	Standard	12.	Bolus
3.	Bolus	13.	Standard
4.	Bolus	14.	Standard
5.	Standard	15.	Bolus
6.	Standard	16.	Standard
7.	Bolus	17.	Bolus
8.	Bolus	18.	Standard
9.	Bolus	19.	Bolus
10.	Standard	20.	Standard

We will repeat this organization for subsequent sets of 20 participants to maintain relatively equal groups as participants are added.

- We plan to enroll a total of 100 participants. We should be able to meet the goals of the study with 86 participants. Please see Appendix A for calculation of study size.
- We expect the study to last a total of 20 months:
  - 6 months for initial enrollment
  - 12 months for data gathering
  - 2 months for analysis and write up

V. ABOUT THE SUBJECTS

- We plan to enroll a total of 100 participants.
- We anticipate 86 participants will complete the study.
- The subject's population will include residents of southeastern Colorado. We will include men and women, age 18-75. All ethnic groups will be included. All participants will be seen at Parkview Adult Medicine for primary care.
- Inclusion criteria will include:
  1. 18-75 years old
  2. Serum 25(OH)D level <20ng/mL
  3. Patient of Parkview Adult Medicine Clinic
  4. Not currently on vitamin D supplementation >5,000IU daily.
  5. No ergocalciferol administration within the last week.
- Exclusion criteria will include:
  1. History of hypercalcemia or hyperparathyroidism due to risk of elevation of calcium levels with administration of vitamin D.
  2. History of chronic kidney disease with a baseline creatinine >1.1mg/dL as this can alter the metabolism of vitamin D.
  3. History of gastric absorptions abnormalities such as previous intestinal surgery, Celiac disease, or inflammatory bowel disease as this can alter the absorption of vitamin D.
  4. History of bone diseases such as Paget's disease or osteoporosis (on treatment)or granulomatous conditions as these can alter vitamin D metabolism and calcium levels.
  5. History of thyrotoxicosis as this can alter vitamin D metabolism.
  6. Subjects on anticonvulsants, barbiturates, steroids, or calcium supplementation >1200mg/day as these can increase risk of elevated calcium levels.
  7. Subjects with known malignancy as metabolism could be affected by both the malignancy and chemotherapy.
  8. Subjects who are pregnant or breastfeeding as vitamin D metabolism and needs are known to be altered during pregnancy.
  9. Patients who do not speak English at a conversational level as all communication with the investigators and the study paperwork will be in English.
  10. Inpatient hospitalization at the initiation of the study dosing as this study is specifically focusing on outpatient treatment. Participants found to have Vitamin D deficiency while hospitalized will be considered for inclusion after they are stabilized and discharged from the hospital.

VI. VULNERABLE POPULATIONS

- Educationally disadvantaged individuals will be considered for the study. The forms and questionnaires will be written in language to attempt to make them understandable to everyone, including educationally disadvantaged individuals.
- Economically disadvantaged individuals will be considered for the study. No monetary incentives will be provided for participation in the study to avoid coercion to participate.

VII. **RECRUITMENT METHODS**

- The study population will be recruited from patients of the Parkview Adult Medicine Clinic (PAMC) after routine Vitamin D testing.
- Pre-screening will be done by the providers caring for patients both outpatient at PAMC and inpatient at Parkview Medical Center. These providers are the ones ordering/initially getting the results of routine Vitamin D level testing. They will be the first to inquire about the patients participating in the study. If patients do express interest, their contact information will be shared with the investigators for formal enrollment and consent.
- Recruitment flyers will be hung in exam rooms at PAMC for participants in read and express interest to their providers. Recruitment flyer can be found in Appendix B.
- Participants will not be forced to check their vitamin D level for sole purpose of screening for study participation. Investigators will be honest regarding potential benefits and risks of participating in the study and will be forthcoming with answers to all questions from the participants.

List recruitment methods/materials and attach a copy of each:

1. Flyer to be hung in the Parkview Adult Medicine Clinic (Appendix B)

VIII. **COMPENSATION**

- The participants will not be compensated monetarily for participation in this study.

