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A Pilot Study of Vitamin D Replacement in Patients with Non-Hodgkin's Lymphoma or Chronic Lymphocytic Leukemia with Low Vitamin D Levels

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A Pilot Study of Vitamin D Replacement in Patients with Non-Hodgkin's Lymphoma or Chronic Lymphocytic Leukemia with Low Vitamin D Levels

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ABSTRACT:

Title: A Pilot Study of Vitamin D Replacement in Patients with Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia with Low Vitamin D Levels

Objectives: To evaluate the Primary End Point, the 3 year progression-free survival (PFS), defined as time from the time of study entry of "watch and wait" patients or newly diagnosed NHL or CLL until relapse, progression, starting new therapies or death from any cause. To evaluate changes in the levels of serum vitamin D levels during therapy with daily oral Vitamin D supplementation. To evaluate the Secondary End Point, the overall survival (OS), defined as defined as time from the time of study entry of "watch and wait" or newly diagnosed NHL or CLL until death from any cause.

Eligibility: Patients with histologically confirmed newly diagnosed or previously untreated (patients may be under no treatment "wait and watch" or have received two cycles of chemotherapy or localized radiation therapy before informed consent) non-Hodgkin's lymphoma (NHL) or chronic lymphocytic lymphoma (CLL) with low vitamin D levels.

Intervention: All patients will have a serum 25-hydroxyvitamin D [25(OH) D] drawn at time of enrollment

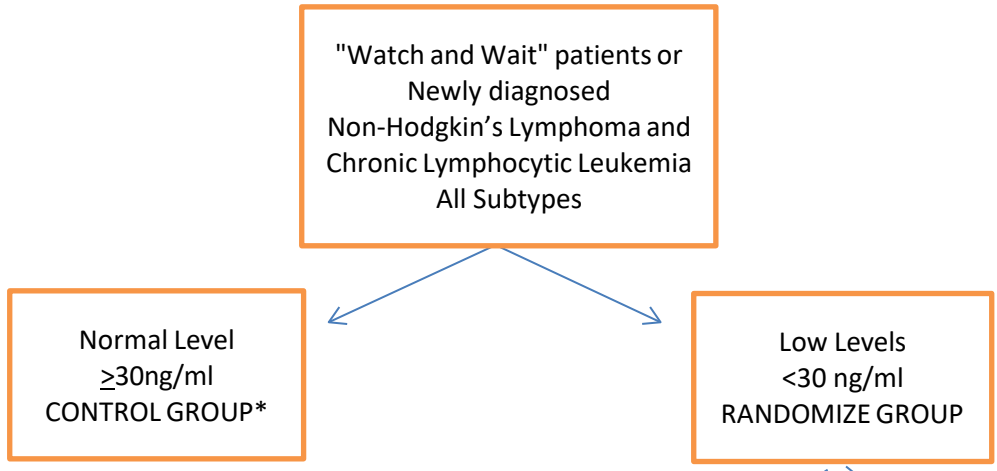
Subjects with a **normal level** of serum Vitamin D 30-100 ng/ml at time of enrollment will be automatically enrolled in the controlled group and will be followed only for long-term progression free survival and outcome. No further evaluation of serum 25-hydroxyvitamin D [25(OH) D] will be obtained.

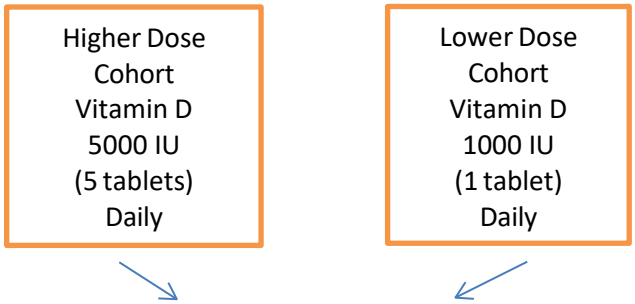
Subjects found to have **low levels** of serum Vitamin D <30 ng/ml at time of enrollment will be randomized on a 1:1 basis to receive vitamin D 5000 IU daily (Higher Dose Cohort) or vitamin D 1000 IU daily (Lower Dose Cohort) stratified by disease group (aggressive NHL or indolent NHL/CLL).

Evaluation: Serum 25-hydroxyvitamin D levels will be assessed at baseline, 6 months from baseline, 12 months from baseline, and then year 2 and 3. If subject is at a normal level of 25-hydroxyvitamin D [25(OH) D], no change in intervention will be made. If the subject has a low level of vitamin D, which is defined as < 30 ng/ml, then the dose that they are currently enrolled in will be increased by 1000 IU (e.g. 5000 IU increase to 6000 IU; 1000 IU increase to 2000 IU). There will be a maximum dose of 10000 IU daily. If a subject has an elevated level of vitamin D, which is defined as > 100 ng/ml, then the dose will be held for one month and the level will be rechecked. If the level returns < 100 mg/ml, the dose will be cut in half and re-tested in two months. PFS and OS will be assessed at the end of study (3 years).

Schema:

A Pilot Study of Vitamin D Replacement in Patients with Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia With Low Vitamin D Levels





Analysis

a. Baseline
b. 6 months
c. 12 months
d. year 2 and 3

Evaluate serum 25 (OH) D

*Control group will not have any further lab testing done after baseline.

Randomization will be performed on a 1:1 basis and stratified by disease group (aggressive NHL or indolent NHL/CLL).

Dose Modifications at 6 mo, 12 mo, and year 2 and 3:

Low level of 25(OH) D < 30 ng/ml the dose that they are currently enrolled in will be increased 1000 IU (e.g. 5000 IU increase to 6000 IU; 1000 IU increase to 2000 IU). There will be a maximum dose of 10000 IU daily

Elevated level of 25(OH) D > 100 ng/ml then the dose will be held for one month and a level will be rechecked. If the repeat level is < 100 mg/ml, the dose will be cut in half and re-tested in two months.

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Section 1.0 Objectives:

1.1 Primary Objectives

1.1.1 To evaluate the **Primary End Point,** the 3 year progression-free survival (PFS), defined as time from the time of study entry of "watch and wait" or newly diagnosed NHL or CLL until relapse, progression, starting new therapies or death from any cause. Response will be determined by the principal investigator or the lead site investigators. The 3 year PFS of the low dose and high dose groups will each be compared to a historical fixed expected 3-year PFS of 45%.

1.2 Secondary Objectives

1.2.1 To evaluate changes in the levels of serum vitamin D levels during therapy with daily oral Vitamin D supplementation

1.2.2 To evaluate the **Secondary End Point,** the overall survival (OS), defined as defined as time from the time of study entry of "watch and wait" patients or newly diagnosed NHL or CLL until death from any cause. For subjects who are still alive at the time of the study analysis at 3 years or are lost to follow-up, survival will be censored at the last recorded date that the subject was known to be alive.

Section 2.0 Background:

Vitamin D deficiency is a common problem in the Unites States.1 Multiple studies have demonstrated that 25% to 50% of patients evaluated in the clinical setting have insufficient levels of vitamin D.2,3,4 Vitamin D has long been recognized as essential for the efficient absorption and utilization of dietary calcium as well as for bone and muscle health. Intestinal calcium absorption is significantly enhanced by the presence of adequate vitamin D and is conversely reduced in deficiency of this micronutrient.[3] There are some studies that have shown that lower vitamin D levels have been reported to increase risk for fractures, falls, functional limitations, some types of cancer, diabetes, cardiovascular disease, depression, and death.[1,2,3] There are limited studies that have evaluated vitamin D deficiency in lymphoma but even fewer that have looked at the effects of vitamin D in the clinical setting and the impact it has on event free survival and overall survival.[2]

Lymphomas are types of cancer derived from lymphocytes that often develop into lymphatic tissues. Non-Hodgkin lymphomas (NHLs) is the sixth most common type of cancer in U.S. adults.[5] Non-Hodgkin lymphomas are heterogeneous group of hematological malignancies that vary significantly in their severity, from indolent to very aggressive types. Symptoms may include enlarged lymph nodes that are not generally painless, fevers, night sweats, weight loss, and fatigue. Non-Hodgkin lymphomas are treated by combinations of chemotherapy, immunotherapy, radiation, and hematopoietic stem cell transplantation. Risk factors for NHL include autoimmune diseases, HIV/AIDS, infections with human T-lymphotrophic virus, eating a large amount of meat and fat, immunosuppressant medications, and some pesticides.