IX. **CONSENT PROCESS**

- All participants will be patients at the Parkview Adult Medicine Clinic. Providers will be notified of study and inclusion/exclusion criteria. When, through routine testing, patients are found to have vitamin D deficiency the provider ordering the test will initially inquire if their patients are interested in participation. Once participants indicate their interest, the clinic providers will provide the investigators with the name of the interested party. Investigators will then meet with the participant at the Parkview Adult Medicine Clinic to go through the formal consent.
- No change to the informed consent will be needed.
- All providers and investigators will be forthcoming with goals of the study and the idea that participation is entirely voluntary. Investigators will not approach patients that are not under their care in clinic without first being notified by the appropriate provider. No benefits will be provided to the providers for referring their patients to the study.
- Participants who do not speak English and would require a consent form translator will not be included in the study.

X. **PROCESS TO DOCUMENT CONSENT IN WRITING**

- After participants are pre-screened by and express interest in participation to their PCP, study investigators will reach out to schedule the initial study meeting. At this meeting, the participant will meet with one of the investigators to go through the written consent and sign. A copy of the signed consent will be given to the participant.

XI. **PROCEDURES**

- **Initial, pre-study encounter:**
  - Participants will have their 25(OH)-D level drawn for routine screening purposes outpatient or inpatient. The ordering provider/team will recognize level <20ng/dL as potential candidate for the study and inquire regarding interest for participation.
  - If individual expresses interest in participation, their provider will provide the investigators with the measured vitamin D level and the prospect's contact information.
- **Phone call #1:**
  - Investigator will contact prospective participant to schedule initial screening encounter.
  - Phone call should take no more than 2-5 minutes.
- **Encounter #1:**
  - Participant will meet with one (or more) investigator to go through consent. The participant will be given a signed copy of the consent.
  - The participant and investigator will go through the screening questionnaire (Appendix C) and collect routine vital signs (Appendix D).
  - The participant will go to the Parkview outpatient lab to have complete metabolic panel for screening of renal function and calcium levels.
  - Visit should take approximately 45 minutes total.

IF PARTICIPANT MEETS ALL INCLUSION CRITERIA AND NONE OF THE EXCLUSION CRITERIA, THEY WILL PROCEED TO THE NEXT STEPS:

- **Randomization:**
  - As noted above, participants will be randomized into either Group 1 (large-bolus cholecalciferol) or Group 2 (standard treatment) based on their enrollment position.
- **Study meds:**
  - Based on the randomization group, participants will have a prescription for the assigned therapy sent to the Pharmacy at Parkview. They will be instructed to pick up the medications and start the medications the next non-weekend morning (pick-up meds on Friday-Sunday then start on Monday. Other days, start on the following day).
    - Group 1 will take six 50,000IU cholecalciferol tablets one time.
    - Group 2 will take one 5,000IU cholecalciferol capsule daily.

- **Phone call #2:**
  - Participants will be called and instructed to pick up the medications and start the medications the next non-weekend morning (pick-up meds on Friday-Sunday then start on Monday. Other days, start on the following day).
    - Group 1 will take six 50,000IU cholecalciferol tablets one time.
    - Group 2 will take one 5,000IU cholecalciferol capsule daily.
  - Phone call should take no more than 2-5 minutes.

- **Encounter #2:**
  - One week after starting the study medications, participants will return to clinic and go through the follow-up questionnaire (Appendix E) with one of the investigators.
  - Participant will go to the Parkview outpatient lab to have their BMP and Vitamin D level drawn.
  - Visit should take approximately 30 minutes total.
- **Encounters #3, #4, #5, #6:**
  - Three, six, nine, and twelve months after starting the study medications, participants will return to clinic to go through the same follow-up questionnaire as Encounter #2.
  - At all visits, participants will once again have BMP and vitamin D levels drawn at the Parkview outpatient lab.
  - Each visit should take approximately 30 minutes total.
  - Participants in the standard treatment group will get new prescriptions for 2000IU Vitamin D at encounters 3, 4, and 5.