2.1 Sources of Vitamin D

There are three ways in which humans obtain vitamin D; two are obtained naturally (food and sun), and one is artificial (supplements which includes fortificants). The partition of intake across the three sources depends on dietary habits, and exposure of skin to solar ultraviolet (UV)-B radiation.[6] A combination of dietary intake of foods rich in vitamin D in addition to regular periods of skin exposure to the sun can provide the body with an adequate supply of this micronutrient. However, the average person's lifestyle allows little time to be spent outdoors along with the risk of melanoma, and diets are usually replete with highly processed foods; thus, vitamin D intake and synthesis is seldom adequate to avoid deficiency.[6] Fatty fish and vitamin-D enriched dairy products can supply a small amount of the estimated 3000-5000 IU of vitamin D that is needed daily.[6] However, the average dietary intake nationwide is typically less than 5% of the body's vitamin D requirement.[6]

2.2 Definition

Total serum 25-hydroxyvitamin D [25(OH) D] is the major form of vitamin D that circulates in the body and is used to assess inadequacy or deficiency. 25(OH) D is converted to 1,25-dihydroxyvitamin D [1,25 $(OH)_2D$] considered the physiologically active form of vitamin D, via the action of 1-α-hydroxylase. While much of the conversion occurs in the kidney, multiple other tissues (including lymphoma cells) also have 1-α-hydroxylase activity, and can thus regulate 1,25 $(OH)_2D$ levels at the local tissue level. Once formed, 1,25 (OH)2D exerts its effects through binding to the vitamin D nuclear transcription factor receptor, where it may regulate the expression of nearly 200 genes.[7]

Vitamin D insufficiency is defined as serum 25(OH) D <30 ng/mL although consensus guidelines for the diagnosis of vitamin D insufficiency have not been established because opinions differ on what constitutes as a deficiency. The Institute of Medicine (IOM) has concluded that persons are at risk for: vitamin D deficiency at serum 25(OH) D concentrations: <30 nmol/L (<12 ng/mL); risk of inadequacy deficiency if levels range from 30 to 50 nmol/L (12-20 ng/mL); and sufficient if level $\geq$ 50 nmol/L ($\geq$20 ng/mL).[6]

2.3 Detection

Many testing methods are available that measure total serum 25-(OH) D levels. However, the accuracy of these tests to detect vitamin D deficiency is difficult to determine because of the lack of studies that use an internationally recognized reference standard and the lack of consensus on the laboratory values that define vitamin D deficiency. The preferred test for assessment of vitamin D is serum 25-hydroxyvitamin D (25(OH) D). The results of this test are minimally influenced by recent dietary intake or recent sun exposure, and it is considered the most accurate functional indicator of vitamin D stores.[6]

2.4 Risk Factors

A number of factors influence the body's ability to synthesize vitamin D from sun exposure to the skin, including the skin's melanin pigmentation. A person with a darker skin tone will

synthesize less vitamin D with sun exposure compared with a person who has a lighter skin tone. The use of sunscreen, while helpful minimizing the risk of certain skin cancers and other solar damage, likely increases the risk of vitamin D deficiency, as application of sunscreen with a sun protection factor of 8 reduces the capacity of the skin to produce vitamin D by as much as 95%. Obviously, individuals who spend little time outdoors have a significant risk for vitamin D deficiency.[6]

The time of year and place of residence also influence sun-induced vitamin synthesis, with winter sun and northern latitudes providing the weakest effect. Even people who are regularly involved in outdoor activities that facilitate exposure to sunshine can have vitamin D deficiency if little skin is left sun exposed. General guidelines about the amount of sun exposure needed to maintain adequate vitamin D levels are difficult to provide. However, it has been suggested by some researchers that approximately 5 to 30 minutes of sun exposure between 10 AM and 3 PM at least twice a week to the face, arms, legs, or back without sunscreen usually lead to sufficient vitamin D synthesis. This level of sun exposure is unlikely to induce sunburn or increase skin cancer risk.[6]

The use of certain prescription medications and supplements, including phenytoin (Dilantin), phenobarbital, and St. John's Wort, is potentially vitamin D depleting. As a result, patients taking these medications and supplements require two to five times the recommended daily amount of vitamin D.[6]

Vitamin D deficiency is also common in the presence of hepatic or renal disease as well as after gastric bypass. Body mass index $\geq$ 30 kg/m2 is associated with lower serum 25 (OH) D levels compared with non-obese individuals. Additional risk factors for vitamin D deficiency include obesity, $\geq$ 65 years or < 25 years, and fat malabsorption due to conditions such as inflammatory bowel disease and celiac disease.[6]

2.5 Vitamin D Supplements

Vitamin D3 is the preferred form of micronutrient for the treatment of vitamin D deficiency and maintenance of vitamin levels. Serum 25(OH) D can be expected to rise by 1 ng/ml (2.5 nmol/L) for every 100 IU of additional vitamin D each day. Recent data indicates that cholecalciferol (vitamin D3) is substantially more potent than ergocalciferol (vitamin D2) and that safe upper intake level for vitamin D3 is 10,000 IU/day.[8,9,10] The two seem to be absorbed from the intestine and to be 25-hydroxylated in the liver with equal efficiency; however, vitamin D2 seems to upregulate several 24-hydroxylases, leading to increased metabolic degradation of both the administered D2 and endogenous D3.[10] Thus, although it is certainly possible to treat patients satisfactorily with vitamin D2, ergocalciferol seems to have no advantage over vitamin D3 (cholecalciferol), which, as noted, is the natural form of the vitamin and which is, today, less expensive.[11] It should be noted that, in this brief review, all of the evidence brought forth with respect to the relationship of vitamin D status to health and disease has been developed mainly for cholecalciferol (vitamin D3).

Most commercial vitamin D supplements carry vitamin D either as a crystalline powder in a tablet that consists of otherwise inert excipients or in an oily vehicle (as in drops or gel caps).

Whether the vehicle affects absorption of D3 is unclear. The literature on this topic is extremely limited, and studies in which the vehicle was the primary variable are even more limited. Further, the outcome variable in all published studies was not serum D3 but serum 25(OH) D. Maalouf et al. (2008) compared 14,000 IU D3 in ethanol and in a medium-chain fatty acid vehicle. They found a statistically significant, higher increase in 25(OH) D from baseline in the oil group than in the ethanol group.[12] Holvik et al. (2007) examined the effect of 400 IU D3 administered in a multivitamin tablet containing cellulose and other vitamins and fillers versus 400 IU D3 administered in a fish oil capsule and found no significant differences in 25(OH) D response between the two groups.[13] The Grassroots Health project collects data on supplement type and has found no difference in the 25(OH) D concentration achieved with either 5,000 or 10,000 IU daily doses, irrespective of whether the D3 was delivered via a gel cap in oil or as dry powder in a tablet.[14]

Vitamin D, being fat soluble, is often presumed to require co-ingested fat for optimal absorption. However, it should be recognized that for the quantities consumed (in the microgram range), usual solubility considerations may not be pertinent.[15, 16] However, fat malabsorption syndromes are known to lead to vitamin D deficiency, and the mechanism is generally considered to be a specific impairment in the absorption of the fat-soluble vitamin D. [15, 16] Dawson-Hughes et al. (2013) using pharmacokinetic methods in individuals with normal absorptive function, reported equal absorbability for D3 under fasting and high-fat meal conditions, with slightly better absorption from a low-fat meal.[17] Mulligan and Licata (2010), in an observational study of 17 poor responders to oral D preparations, reported greater absorption from a large meal containing fat than from intake on an empty stomach.[18] Too few studies of this issue have been reported to permit a reliable estimate of how much absorption of vitamin D may vary and what factors may influence that absorption.

2.6 Vitamin D Toxicity

Vitamin D, particularly its active hormonal form, calcitriol, is a highly potent molecule, capable of producing serious toxic effects, including death, at milligram intake levels.[25] Nevertheless, despite these appropriate concerns, there is, in fact, a comfortable margin of safety between the intakes required for optimization of vitamin D status and those associated with toxicity.[25] It is worth noting, for example, that a single minimum erythema dosage of ultraviolet radiation (e.g., 15 min in the sun in a bathing suit in July) produces, in a light-skinned individual, 10,000 to 20,000 IU of vitamin D.[25] Repeated day after day, this can add up to substantial vitamin D inputs. Nevertheless, there has never been a reported case of vitamin D intoxication from sun exposure.[25] Controlled metabolic studies, necessarily limited in scope (although extending into the 100s of individuals), showed that dosages up to 50,000 IU/day for 1 to 5 months produce neither hypercalcemia nor hypercalciuria.[25] A recent publication, reviewing the totality of the toxicity data, concluded that there were no cases of intoxication reported for daily intakes of <30,000 IU/d for extended periods and no cases of vitamin D intoxication for serum 25(OH)D levels <200 ng/ml (500 nmol/L).[25] Thus, it was concluded that a daily intake of 10,000 IU should be considered the tolerable upper intake level. There is no known medical reason for dosages approaching that level; hence, there is a comfortable margin of safety between therapeutic and toxic intakes.[25]

2.7 Vitamin D in Cancer

Although the central role of vitamin D is maintaining serum calcium and skeletal homeostasis has been long understood, more recent research has demonstrated that vitamin D may have a multiple effects on cellular differentiation by inhibiting abnormal cellular growth, thereby by minimizing abnormal proliferation, apoptosis and angiogenesis.[4,27] Several studies have suggested that low levels of serum 25 (OH) D levels may be associated with an increase incidence of developing colorectal, breast and other cancers.[28,28,30,31] And low levels of serum 25 (OH) D levels at diagnosis may be associated with poorer prognosis in colorectal, melanoma, breast and lung cancer.[32,33,34,35,36] Despite growing evidence for relationship between vitamin D levels and solid tumor risk, far less is known about vitamin D and the risk of hematologic malignancy.