XII. SPECIMEN MANAGEMENT

- Blood samples from the participants will be labeled with their name and sent through the Parkview outpatient laboratory.
- Specimens will be drawn in the lab and not transported by the investigators or not laboratory staff.

XIII. DATA MANAGEMENT

- Hard copy data (consent, questionnaires) will be kept in a locked file box in clinic. Researchers and faculty-supervisor will be the only ones with access to the locked files. Files will be de-identified by using the patients first and last initial as well as an assigned number (starting with 001 and going up numerically by enrollment place). Hard copies of all data will be destroyed by shredding at the end of the study.
- Data will be transcribed to electronic files. These files will be password-protected and stored on the secure Parkview Medical Center server.

XIV. WITHDRAWAL OF PARTICIPANTS

- Circumstances that would require the patient to be withdrawn would include: not starting the study medication, not returning for scheduled follow-up, or becoming pregnant. Participants will also be withdrawn if they become seriously ill and require hospitalization for an extended period of time for non-study related illness (>10 days).
- Participants that require hospitalization due to effect of study drugs will continued to be monitored for safety but the data will not be included in the final analysis. The study enrollment will stop prematurely if two or more participants require hospitalization.
- Participants in the standard of care arm will be withdrawn if they develop severe adverse reactions from the study medication that prevent continued compliance. If participants in the standard treatment arm have 25(OH)D levels >100ng/mL they will be reduced to taking 2,000IU daily but will not automatically be removed from the study.
- We will recommend that participants who withdraw from the study get a BMP and Vitamin D level drawn within 3 months of withdrawing to ensure no negative effects on their renal function or calcium level and to ensure that they are being treated for vitamin D deficiency.

XV. RISKS TO PARTICIPANTS

- The major risk to human subjects is related to symptomatic hypercalcemia from vitamin D toxicity.
  - These symptoms typically occur at serum 25(OH)D levels >150ng/mL
  - The risk is greater with prolonged high dose vitamin D administration (Kaur).
  - Symptoms of vitamin D toxicity include fatigue, muscle weakness, anorexia, dehydration leading to acute kidney injury, polyuria and polydipsia, confusion, and gastrointestinal effects such as constipation, nausea/vomiting.
  - The risk of vitamin D toxicity is greatest 1 week after administration of the high-dose bolus but the overall risk remains low (Kearns).
  - Large bolus vitamin D administration has been incompletely studies so there are possible unforeseen risks associated with this.
- Participants will undergo blood draws at the initial visit and every three months. When done but persons trained in phlebotomy there is minimal risk. The risks are unlikely but do include unintentional bleeding, bruising, hematoma, or infection. There is also risk of vasovagal events.

XVI. MANAGEMENT OF RISKS

- Overall, the risk of vitamin D toxicity remains very low (Kearns). We will monitor vitamin D and calcium levels one week after starting the study medications. We will also monitor calcium levels every three months.
  - If participants do develop symptoms listed above, treatment of the hypercalcemia will be managed outpatient by the investigators or other provider at PAMC. If symptoms become so severe that they require hospitalization, they will be admitted to Parkview Medical Center and managed by the inpatient IM residents.
- Blood draws will all be done by phlebotomy trained individuals with standard precautions. The site will be clean prior to the blood draw. Direct pressure and bandage will be used after the blood draw. Participants will be asked prior to the blood draw if they have had vasovagal episodes before and if they would like to lay down while having their blood drawn.

XVII. POTENTIAL BENEFITS

- Vitamin D deficiency has historically been associated with bone disorders but research in recent years has shown to play a role in disease states of multiple body systems. Treatment of vitamin D deficiency has been shown to resolve symptoms related to deficiency as well as reduce risk of developing certain health conditions.
- Single, large-bolus treatment also reduces the daily burden of traditional supplementation.
- Results from this study could potentially influence clinical practices for the treatment of vitamin D deficiency.