In *in vitro* and *in vivo* animal models, calcitriol has been shown to have anti-proliferative, pro-differentiate and pro-apoptotic actions in cancer cells. In this manner, vitamin D could limit cancer progression or prevent it. A large number of observational studies have shown that low circulating levels of cholecalciferol, which are related to geographical location, diet and activity, are associated with a higher risk of cancer and cancer-specific worse prognostic. However, data regarding the role of vitamin D in cancer risk, incidence and mortality is still controversial. Some studies suggest a positive correlation between circulating 25(OH) D concentrations in patients with a diagnostic of cancer, although several epidemiologic studies including colorectal, breast, and hepatocellular carcinoma have demonstrated an inverse association between serum 25(OH) D levels and the risk to develop these pathologies. It has not yet been clearly elucidated if low serum 25 (OH) D levels are causative of associative parameters of cancer. Some evidences are described below.[37, 38, 39]

2.8 Vitamin D in Non-Hodgkin's Lymphoma

A pooled analysis of 10 studies found that higher levels of recreational sun exposure, which would be anticipated to increase vitamin D levels was associated with a lower risk for non-Hodgkin's lymphoma.[40] Furthermore, data from 2 prospective cohort studies provide suggestive evidence that low serum 25 (OH) D levels are associated with increased incidence of NHL.[41,42] There are only a few studies that have evaluated the relationship of vitamin D and non-Hodgkin's lymphoma.[32] A study performed by Shanafelt et colleagues (2011) evaluated 390 newly diagnosed CLL patients. The time to treatment (TTT) was HR=1.47; P=.008 and overall survival (OS) was not significant in both cohorts (HR=1.47; P=.07) in the multivariate analysis of the patients adjusting for variables but in the individual cohorts there was a shorter TTT and OS in patients with CLL that were 25 (OH) D insufficient at time of diagnosis.[43]

Another trial performed by Drake et colleagues (2010) evaluated vitamin D insufficiency and prognosis in non-hodgkin's lymphoma.[2] Circulating 25-hydroxyvitamin D [25(OH) D] levels were predictive of event-free survival (EFS) and overall survival (OS) in a prospective cohort of 983 newly diagnosed patients with NHL. 25(OH) D and 1, 25-dihydroxyvitamin D [1, 25(OH) 2D] Median follow-up was 34.8 months; 404 events and 193 deaths of which 168 from lymphoma. For DLBCL, 52% of the patients were 25(OH) D insufficient. After adjusting for known prognostic factors and treatment, 25(OH) D insufficient patients with diffuse large B-cell

lymphoma (DLBCL) had inferior (hazard ratio [HR], 1.41; 95% CI, 0.98 to 2.04) and OS (HR, 1.99; 95% CI, 1.27 to 3.13). The association of 25(OH) D levels with EFS and OS was mainly observed over the range of 15 to 25ng/mL, and was relatively flat above 30 ng/mL.[2]

T-cell lymphoma (which included PTCL and CTCL), 57% of the patients were 25(OH) D insufficient, and after adjustment for known prognostic factors insufficient patients continued to have an inferior EFS (HR, 1.94; 95% CI, 1.04 to 3.61) and OS (HR, 2.38; 95% CI, 1.04 to 5.41). Inferior EFS and OS were observed among TCL patients in both the insufficient (<25 ng/mL) and the lower end of the optimal range (25 to 80 ng/mL) of 25 (OH) D levels. Vitamin D deficiency in mycosis fungoides and Sézary syndrome patients is similar to other cancer patients.[2]

The prevalence of 25 (OH) D insufficiency for the remaining subtypes ranged from 27% to 39%, and there were no associations of 25 (OH) D insufficiency with EFS. There were no association with EFS for the other NHL subtypes. Among patients with DLBCL and T-cell lymphoma, higher 1.25 1, 25 (OH) 2D levels were associated with better EFS and OS, suggesting that any putative tumor 1-α-hydroxylase activity did not explain the 25(OH) D associations. 25 (OH) D insufficiency was associated with inferior EFS and OS in DLBCL and T-cell lymphoma. One potential interpretation of the association of low 25 (OH)D levels with inferior DLBCL and TCL prognosis is that patients with larger tumor burden might have increased conversion of 25 (OH) D to 1,25 (OH)2D due to increased 1- α-hydroxylase activity from the tumor, leading to artificially low serum 25(OH)D levels. This study did not support the hypothesis that the association of lower 25 (OH) D levels were poor prognosis in DLBCL and TCL is confounded by tumor production of 1- α-hydroxylase. Further, these data also indicate that there appears to be a direct association of lower 1, 25 (OH) 2D levels with inferior outcome.[2]

Another study that looked at newly diagnosed follicular lymphoma (FL) was SWOG participants that were previously untreated patients with FL enrolled on a clinical trials involving CHOP chemotherapy plus an anti-CD20 antibody (rituximab or iodine-131 tositumomab) between 1998 and 2008 or participants also previously untreated patients with FL enrolled onto the Lymphoma Study Association (LYSA) PRIMA trial of rituximab plus chemotherapy (randomly assigned to rituximab maintenance versus observation) between 2004 and 2007 had 25-hydroxyvitamin D measured at baseline. The primary end point was progression-free survival (PFS). After a median follow-up of 5.4 years, the adjusted PFS and overall survival hazard ratios for the SWOG cohort were 1.97 (95% CI, 1.10 to 3.53) and 4.16 (95% CI, 1.66 to 10.44), respectively, for those who were vitamin D deficient (< 20 ng/mL; 15% of cohort). After a median follow-up of 6.6 years, the adjusted PFS and overall survival hazard ratios for the LYSA cohort were 1.50 (95% CI, 0.93 to 2.42) and 1.92 (95% CI, 0.72 to 5.13), respectively, for those who were vitamin D deficient (< 10 ng/mL; 25% of cohort). Conclusion of this study demonstrated that although statistical significance was not reached in the LYSA cohort, the consistent estimates of association between low vitamin D levels and FL outcomes in two independent cohorts suggests that serum vitamin D might be the first potentially modifiable factor to be associated with FL survival.[44]

We propose to conduct a Pilot study evaluating the effects of vitamin D supplementation on the 3-year PFS and OS of patients with newly diagnosed or previously untreated (patients may be under no treatment “wait and watch” or have received two cycles of chemotherapy before informed consent) Non-Hodgkin’s Lymphoma or CLL.

Section 3.0: Eligibility Criteria:

3.1 Inclusion

1. Patients must have histologically confirmed newly diagnosed or previously untreated (patients may be under no treatment “wait and watch” or have received two cycles of chemotherapy or localized radiation therapy before informed consent) Non-Hodgkin’s Lymphoma or CLL.
2. Patients must be 18 years of age or older (19 years or older in Nebraska).
3. Patients must have serum 25-hydroxyvitamin D [25(OH) D] drawn at time of enrollment. (NOTE: subjects currently taking Vitamin D supplements are eligible for screening. See Exclusion 2.)
4. Simultaneous participation in other therapeutic clinical trials will be allowed.
5. Patients must be aware of the neoplastic nature of his/her disease and willingly provide written, informed consent after being informed of the procedure to be followed, the nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts.

3.2 Exclusion

1. History of uncontrollable allergic reactions to vitamin D
2. Currently taking vitamin D supplement ≥ 1000 IU/day
3. History of Paget’s disease.
4. Hypercalcemia
5. Any other clinically significant medical disease or condition laboratory abnormality or psychiatric illness that, in the Investigator’s opinion, may interfere with protocol adherence or a subject’s ability to give informed consent.
6. Inability to cooperate with the requirements of the protocol.

Section 4.0: Registration and Randomization Procedures:

4.1 Recruitment

Patients with newly diagnosed or previously untreated (patients may be under no treatment “wait and watch” OR have received two cycles of chemotherapy before informed consent) Non-Hodgkin’s Lymphoma or CLL may be eligible for this trial.

Screening eligibility based on standard clinical care will be performed by the treating physician at the time of encounter. On initial presentation, a history and physical examination are performed, laboratory data obtained, radiologic/imaging, or bone marrow evaluations for staging will be performed per standard practice and as clinically indicated and is at the discretion of the treating physician.

The patient's primary oncologist will make the decision as to screened eligibility of the candidate based on the eligibility criteria listed in Section 3.0 prior to offering consent.

If the patient is screened as potentially eligible, he/she will then be offered the option to participate. An informed consent will be signed by the patient after thorough review of the study is completed by the physician and his/her designee.

Some insurance carriers may decline to cover the costs of usual medical care if the patient is participating in a clinical trial. The patient will be provided assistance by the research nurse coordinator or designated staff in determining if the insurance carrier will decline coverage. Insurance carriers may or may not pay for study related expenses. The patient can then decide if they wish to participate.

4.2 Eligibility Verification/Registration:

Before subjects are registered to the study, the Eligibility Checklist (Appendix A) must be completed to verify the subject meets the eligibility criteria. This will be used as source documentation once it has been reviewed, signed, and dated, which should be done prior to registration by the treating physician.

Date of Enrollment: The date of consent will be considered the date of enrollment.

Subjects will be registered through the sponsor site (UNMC) by contacting the UNMC Project Coordinator. Study personnel from UNMC, affiliate and IRB approved non-UNMC sites will contact the UNMC Project Coordinator if a potential subject appears to meet the eligibility criteria.

The site will email the following information:

- Registration request (which includes the subject's demographics)
- Completed Eligibility Checklist (Appendix A), and
- Signed consent form.

Once the UNMC Research Project Coordinator confirms that all documents have been received, approval for the patient will be given with an assigned study subject number. The UNMC IIT Project Coordinator will send a confirmation of registration email to the site. (Please note: A Study Subject ID number can be assigned prior to final confirmation, if needed.)

Each subject consented to the protocol is loaded into the UNMC Clinical Trial Management System (CTMS) within one week of consent. CTMS registration includes entering the required demographic information (included on the registration request form) as stated in the SRC policies and procedures. For external sites, this is completed by the UNMC Research Project Coordinator.

Section 5.0 Treatment Plan:

This is a Pilot study evaluating the effects of vitamin D supplementation on the outcomes of patients with newly diagnosed or previously untreated (patients may be under no treatment "wait

and watch" OR have received two cycles of chemotherapy or localized radiation therapy before informed consent) Non-Hodgkin's Lymphoma or CLL.