XVIII. PROVISIONS TO MONITOR THE DATA FOR SAFETY OF PARTICIPANTS

- Data will be evaluated at a minimum of once every month to ensure safety of all participants. It will likely be review more frequently than this and on an individual basis for each participant as they have their routine blood draws.

- The investigators or study coordinator will identify, document, and report any adverse events.
- The summarized safety data will be reviewed every three months by the primary investigator.

XIX. PROVISIONS TO PROTECT THE PRIVACY INTEREST OF PARTICIPANTS

- We do not anticipate any impact of the study or study procedures on the participants' privacy interests. All study meetings and lab draws will take part at facilities frequented by all patients of the Parkview Adult Medicine Clinic.

XX. MEDICAL CARE AND COMPENSATION FOR INJURY

- The risk of injury due to participation in this study is exceedingly low. If injury dose occur, participants will be cared for at the Parkview Adult Medicine Clinic. If hospitalization is necessary, participants will be admitted to the Parkview Internal Medicine Residency inpatient teams.
- Participants requiring medical attention due to the study medications will not be compensated monetarily but will also not have to pay for the medical care they receive that is specifically tied to the study.
- The administration at Parkview Medical Center as agreed to cover the cost for patients that require hospital admission due to study participation. Please see Appendix F for approval letter from administration.

XXI. COSTS TO PARTICIPANTS

- Participants will be responsible for travel costs to get to clinic. They will not have to pay for clinic visits, labs, or medication.

XXII. DRUG ADMINISTRATION

- 300,000IU dose
  - Decalcitrol brand
  - 50,000IU tablet preparation
  - Manufactured by Pharmin USA, LLC
  - Packaged and labeled per pharmacy distribution
  - Prescriptions will be sent to The Pharmacy at Parkview for the participants to pick up
  - Recommend storage temperatures 59-86F
  - One-time PO administration of 6 tablets
  - Participants will be walked to the pharmacy to pick up the study medication
- 5,000IU dose
  - Rugby, Vitamin D3
  - Manufactured by Nutri-force
  - Packaging: white bottle with tamper resistant lid, 100 capsules per bottle
  - 

- Daily PO administration of one capsule
- Participants will be walked to The Pharmacy at Parkview to buy OTC 5,000IU capsules. They will be asked to bring bottle to follow-up every three months to count capsules remaining. They will get a new bottle every three months. Participants will be allowed to keep leftover capsules.

XXIII. **INVESTIGATIONAL DEVICES**

- Investigational devices will not be used during this study.

XXIV. **MULTI-SITE STUDIES**

- Study will be performed only at the Parkview Adult Medicine Clinic.

XXV. **SHARING OF RESULTS WITH PARTICIPANTS**

- All personal results will be shared with the individual participants at the end of the trial.

References:

1. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011, 96(7): 1911-1930.
2. Holick MF, Chen TC. *Vitamin D deficiency: a worldwide problem with health consequences.* Am J Clin Nutr. 2008;87 supp:1080s-1086s.
3. Williams S, Malatesta K, Norris K. Vitamin D and chronic kidney disease. *Ethn Dis.* 2009; 19(5): 8-11.
4. Stokes CS, Volmer DA, Grunhage F, Lammert F. Vitamin D in chronic liver disease. *Liver International: Official Journal of the International Association for the Study of the Liver.* 2013; 33(3): 338-352.
5. Forman JP, Giovannucci E, Holmes MD, et al. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. Hypertension. 2007;49:1063–1069
6. Anathakrishnan AN. Vitamin D and inflammatory bowel disease. *Gastroenterol Hepatol*. 2016; 12(8): 513-515.
7. Reid IR. Vitamin D effect on bone mineral density and fractures. *Endocrinol Metab Clin N Am*. 2017; 46: 935-945.
8. Boonen S, Vanderschueren D, Haentjens P, Lips P. Calcium and vitamin D in the prevention and treatment of osteoporosis - a clinical update. *J Intern Med*. 2006;259:539–552.
9. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation*. 2008;117:503–511.
10. Witham MD, Dove FJ, Dryburgh M, et al. The effect of different doses of vitamin D(3) on markers of vascular health in patients with type 2 diabetes: a randomised controlled trial. *Diabetologia*. 2010;53:2112–2119
11. Autier P, Gandini S. Vitamin D supplementation and total mortality: A meta-analysis of randomized controlled trials. *Arch Intern Med*. 2007; 167(16): 1730-1737.
12. Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab.* 2004, 89: 5387-5391.
13. Smith EM, Tangpricha V. Driving up the dose: Implications for high-dose vitamin D therapy. *Endocr Pract.* 2015; 21(10): 1178-1180.