5.1 Randomization plan

This is a randomized study. All subjects will have a serum 25-hydroxyvitamin D [25(OH) D] drawn at time of enrollment. (NOTE: Only subjects currently taking < 1000 IU Vitamin D supplements are eligible for screening.) Subjects found to have **low levels** of serum 25-hydroxyvitamin D [25(OH) D] <30 ng/ml will be randomized on a 1:1 basis to vitamin D 5000 IU daily (Higher Dose Cohort) or vitamin D 1000 IU daily (Lower Dose Cohort) and stratified by disease group (aggressive NHL or indolent NHL/CLL).

The randomization schedule is generated by the study statistician. The randomization schedule is then provided to the UNMC research pharmacist.

Site study personnel will complete the Subject Randomization Request for those subjects meeting criteria for randomization and submit this along with the registration request documents outlined in Section 4.2 to the UNMC project coordinator. The UNMC research pharmacist will assign a randomization number and cohort. When finalizing the registration procedures, the randomization assignment is sent to study personnel by the UNMC project coordinator.

5.2 Evaluations

Pre-treatment Evaluations Within One Month (30 Days) of Consent:

- History and physical
- Calcium level
- Serum 25-hydroxyvitamin D [25(OH) D]
- Height and weight
- Vital signs, including blood pressure

If subjects have a **normal level** of serum 25-hydroxyvitamin D [25(OH) D] ≥ 30 ng/ml at time of enrollment, the subject will automatically be enrolled in the controlled group and will be followed only for long-term progression free survival and outcome. No further evaluation of serum 25-hydroxyvitamin D [25(OH) D] will be obtained. (NOTE: Subjects currently taking Vitamin D supplements will be encouraged to continue their supplementation.)

If subjects are found to have **low levels** of serum 25-hydroxyvitamin D [25(OH) D] <30 ng/ml at time of enrollment, the subjects will be randomized to receive either vitamin D 5000 IU (5 tablets) daily (Higher Dose Cohort) or vitamin D 1000 IU (one tablet) daily (Lower Dose Cohort) for three years. To provide a means of ensuring oral routes of medication adherence of patients while participating in a clinical trial, **Appendix D** "Oral, Sublingual, and/or Buccal Route Medication Adherence Standard Procedure (V 1.0 11-25-2013)" will be followed. (NOTE: Subjects who were currently taking Vitamin D supplements at the time of screening will be asked to discontinue the use of their Vitamin D supplementation and use only the Vitamin D dosing and supply instructed by the study.)

UNMC subjects will take oral over the counter supply through UNMC pharmacy.

Subjects at affiliate and Non-UNMC IRB approved sites will take oral over the counter Vitamin D 1000 IU (vitamin D-3, (cholecalciferol)) tablets. Investigators will need to prescribe the appropriate dose in which the subject is randomized.

Follow-up Evaluations

Subjects randomized to the Vitamin D cohorts: at 6 months, 12 months, and year 2 and 3 (Day 1095) (+/- 30 days) from registration confirmation:

- Serum 25-hydroxyvitamin D [25(OH) D] (Levels will be measured at a location convenient for the patient, for example, at their local primary care provider office.)

After year 3 (1095 days), the investigator will discuss continuation of Vitamin D supplementation recommendations with the subject. The supply of any recommendations for continued Vitamin D will be at the subjects cost.

Control group subjects: disease status must be assessed at the end of 3 years. Three years is defined as from the time of registration confirmation to day 1095 (+/- 180 days). For subjects no longer being followed by the study site, an attempt should be made by contacting the referring physician or reaching out to the subject at the 3-year time point to assess survival or progression free survival status. Contact and subject status should be documented in the medical record.

Covid Visit Exceptions:

If a subject visit is cancelled due to Covid concerns, then the study staff will confirm with the subject that they have an adequate supply of the study vitamin D supplement to continue daily dosing as prescribed.

The lab work required for the study will be collected at their next visit.

The Vitamin D administration diary may be collected at their next visit or via US Mail.

The visit will be documented as delayed due to Covid. The visit schedule will otherwise be maintained so that subject is on study for 3 years per protocol. The above will be fully documented in the medical record.

Dose Modifications based on vitamin D levels at 6 month, 12 month and year 2 and 3.

If subject is at a **normal level** (30-100 ng/ml) of 25-hydroxyvitamin D [25(OH) D], no change in intervention will be made.

If the subject has a **low level** of 25-hydroxyvitamin D [25(OH) D], which is defined as [OH] D< 30 ng/ml, then the dose that they are currently enrolled in will be increased 1000 IU (e.g. 5000

IU increase to 6000 IU; 1000 IU increase to 2000 IU). There will be a maximum dose of 10000 IU daily.

If a subject has an **elevated level** of 25-hydroxyvitamin D [25(OH) D], which is defined as [OH] D> 100 ng/ml, then the dose will be held for one month and a level will be rechecked. If the repeat level is < 100 mg/ml, the dose will be cut in half and re-tested in two months.

After the 12 month time point, if Vitamin D levels are not within normal limits, the investigator may manage subjects as clinically indicated, i.e. levels can be monitored more frequently than annually. Dose adjustment will be managed according to guidelines above or as recommended by the patient's primary care physician or Endocrinologist.

5.3 Removal of Patients from Protocol Therapy

If at any time the constraints of this protocol are detrimental to the patient's well-being, or if the patient is unable to comply with the requirements of the protocol, the patient will be removed from protocol therapy.

5.4 Development of intercurrent medical problems that would make continued protocol therapy detrimental to the patient's safety

If a non-treatment related intercurrent illness is expected to be of limited nature, then treatment may be delayed for more than 2 weeks. In this case, the patient would need to be re-evaluated before resuming protocol therapy.

5.5 Patient chooses to discontinue treatment or follow-up

In this event, the reason(s) for withdrawal will be documented.

The reason(s) for withdrawing the patient from the treatment portion of the study will be documented in the case report form. If available, the following information will be recorded in the case report form: date of disease relapse, date of death, cause of death, and autopsy report.

Section 6.0 Measurement of Effect:

To avoid assay variability which can confound vitamin D determinations a radioimmunoassay method will be used to measure all vitamin D measurements by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (this is the Nebraska Medicine's standard). Calibration used a 6-point standard curve over a concentration range 0-100 ng/mL. This is the preferred test for assessment of vitamin D is serum 25-hydroxyvitamin D (25(OH) D). The reason for this test is because it is minimally influenced by recent dietary intake or recent sun exposure, and it is considered the most accurate functional indicator of vitamin D stores. However, if this method is not available, the method used by the local lab will be acceptable.

Study ranges used:

- <30 is considered inadequate
- 30-80 Adequate

- >150 Potentially toxic vitamin D level

6.1 Toxicity criteria

This trial will assess only the grade 3 and 4 toxicities related to the Vitamin D administration. The NCI Common Toxicity Criteria Adverse Events (CTCAE) Version 4 (Appendix B) will be used to grade toxicity. It is available at the following internet site:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

6.2 Survival

Subjects will be analyzed with respect to overall and progression-free survival.

Overall survival is defined as time from study entry until death from any cause. For subjects who are still alive at the time of the study analysis or are lost to follow-up, survival will be censored at the last recorded date that the subject was known to be alive.

Progression-free survival is defined as time from study entry until the first notation of clinical progression, relapse, starting new therapies or death from any cause. For subjects who are still progression-free at the time of the study analysis or are lost to follow-up, progression-free will be censored at the last recorded date that the subject was known to be progression-free.

Response will be determined by the Principal Investigator or the lead site investigators.

Section 7.0 Study Parameters:

	Low Levels <30 ng/mL - RANDOMIZED GROUP					
	Pre-Treatment (within 30 days of Consent)	First Dose	6 months Day 182 (+/- 30 Days)	12 months Day 365 (+/- 30 Days)	Year 2 Day 730 (+/- 30 Days)	Year 3 Day 1095 (+/- 30 Days) End of Study
History & Physical	X					
Height, Weight, Vital Signs	X					
Monitor for Vitamin D related AEs			X	X	X	X
Serum Calcium	X					
Serum 25-hydroxyvitamin D [25(OH) D]	X		X	X	X	X
Vitamin D		X - Daily Dosing at Home for 3 years				
Long-term progression free survival and outcome[1]						X

Normal Level ≥30ng/ml - CONTROL GROUP*		
Followed only for long-term progression free survival and outcome. No further evaluation of serum 25-hydroxyvitamin D [25(OH) D] will be obtained. (NOTE: subjects currently taking Vitamin D supplements will be encouraged to continue their supplementation.)		
Required studies	Pre-Treatment (Within 30 days of Consent)	Year 3 - Day 1095 (+/- 180 Days) End of Study
History & Physical	X	
Height, Weight, Vital Signs	X	
Serum Calcium	X	
Serum 25-hydroxyvitamin D [25(OH) D]	X	
Long-term progression free survival and outcome[1]		X

[1] Progression defined as relapse, progression, or starting new therapies, or death

Section 8.0 Drug Formulation and Procurement (per UNMC Lexicomp Online):

8.1 Clinical Overview

Vitamin D (Natural Products Database)

Common Name(s): Sunshine vitamin; Vitamin D

8.1.1 Uses

Vitamin D, long recognized as playing a role in bone and calcium homeostasis, is being investigated for use in cardiovascular disease, cancer, diabetes, infections, multiple sclerosis, psoriasis, respiratory health, and other conditions. More clinical trials are needed.

8.1.2 Dosing

The American Academy of Pediatrics recommends 400 units/day of vitamin D in infants and adolescents. Clinical data are not yet sufficiently robust to make definitive recommendations for therapeutic dosages of vitamin D; however, in the elderly, 700 to 1,000 units/day have been shown to reduce the risk of falls.

8.1.3 Contraindications

Contraindications have not been identified.

8.1.4 Pregnancy/Lactation

Routine use of supplemental vitamin D during pregnancy is not supported by safety evidence. However, adequate maternal intake of vitamin D-containing foods during lactation ensures that breast-fed infants receive sufficient vitamin D.

8.1.5 Interactions

The use of statins has been shown to increase serum vitamin D levels. Corticosteroids decrease the metabolism of vitamin D and orlistat reduces its absorption; phenobarbital and phenytoin increase the hepatic metabolism of vitamin D.

8.1.6 Adverse Reactions

High doses of vitamin D have rarely produced adverse events in clinical trials.

8.1.7 Toxicology

Toxicity due to vitamin D is considered to manifest at serum levels greater than 150 ng/mL of 25-hydroxyvitamin D. Symptoms of hypervitaminosis D include fatigue, nausea, vomiting, and weakness associated with hypercalcemia. (Page 27 sites more toxicity details)

8.1.8 Source

Vitamin D3 (cholecalciferol) is synthesized in the skin by transformation of 7-dehydrocholesterol exposed to ultraviolet B rays of the midday sun. Vitamin D binding protein transports D3 to the liver, where it is hydroxylated to the inactive 25-hydroxyvitamin D form (calcidiol). In the kidneys, it is further hydroxylated by the enzyme 1-alpha-hydroxylase to active 1, 25-dihydroxyvitamin D (calcitriol).[Ref]

Vitamin D as ergocalciferol (vitamin D2) is found in some plants and in salmon, sardines, mackerel, tuna, cod liver oil, shiitake mushrooms, egg yolk, and fortified foods.[Ref] Deficiency may result from decreased absorption (such as in cystic fibrosis, celiac and Crohn diseases, and drug interactions), increased catabolism (caused by anticonvulsant and antiretroviral therapy and some immunosuppressant drugs), and hepatic and renal failure, as well as from inadequate intake.[Ref]

8.1.9 Chemistry

Vitamin D is a hormone precursor and acts to control calcium absorption in the small intestine. It affects parathyroid hormone, which in turn affects the metabolism of skeletal mineralization and calcium homeostasis in the blood. Additionally, effects on cytokines and immune-modulating effects are reported.[Ref]

The accepted biomarker is 25-hydroxyvitamin D (or calcidiol). Only in advanced renal disease are measurements of 1, 25-dihydroxyvitamin D (calcitriol) relevant.[Ref] Concern over standardization of assays exists.[Ref]

8.2 Uses and Pharmacology

8.2.1 Cancer

8.2.1.1 Animal data

Preclinical studies have shown an effect of vitamin D on a variety of cancer cell lines. Cell cycle interruption, apoptosis, and other mechanisms have been demonstrated.[Ref]

8.2.1.2 Clinical data

Meta-analyses of observational studies suggest a lower incidence of cancer with higher vitamin D serum levels.[Ref] Particular attention has focused on breast, colon, and prostate cancer. In the Women's Health Initiative study, no association was found between vitamin D and breast cancer[Ref] while the Health Professionals Follow-Up Study suggested a decreased risk of cancer with increasing 25-hydroxyvitamin D levels.[Ref] In a meta-analysis evaluating the effects of vitamin D supplementation on overall mortality risk, a subgroup analysis (n = 13 in studies) of long-term vitamin D supplementation for at least 3 years revealed a significant reduction in cancer mortality (relative risk [RR] = 0.88; 95% confidence interval [CI], 0.79 to 0.98).[Ref]

The American Society of Clinical Oncology clinical practice guideline adaptation for the screening, assessment, and management of fatigue in adult survivors of cancer (2014) notes that results from small pilot studies on the effectiveness of supplements, such as vitamin D, for managing cancer-related fatigue are equivocal (inconclusive).[Ref]

8.2.2 Cardiovascular

Vitamin D is thought to exert cardiovascular effects by a number of mechanisms, including effects on the renin-angiotensin-aldosterone system, homeostasis of calcium, and secondary effects on hyperparathyroidism and insulin resistance.[Ref]

8.2.2.1 Animal data

Available data from large clinical trials make animal data largely redundant.

8.2.2.2 Clinical data

No clinically important effect on coronary or cerebrovascular risk or outcomes was found with vitamin D and calcium supplementation over 7 years in the Women's Health Initiative randomized trial.[Ref] Other systematic reviews of clinical trials have largely found no effect of vitamin D supplementation on cardiovascular outcomes and hypertension.[Ref] Based on limited trial data in populations with vitamin D insufficiency, moderate to high doses of vitamin D increase the serum vitamin D metabolite status and may reduce cardiovascular risk; however, further studies are required before a definitive place in therapy can be established.[Ref] In a meta-analysis evaluating the effects of vitamin D supplementation on overall mortality risk, a subgroup analysis (n = 13 in studies) of long-term vitamin D supplementation for at least 3 years revealed no reduction in cardiovascular mortality.[Ref]

8.2.3 Diabetes

8.2.3.1 Animal data

Animal studies suggest vitamin D exerts effects on the homeostasis of glucose metabolism, as supplementation in animals has led to decreases in plasma glucose.[Ref] A direct effect on insulin

secretion has been suggested, as well as effects on insulin receptor expression, insulin sensitivity, and direct action on insulin itself.[Ref]

8.2.3.2 Clinical data

Epidemiological data support a role of vitamin D in reducing the incidence of diabetes. Vitamin D supplementation in infants has been associated with a decreased risk of type 1 diabetes, and a meta-analysis has demonstrated an association between low vitamin D status and the prevalence of type 2 diabetes or metabolic syndrome.[Ref] However, limited, small studies have shown equivocal results on the impact of vitamin D on serum glucose.[Ref] A 12-month, double-blind, randomized controlled trial (n = 86) in adults with type 2 diabetes mellitus and vitamin D deficiency (median, 11.9 ng/mL), found that vitamin D supplementation (1,904 units/day) for 6 months did not significantly affect blood glucose, insulin levels, HbA_{1c}, systolic blood pressure, or body weight. However, a significant correlation was observed between vitamin D levels and HbA_{1c} with the lowest HbA_{1c} occurring at less than 20 ng/mL.[Ref] Similar results were seen in another double-blind randomized clinical trial conducted in 158 Koreans with type 2 diabetes and vitamin D deficiency or insufficiency who supplemented their diet with 2,000 units/day of vitamin D3 plus calcium for 24 weeks. Neither glycemic control nor HbA_{1c} were significantly different in patients treated with vitamin D plus calcium compared with those treated with only calcium supplementation.[Ref] Interestingly, in a meta-analysis evaluating the effects of vitamin D supplementation on overall mortality risk, a subgroup analysis (n = 13 in studies) of long-term vitamin D supplementation for at least 3 years revealed a reduction in mortality only when vitamin D plus calcium was compared with placebo but not when compared with calcium, and not when vitamin D alone was compared with placebo. Other long-term subgroup benefits appeared in patients younger than 80 years, with a dose of 800 units or less, and in patients with a baseline 25-hydroxyvitamin D level less than 50 nmol/L. The meta-analysis primary outcome (n = 42 intervention randomized clinial trials; N = 85,466 patients) identified a decrease in all-cause mortality when vitamin D supplementation was continued for 3 years or longer (P = 0.001); heterogeneity was insignificant.[Ref]

As a component of medical nutrition therapy for patients with type 1 or type 2 diabetes, the American Diabetes Association Standards of Care (2014 and 2015) does not support routine supplementation with micronutrients such as vitamin D to improve glycemic control (low-quality evidence).[Ref]

8.2.4 Infectious disease

Vitamin D receptors are ubiquitous in the body and are found in immune system-related cells, such as B and T lymphocytes, neutrophils, and macrophages. An emerging role is being described for vitamin D in immune response.[Ref]

The Randomized Evaluation of Calcium or Vitamin D (RECORD) trial investigated the effect of vitamin D supplementation (800 units/day) on self-reported infections and antibiotic use but did not find a statistically significant association.[Ref] A single dose of vitamin D demonstrated an enhanced immune response in a randomized clinical trial in tuberculosis patients[Ref] while a systematic review of clinical trials evaluating the effect of vitamin D supplementation (largely in

tuberculosis, influenza, and other viral infections) concluded that further studies are warranted.[Ref]

Despite a significant increase in serum 25-hydroxyvitamin D, the recurrence of bacterial vaginosis in women being treated at an urban sexually-transmitted disease clinic was not significantly reduced by vitamin D supplementation (50,000 units × 9 doses) over 24 weeks. The trial was a randomized, placebo-controlled, double-blind study (N = 118).[Ref]

8.2.5 Multiple sclerosis

Theoretical and epidemiological models support a place in therapy for vitamin D in multiple sclerosis. An inverse relationship has been demonstrated between vitamin D levels and multiple sclerosis, especially in patients younger than 20 years of age, while the development of multiple sclerosis in women has been associated with low 25-hydroxyvitamin D levels. Lower serum vitamin D and severity of multiple sclerosis, as well as incidence of relapses, has also been demonstrated.[Ref]

Little prospective data exist; however, a small clinical study (N = 12) showed a decrease in the number of lesions with magnetic resonance imaging with administration of 1 mg (40,000 units) daily over 28 weeks.[Ref] No serious adverse events were reported at this dosage, and no hypercalcemia or hypercalciuria was reported.

8.2.6 Renal

8.2.6.1 Animal data

Available data from large clinical trials make animal data largely redundant.