14. Ilahi M, Armas LA, Heaney RP. Pharmacokinetics of a single, large dose of cholecalciferol. *Am J Nutr*. 2008; 87(3): 688-691.
15. Kearns MD, Binongo JNG, Watson D, et al. The effect of a single, large bolus of vitamin D in healthy adults over the winter and following year: a randomize, double-blinded, placebo-controlled trial. *Euro J of Clin Nutr*. 2015; 69: 193-197.
16. Kearns MD, Alvarez JA, Tangpricha V. Large, single-dose, oral vitamin D supplementation in adult populations: A systemic review. *Endocrin Pract*. 2014; 20(4): 341-351.
17. Premaor MO, Scalco R, da Silva MJ, et al. The effect of a single dose versusa daily dose of cholecalciferol on the serum 25-hydroxycholecalciferol and parathyroid hormone levels in the ederly with secondary hyperparathyroidism living in a low-income housing unit. *J Bone Miner Metab*. 2008;26:603-608.
18. Stricker H, Tosi Bianda F, Guidicellli-Nicolosi S, et al. Effect of a single, oral, high-dose vitamin D supplementation on endothelial function in patients with peripheral arterial diseas: a randomised controlled pilot study. *Eur J Vasc Endovasc Surg.* 2012;44:307-312.
19. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose vitamin D3 and mental well-being: Randomised controlled trial. *Brit J of Psych*. 2011; 198: 357-364.
20. Kaur P, Mishra SK, Mithal A. Vitamin D toxicity resulting from overzealous correction of vitamin D deficiency. *Clin Endocrinol*. 2015; 83: 327-331.
21. Koul PA, Ahmad SH, Ahmad F, et al. Vitamin D toxicity in adults: A case series from an area with endemic hypovitaminosis D. *Oman Med J*. 2011; 26(3): 201-204
22. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: When to test and how to treat. *Mayo Clin Proc*. 2010; 85(8): 752-758.
23. Rode A, Fourlanos S, Nicoll A. Oral vitamin D replacement is effective in chronic liver disease. *Gastroenterol Clin Biol*. 2010; 34: 618-620.

Appendix A: Confidence interval and sample size calculations

For Confidence interval of 95%

- 85 participants (rounded to nearest integer)

For Power of 90%

- 58 participants

Assumptions:

- Acceptable error rate of 3 units
- Significant data meaning > 6 unit change from baseline
- Standard deviation on 6.7
- The latter 2 were taken from Premaor et al.

Calculation for Confidence interval:

$$n_i = 2\left(\frac{Z\sigma}{E}\right)^2$$

N = sample size

Z = constant for desired confidence interval = 1.96

σ is the standard deviation of the outcome of interest = 6.7

E = acceptable margin of error = 3

This was then multiplied by 2 (for the treatment group vs control group) and then divided by .9 (assuming a 90% retention rate)

Calculation for Power:

$$n_i = 2\left(\frac{Z_{1-\alpha/2} + Z_{1-\beta}}{ES}\right)^2$$

N = sample size

$Z_{1-\alpha/2}$ = constant for standard normal distribution of 1-alpha/2= 1.96

Z_{1-} = constant for standard normal distribution of 1-beta= 1.282 (if power of 90%)

ES = Effect Size = $\frac{|\mu_1 - \mu_0|}{\sigma}$

Numerator is the expected difference between popultions (taken from 9 month difference of Premoar et al)

σ is the standard deviation of the outcome of interest = 6.7

This was then multiplied by 2 (for the treatment group vs control group) and then divided by .9 (assuming a 90% retention rate)

Appendix B: Recruitment Flyer

Do you have Vitamin D deficiency?