8.2.6.2 Clinical data

As kidney function is impaired, the inability to maintain adequate phosphorus and calcium levels results in compensatory mechanisms involving parathyroid hormone. Resultant increases in bone metabolism to release calcium to the system cause bone deformation, pain, and an increased risk of fractures. Supplementation of vitamin D suppresses parathyroid hormone, but it may also slow the progression of chronic kidney disease via novel pathways. Vitamin D analogs, such as paricalcitol, may exert anti-inflammatory effects, as well as affect the renin-angiotensin systems and decrease morbidity and mortality. However, studies are limited.[Ref] A randomized, double-blind trial in chronic dialysis patients (n = 50) observed no improvement in cardiac function as measured by 24-hour blood pressure, arterial stiffness, and cardiac function in patients treated for 6 months with 75 mcg (3,000 units) or placebo. Although, left ventricular end-diastolic function was increased significantly in the treatment group (P = 0.024).[Ref]

8.2.7 Other uses

8.2.7.1 Alopecia

The role of vitamin D and its receptors is not well understood, but the potential for topical calcitriol to upregulate the receptors has been evaluated in animal models of chemotherapy-

induced alopecia. Hair loss is not prevented; however, hair regrowth over the entire animal has been demonstrated.[Ref] Limited clinical studies have produced varying results, possibly dependent on the chemotherapeutic agent.[Ref]

8.2.7.2 Atopic eczema/dermatitis

A 2012 Cochrane review identified 2 randomized clinical trials evaluating vitamin D for atopic eczema/dermatitis that met criteria for analysis. Vitamin D supplementation alone did not provide significant benefit over placebo in any of the primary, secondary, or tertiary outcomes. However, vitamin D (cholecalciferol 1,600 units) and E (600 units alpha-tocopherol) combination therapy resulted in a significant difference in severity scores at the end of 60-day treatment, as well as improvement in dryness, pruritis, and erythema compared with placebo in 52 adults and children older than 13 years of age.[Ref]

8.2.7.3 Dementia/Depression

Observational studies and animal models suggest a role for vitamin D in treating dementia. Vitamin D exerts antioxidant effects, and receptors are found in the human cortex and hippocampus. Correlations between the Mini-Mental State Examination scores and vitamin D serum levels, as well as global cognitive function, have been shown.[Ref] One clinical trial demonstrated an improvement in mild depression with vitamin D supplementation.[Ref]

8.2.7.4 Falls in the elderly

Systematic reviews have been conducted on the effects of supplemental vitamin D and the risk of falls in the elderly.[Ref] Low doses (200 to 600 units/day) showed no effect, while higher doses (700 to 1,000 units/day) reduced the risk of falling in the elderly by 19% to 22%.[Ref]

8.2.7.5 Mortality

A meta-analysis of 32 studies published and indexed between 1966 and 2013 evaluated the relationship between vitamin D (25-hydroxyvitamin D) and all-cause mortality in healthy participants as well as patients in clinic cohorts. The age-adjusted death rate in individuals with vitamin D levels in the lowest quantile (0 to 9 ng/mL) was almost twice that of those in the highest quantile (more than 35 ng/mL). The pooled dose-response curve declined steeply between 0 and 30 to 39 ng/mL and flattened at greater than 50 ng/mL, with all-cause mortality being significantly higher when levels were up to 30 ng/mL ($P < 0.01$).[Ref]

8.2.7.6 Psoriasis

Topical synthetic vitamin D (eg, tacalcitol) may be an alternative to topical steroids and may inhibit keratinocyte proliferation, as well as influence immune modulation.[Ref]

8.2.7.7 Respiratory health

Vitamin D appears to be capable of inhibiting the pulmonary inflammatory response and enhancing pulmonary defense against pathogens. Population-based studies support an association between circulating vitamin D levels and lung function.[Ref] The use of vitamin D in

cystic fibrosis is based on knowledge of vitamin insufficiency due to pancreatic insufficiency; however, evidence of benefit is lacking for vitamin D supplementation despite routine use.[Ref] Addition of high-dose vitamin D3 (100,000 units for 1 dose, then 4,000 units/day x 28 weeks) to inhaled corticosteroid therapy (ciclesonide 320 mcg/day) in adults with symptomatic asthma and low vitamin D3 levels who failed previous treatment, did not significantly alter the rate of first treatment failure or overall treatment failure.[Ref]

8.2.7.8 Dosing

Clinical response to vitamin D does not always correspond with serum levels of the markers.[Ref] Generally, a serum level of less than 20 ng/mL of 25-hydroxyvitamin D constitutes a deficiency in adults and children.[Ref]

The American Academy of Pediatrics recommends 400 units/day vitamin of D in infants and adolescents.[Ref]

To maintain a serum 25-hydroxyvitamin D level of 25 ng/mL, independently living elderly adults required vitamin D 7.9 to 42.8 mcg daily in a clinical study[Ref] (20 mcg is equivalent to 800 units).[Ref] Data from clinical studies are not yet sufficiently robust to make definitive recommendations for therapeutic dosages of vitamin D; however, in the elderly, 700 to 1,000 units/day have been shown to reduce the risk of falls.[Ref]

8.2.7.9 Pregnancy/Lactation

The safety and efficacy of vitamin D in pregnancy has not been confirmed. Clinical trials have evaluated the excretion of vitamin D in breast milk by mothers given supplementation. Adequate levels of vitamin D are achieved in breast-fed infants from mothers with a vitamin D intake of 400 units/day. All milk formulas sold in the United States contain at least 400 units/L of vitamin D.[Ref]

8.3 Interactions

The use of statins has been shown to increase serum vitamin D levels.[Ref] Corticosteriods decrease the metabolism and orlistat reduces absorption of vitamin D, while phenobarbital and phenytoin increase the hepatic metabolism of vitamin D.[Ref]

8.4 Adverse Reactions

High doses of vitamin D have rarely produced adverse events in clinical trials.[Ref]

Apart from the obvious hazards, prolonged sun exposure alone cannot cause vitamin D overdose because sunlight destroys excess vitamin D3.[Ref]

8.5 Toxicology

Toxicity due to vitamin D is considered to manifest at levels greater than 150 ng/mL of serum 25-hydroxyvitamin D. Symptoms of hypervitaminosis D include fatigue, nausea, vomiting, and weakness associated with hypercalcemia.[Ref] Reports of toxicity exist for children administered

high-dose vitamin D after World War II in Europe. Hypercalcemia, nephrocalcinosis, adverse cardiovascular effects, early aging, and premature death were reported.[Ref]

Hypervitaminosis D in 2 young brothers was reported subsequent to an overdose of an OTC vitamin D supplement that resulted from 2 simultaneous dosing errors; the OTC product (Merluzzovis cod liver oil-based capsules) contained approximately 1,000 times the labeled vitamin D content per capsule, and the mother administered twice the dose as recommended on the label. After 1 month of supplementation, the 12-year-old had received a total of 7,632,000 units (254,490 units/day instead of the recommended 400 units/day) and was hospitalized for abdominal pain, constipation, vomiting, hypercalcemia, suppressed parathyroid, and acute renal failure. The 15-year-old brother had received a total of 3,180,000 units over the previous 2 weeks, was asymptomatic, normocalcemic, and had normal renal function. Their vitamin D levels were well over the toxic lower limit (150 ng/mL) and were 535 ng/mL and 484.9 ng/mL, respectively. The 12-year-old was normocalcemic and had normal renal function within 1 month of discharge.[Ref]

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Disclaimer

This information relates to an herbal, vitamin, mineral or other dietary supplement. This product has not been reviewed by the FDA to determine whether it is safe or effective and is not subject to the quality standards and safety information collection standards that are applicable to most prescription drugs. This information should not be used to decide whether or not to take this product. This information does not endorse this product as safe, effective, or approved for treating any patient or health condition. This is only a brief summary of general information about this product. It does NOT include all information about the possible uses, directions, warnings, precautions, interactions, adverse effects, or risks that may apply to this product. This information is not specific medical advice and does not replace information you receive from your health care provider. You should talk with your health care provider for complete information about the risks and benefits of using this product.

This product may adversely interact with certain health and medical conditions, other prescription and over-the-counter drugs, foods, or other dietary supplements. This product may be unsafe when used before surgery or other medical procedures. It is important to fully inform your doctor about the herbal, vitamins, mineral or any other supplements you are taking before any kind of surgery or medical procedure. With the exception of certain products that are generally recognized as safe in normal quantities, including use of folic acid and prenatal vitamins during pregnancy, this product has not been sufficiently studied to determine whether it is safe to use during pregnancy or nursing or by persons younger than 2 years of age.

Section 9.0 Toxicity Reporting Guidelines:

This protocol will comply with monitoring and adverse event reporting requirements of the UNMC/Fred & Pamela Buffett Cancer Center Data Monitoring plan. The protocol will adhere to the institutional and FDA guidelines for the toxicity reporting.

Grade 3 and 4 adverse events (AEs) related to the Vitamin D administration will be graded according to the National Cancer Institute Common Terminology, Criteria for Adverse Events (NCI-CTCAE), version 4.0, which can be accessed at the following URL.

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

The over the counter agent used in the protocol is commercially available with a well-characterized toxicity profile.

All subjects will be closely followed for grade 3 and 4 toxicity/adverse events related to the Vitamin D administration from the time that the first dose of study drug is administered and ending 30 days following the final therapy. Adverse events will be assessed by reports from subjects of Vitamin D related **grade 3 or higher** adverse events to their physician-investigators, standard laboratory results and by physical examinations. Vitamin D related Only **prescription** medication taken to relieve symptoms of the Vitamin D related AE will be recorded in addition to the outcome. All other/routine concomitant medications WILL NOT be recorded. Deaths occurring within 30 days of study treatment regardless of relationship will be reported to the UNMC DSMC. Only fatal AEs will be reported to the UNMC IRB per the IRB's policy and procedures.

In addition to complying with all applicable regulatory reporting laws and regulations, vitamin D related serious adverse events and toxicities for all subjects will be reported to the University of Nebraska Medical Center, Institutional Review Board (IRB) and Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) and the FDA (if applicable).

9.1 Adverse Experiences Definitions:

9.1.1 Adverse Event

A Vitamin D related adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which possibly has a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product.

A Vitamin D related adverse event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event if related to Vitamin D. Laboratory abnormalities and changes in vital signs are considered to be adverse events if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol specific criteria and/or if the investigator considers them to be adverse events related to Vitamin D. In general, if a laboratory abnormality or change in vital sign is associated with a specific diagnosis that is being reported concurrently as an adverse event (e.g. elevated creatinine with renal failure) the findings that support the diagnosis do not need to be reported as separate adverse events unless the investigator feels it is appropriate.

9.1.1.1 Treatment-emergent Adverse Event

Treatment-emergent Vitamin D related adverse event is defined as any adverse event with onset or worsening from the time that the first dose of study drug is administered until 30 days after the final dose of study drug is administered.

9.1.1.2 Unexpected Adverse Event

An unexpected Vitamin D related adverse event is any adverse drug event that is not listed in the current labeling/Investigator’s Brochure. This includes events that may be symptomatically

and pathophysiologically related to an event listed in the labeling, but differ from the labeled event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. “Unexpected,” as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

9.1.2 Serious Adverse Event

A Vitamin D related serious adverse event is one that at any dose (including overdose) that:

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]

[1]“Life-threatening” means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.
[2]“Persistent or significant disability or incapacity” means that there is a substantial disruption of a person’s ability to carry out normal life functions.
[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred.

Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

9.2 Adverse Event Reporting Per University of Nebraska Medical Center, IRB and Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC):

This protocol will adhere to all institutional guidelines for adverse event reporting.

9.2.1 IRB Reporting

All Vitamin D related internal serious adverse events (SAEs) must be reported to the local IRB promptly per institutional human research protection program policies.

9.2.2 Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) Reporting

All Vitamin D related adverse events grade 3 or higher (expected or unexpected) will be reported to the University of Nebraska Medical Center, Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) in accordance with DSMC guidelines.

In its initial review, the DSMC will make a recommendation for the frequency of DSMC monitoring based on an assessment of risk associated with study-associated therapy, per the DSMC policy.

Detailed policy and procedures for this section may be reviewed at:
http://www.unmc.edu/cancercenter/clinical/prms.html

Attribution of AE: The likelihood of relationship of the AE to the study drugs will be determined by the investigator based on the following definitions:

- **Not Related:** The subject was not exposed to the study treatment or another cause is obvious.
- **Probably Not Related:** The AE is most likely explained by another cause, and the time of occurrence of the AE is not reasonably related to the study treatment.
- **Possibly Related:** Study treatment administration and AE occurrence reasonably related in time, and the AE is explained equally well by causes other than study treatment, or treatment administration and AE occurrence are not reasonably related in time, but the AE is not obviously a result of other causes.
- **Probably Related:** Study treatment administration and AE occurrence are reasonably related in time, and the AE is more likely explained by study treatment than by other mechanisms.
- **Definitely Related:** There occurrence and timing of the AE are clearly attributable to the study treatment.

Severity Grade of AE. The severity of events reported on the AE case report form will be determined by the principal investigator according the NCI Common Toxicity Criteria (CTC version 4.0). Copies of the AE report will be submitted to the IRB as indicated in Section 9.1.1.

9.3 Auditing

The UNMC Fred & Pamela Buffett Cancer Center Scientific Review Committee (SRC) will review this protocol on at least an annual basis.

This study will undergo audit on at least a semi-annual basis by the UNMC Fred & Pamela Buffett Cancer Center Audit Committee.

Detailed policy and procedures for this section may be reviewed at:
http://www.unmc.edu/cancercenter/clinical/prms.html

Section 10.0 Statistical Considerations:

Primary Objective

To evaluate the **Primary End Point,** the 3 year progression-free survival (PFS), defined as time from the time of study entry of the "watch and wait" or newly diagnosed NHL or CLL until relapse, progression, starting new therapies or death from any cause. Response will be determined by the principal investigator or the lead site investigators. The 3 year PFS of the low dose and high dose groups will each be compared to a historical fixed expected 3-year PFS of 45%.

Secondary Objectives

To evaluate changes in the levels of serum vitamin D levels during therapy with daily oral Vitamin D supplementation.

To evaluate the **Secondary End Point,** the overall survival (OS), defined as defined as time of study entry of "watch and wait" or newly diagnosed NHL or CLL until death from any cause. For subjects who are still alive at the time of the study analysis at 3 years or are lost to follow-up, survival will be censored at the last recorded date that the subject was known to be alive.

Study Endpoints

The **primary end point** is 3 year progression-free survival (PFS), defined as time of study entry of "watch and wait" or diagnosed NHL or CLL until relapse, progression, starting new therapies or death from any cause. Response will be determined by the principal investigator or the lead site investigators.

The **secondary end point** is 3 year overall survival (OS), defined as defined as time of study entry of "watch and wait" or newly diagnosed NHL or CLL administered on trial until death from any cause.

10.1 Patient Accrual

Subjects found to have low levels of serum Vitamin D <30 ng/ml at time of enrollment will be randomized on a 1:1 basis to receive vitamin D 5000 IU daily (Higher Dose Cohort) or vitamin D 1000 IU daily (Lower Dose Cohort) stratified by disease group aggressive NHL (fast-growing tumors) or indolent NHL/CLL (slow-growing tumors).

The sample size calculations are based on the primary endpoint of 3-year PFS. The expected PFS for patients with low levels of serum Vitamin D is 45%.[44] The 3 year PFS of the low dose and high dose groups will each be compared to a historical fixed expected 3-year PFS of 45%.[44] The sample size calculations are based on a single arm survival calculation based on an assumption of exponentially distributed PFS times using a 3-year PFS of 60% for each of the randomized arms (low dose or high dose). Therefore, the sample size calcuations are based on detecting a 15% difference in 3-year PFS for each randomized arm (low dose or high dose) vs.

a historical fixed expected PFS of 45%. Since such single arm studies are typically conducted as a one-sided test, we use alpha =0.025, however, no other adjustments will be made for multiplicity. Sample size calculations were conducted using the SWOG statistical calculator found at https://www.swogstat.org/stat/public/one_survival.htm.

Using a one sided test with accrual time of 2 years, follow-up time of 3 years, alpha=0.025, a null PFS of 45% and an alternative PFS of 60% a total of 230eligible patients will be enrolled in the normal serum Vitamin D group based on current accrual rate and until 70 eligible patients in each randomized arm (low or high dose) to provide 80% power. These results assume that two sequential tests are made (1 interim analysis and the final analysis) using the O'Brien-Fleming spending function to determine the test boundaries. Our final enrollment is projected to be 370 patients expecting a ~10% loss to follow-up/inevaluability rate.

10.2 Statistical Methods

10.2.1 Intention-to-Treat

The intention-to-treat (ITT) population will include all subjects who were randomized to study treatment in the randomized part of the study. In analyses based on the ITT population, subjects will be assigned to the treatment group they were randomized to. Subjects in the non-randomized group will be analyzed in the "Normal Level" group.

10.2.2 General Considerations

All efficacy analyses will be performed using the ITT population. For this Pilot study, no adjustments for multiplicity will be carried out. All statistical tests will be performed using two-sided tests with a 0.025 level of significance unless otherwise specified.

Continuous variables will be summarized using descriptive statistics, i.e. number of subjects (N), mean, median, standard deviation, 25th percentile, 75th percentile, minimum and maximum. Categorical variables will be summarized using frequencies and percentages.

10.2.3 Analysis for the Primary Endpoint

The primary endpoint of 3-year PFS will be presented using Kaplan-Meier curves and will be presented for the normal serum Vitamin D control group and the low and high dose randomized groups. Each randomized group (low and high dose) will be compared to a historical fixed expected 3-year PFS of 45% using a one-sample logrank test following the method of Woolson (1981)[45].

10.2.4 Analysis for the Secondary Endpoint

The secondary endpoint of 3-year OS will be analyzed as described for the primary endpoint, using a historical fixed outcome of 80%. [45]

10.2.5 Safety

The incidence of adverse events (AEs) and serious adverse events (SAEs) will be described for the low dose and high dose groups and compared between groups using a Chi-square. The frequency of occurrence of overall toxicity, categorized by toxicity grades, will be described for the low dose and high dose groups and compared between groups using a Chi-square.

10.3 Evaluable Patient

Histologically confirmed disease.

No premature discontinuation before completion of vitamin D cycles for reasons other than disease progression, starting new therapies, death, or study drug related unacceptable toxicity**.**

10.4 Stopping Rules

10.4.1 Interim Analyses

One interim monitoring analysis for efficacy will be conducted after n=35 patients in each randomized arm (35 patients in the low dose group and 35 patients in the high dose group) have enrolled. Two separate tests will be conducted to compare 1- the PFS in the low dose arm to the fixed expected value of 45% and 2- the PFS in the high dose arm to the fixed expected value of 45%. We will use an O'Brien-Fleming-type spending function to assess whether the interim results are sufficient to conclude that vitamin D supplementation in either the low dose or high dose arm is effective in increasing the PFS to 60%. The monitoring boundary p-values associated with the 1 interim look using the O'Brien-Fleming spending function will be 0.001525 with the final analysis being done with p=0.024501. The type I error associated with this monitoring plan is approximately 0.025. If $\geq$10% of patients in either Vitamin D arm has severe adverse events that are felt to be directly related to the Vitamin D supplement, the study will be stopped.