You could participate in a research study!

What:

Comparing treatment of Vitamin D deficiency with standard replacement versus single large dose of Vitamin D

Ask your PCP about participating if:

1. You are 18-75 years old
2. Have low Vitamin D
   a. Less than 20ng/mL

Or contact the Parkview Adult Medicine Clinic to get in touch with Dr. Stephanie Franquemont

311 W 14th St, Pueblo, CO — — — 719/595-7585

Appendix C: Screening Questionnaire

Treatment of Vitamin D deficiency with large bolus cholecalciferol in the outpatient setting

Screening Questionnaire

Participant #: | | | |

Participant initials: | | | |

Demographics:

Sex: Male Female

Age: _____

Race: Caucasian Hispanic African American Asian Native American Other

Screening questions:

Do you speak conversational English? Y N

Who is your PCP? _____

Are you currently taking Vitamin D? Y N

If so, how much? _____

If so, ergocalciferol or cholecalciferol? _____

Are you pregnant or breast feeding? Y N

Do you have a history of:

1. hypercalcemia (high calcium level) Y N
2. hyperparathyroidism (high PTH level) Y N
3. CKD w/ baseline Cr >1.1mg/dL Y N
4. previous intestinal surgery Y N
5. Celiac disease Y N
6. Crohn's disease Y N
7. ulcerative colitis Y N
8. Paget's disease or other bone disorder Y N
9. osteoporosis Y N
10. granulomatous conditions Y N
11. thyrotoxicosis (high thyroid levels) Y N
12. active cancer or current chemotherapy treatment Y N

Date _____ Investigator Initials_____

Appendix D: Data collection sheet for initial visit

Treatment of Vitamin D deficiency with large bolus cholecalciferol in the outpatient setting

Screening visit data collection:

Participant #: | | | |

Participant initials: | | | |

Prescreening 25(OH)D level (ng/mL): _____

Vital signs:	**Reading One**	**Reading Two**
	Time_____	**Time**_____
Height:	_____	_____
Weight:	_____	_____
BMI (calculated):	_____	_____
Temperature:	_____	_____
Heart rate:	_____	_____
Blood pressure:	_____	_____
Respiratory rate:	_____	_____

Fitzpatrick skin type: I II III IV V VI

Appendix E: Follow-up Questionnaire

Treatment of Vitamin D deficiency with large bolus cholecalciferol in the outpatient setting

Follow-up Visit:

Participant #: | | | |

Participant initials: | | | |

Visit: 1wk 3mo 6mo 9mo 12mo

Vital signs:	**Reading One** Time_____	**Reading Two** Time_____
Height:	_____	_____
Weight:	_____	_____
BMI (calculated):	_____	_____
Temperature:	_____	_____
Heart rate:	_____	_____
Blood pressure:	_____	_____
Respiratory rate:	_____	_____

Number of missed vitamin D doses since last visit: _____

Adverse Events:_____

_____

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_____

Adverse Reactions:_____

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Initials_____

Appendix F: Letter from Michael Baxter, CEO of Parkview Medical Center

November 28, 2018

Attention:
I.R.B.
Dr. Stephanie Franquemont:

RE: Vitamin D Deficiency Clinical Trial

Parkview Medical Center supports the clinical trial for the Vitamin D dosage project. Parkview will work directly with patients involved in the study and provide assurances the patient will not be held liable for any copays or deductibles related to required hospital inpatient care related to the patient's participation in the study.

Please utilize this document in the file as formal notification of Parkview's support.

Sincerely,

Michael T. Baxter,
President/CEO

Caring For You®

719 .584 .4000 • 400 West 16th St, Pueblo, CO 81003