Section 11.0 Records to Be Kept:

11.1 Quality Assurance

Complete records must be maintained in a research chart on each patient treated on the protocol. These records should include primary documentation (e.g., lab report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.) which confirm that:

- The patient met the eligibility criteria.
- Signed informed consent was obtained prior to treatment.
- Treatment was given according to protocol (dated notes about doses given and reasons for any dose modifications).
- Toxicity was assessed according to protocol (laboratory report slips, etc.).
- Response was assessed according to protocol (x-ray, scan, lab reports, dated notes on measurements & clinical assessment, as appropriate).

11.2 Electronic Data Capturing (EDC) System

Data will be stored electronically for this study in the Advarra EDC system contained on the company's secure server. Data forms will not differ from the paper versions with the exception of an electronic format containing the UNMC Fred & Pamela Buffett Cancer Center and Advarra logo.

Advarra EDC provides for remote data collection that meets FDA 21 CFR Part 11 requirements as well as HIPAA and other regulatory requirements designed to enhance data security and protect patient confidentiality. Authorized users log into Advarra through a secure connection and must provide a valid username, password, and database ID. This data may be made available to the public at large.

Section 12.0 Patient Consent Form Statement:

12.1 Human Subjects Research Protection Training

All personnel involved in this research project will have completed the OHRP-approved computer based training course on the Protection of Human Research Subjects. All clinical and correlative research included in this application will have approval by the institutional review board.

12.2 Study Population

Subjects are from all socio-economic groups and will be entered into the study without bias with respect to gender or race. Attempts will be made to recruit minorities. No vulnerable subjects will be included in the study.

12.3 Recruitment and Informed Consent

Subjects with an initial diagnosis of cancer seen and evaluated at IRB approved sites will be available for recruitment. These subjects will be informed of the nature of this study, and will be asked to participate on a voluntary basis after informing them of the possible risks and benefits of the study. A number of public registries may be accessible to health care providers and prospective subjects as listed below.

National Library of Medicine – NCT02553447; http://clinicaltrials.gov ()

National Cancer Institute – NCI-2015-01502; http://www.cancer.gov ()

12.4 Subject Competency

Subjects will be eligible to participate in the study only if they are competent to give informed consent. A subject that the investigator judges to be incompetent will not be enrolled.

12.5 Process of Informed Consent

If the patient chooses to be participate in this study, informed consent will be obtained by the investigators. The study and procedures involved, including the risks, will be explained in detail

to each subject. It will be clearly explained to the subject that this is a research study and that participation is entirely on a voluntary basis. Subjects will be given the option to discuss the study with a family member, friend, counselor or, another physician. The participating investigators will be available to discuss the study with them.

12.6 Subject/Representative Comprehension

When the process of informed consent is completed, the subject will be asked to state in his/her own words, the purpose of the study, the procedures that will be carried out, potential risks, potential benefits to the subject, the alternatives and the right to withdraw from the study. If there is any indication that a given subject's comprehension is anything less than accurate, the points of confusion will be discussed and clarified.

12.7 Information Purposely Withheld

The results of the tests done solely for research purposes will not be disclosed to the subject. No other information will be purposely withheld from the subject.

12.8 Potential Benefits of the Proposed Research to the Subjects

Normal Vitamin D levels are associated with improved bone health and possibly improved progression-free and overall survival in patients with NHL and CLL.

12.9 Potential Benefits to Society.

Information obtained from this study may help other patients by contributing to the knowledge of the biology of cancers, and to understand the potential clinical benefit of this regimen.

12.10 Potential Risks

A rare but potential harm of treatment with oral vitamin D is toxicity, which may lead to hypercalcemia, hyperphosphatemia, suppressed parathyroid hormone, and hypercalciuria. However, the 25-(OH) D level associated with toxicity (often defined as >500 nmol/L [>200 ng/mL]) is well above the level considered to be sufficient. Treatment with vitamin D plus calcium may also be associated with increased risk for kidney stones; vitamin D alone does not seem to increase this risk. It is believed the treatment option outlined in the study will not pose significant additional risks compared to conventional treatment.

12.11 Therapeutic Alternatives

If subjects choose not to participate in this study, they may elect to receive standard therapy as per their primary oncologist, which may include no evaluation of vitamin level in the oncology setting and/or treatment recommendations that may or may not be similar to treatment as described in this protocol per individual practitioner.

12.12 Risk/Benefit Relationship

The risks involved with the use of Vitamin D supplementation at standard doses are minimal. The potential benefits might be improved bone health and improved PFS and OS.

Section 13.0 References

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Section 14.0 Data Forms

Please refer to the Study Site Manual for the forms.

Appendix A: Eligibility checklist

Date Completed:	**IRB# 556-15** **Title**: A Pilot Study of Vitamin D Replacement in Patients with Non-Hodgkin's Lymphoma or Chronic Lymphocytic Leukemia with Low Vitamin D Levels **PI:** Julie Vose, MD	Checklist Version # 6.X Dated: XXMmmYYYY		
Site:				
Subject ID#:	Subject Initials:	Waiver #:		
Inclusion Criteria: Response should be YES		Yes	No	NA
1. Histologically confirmed newly diagnosed or previously untreated Non-Hodgkin's Lymphoma or CLL (Subjects may be under no treatment "wait and watch" OR have received two cycles of chemotherapy or localized radiation therapy before informed consent.)		☐	☐	☐
2. 18 years of age or older (19 years or older in Nebraska).		☐	☐	☐
3. Serum 25-hydroxyvitamin D [25(OH) D] drawn at time of enrollment (NOTE: Subjects currently taking < 1000 IU/day Vitamin D supplements are eligible for screening.)		☐	☐	☐
		Record 25(OH) D:		
4. Simultaneous participation in other therapeutic clinical trials will be allowed.		☐	☐	☐
5. Subject must be aware of the neoplastic nature of his/her disease and willingly provide written, informed consent after being informed of the procedure to be followed, the nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts.		☐	☐	☐
Exclusion Criteria: Response should be NO		Yes	No	NA
1. History of uncontrollable allergic reactions to vitamin D.		☐	☐	☐
2. Currently taking vitamin D supplement ≥ 1000 IU/day.		☐	☐	☐
3. History of Paget's disease.		☐	☐	☐
4. Hypercalcemia		☐	☐	☐
5. Any other clinically significant medical disease or condition, laboratory abnormality, or psychiatric illness that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.		☐	☐	☐
6. Inability to cooperate with the requirements of the protocol.		☐	☐	☐
All questions regarding eligibility for potential subjects should be directed to the UNMC IIT Office at IITOffice@unmc.edu.				

Eligibility:	☐ Subject satisfies all criteria. ☐ Subject not formally eligible, but admitted to this study because (state reason):
ELIGIBILITY reviewed and confirmed. (Reviewer - Study Nurse Coordinator(s) or PI designee) Reviewer Signature _____ Date_____ Printed Name of Reviewer: _____	

Appendix B: NCI Common Toxicity Criteria Version 4.0 (CTCAE)

Toxicity will be scored using NCI CTC Version 4.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.0 can be downloaded from the CTEP homepage: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

All appropriate treatment areas have access to a copy of the CTC Version 4.0.

Minor editorial updates have been made to CTCAE v4.0, which are represented in v4.03. These edits do not change the meaning of v4.0 content and all previous versions (CTCAE v4.0, v4.01, v4.02) are still valid and referred to as CTCAE v4.0. Version 4.03 includes clarifications for a select few grading scales and adverse event term definitions. Most of the revisions are associated with grading scales that include a quantitative component. A list of changes is located at http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

An updated version (4.03) is now in use as of June 14, 2010.

Appendix C: FDA MEDWATCH form

Available on-line at
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

Appendix D: Oral, Sublingual, and/or Buccal Route

Medication Adherence Standard Procedure - V 1.0 11-25-2013

PURPOSE

To provide a means of ensuring oral, sublingual and/or buccal routes of medication adherence to patients while participating in a clinical trial.

1. A physician's order will be completed by study patients or representative for oral, sublingual and/or buccal administration per IRB approved protocol.
2. To ensure the consistent and safe administration of medications not given under the direct supervision of study staff (at home), there will be a "Medication Information Sheet" and a calendar to document times of drug administration.
3. To record medication adherence Study staff will document results of medication reconciliation and or medication return in the patient's chart.
4. Maintain documentation of medications returned or sent to investigational pharmacy for destruction (if applicable).

PROCEDURE

1. Protocol specific information regarding the individual medication(s) should be listed on the form "Medication Information Sheet" and given to the patient at the start of the study and throughout treatment if necessary to help ensure adherence.
2. Name, dose and route of each medication should be listed under 'How to take your Medication' on the "Medication Information Sheet".
3. Patients will be given a monthly "Medication Calendar". The calendar will have a place for the patient to record the time that the medication(s) were taken.
4. The research nurse will review the patient's "Medication Calendar" for adherence to the study regimen for oral medication administration. Adherence will be noted in the patient's chart. For UNMC subjects, medication reconciliation will be done. If there is medication to be returned/destroyed, it will be sent to the Nebraska Medical Center Investigational Pharmacist for return/destruction in accordance to the Nebraska Medical Center Destruction of Investigational product, Policy #4.860.

Medication Information Sheet

Subject Initials**:** Study ID #:

Title: A Pilot Study of Vitamin D Replacement in Patients with Non-Hodgkin's Lymphoma or Chronic Lymphocytic Leukemia with Low Vitamin D Levels

IRB# **556-15** Date**:**

Medication: Vitamin D is a pill.

How to take your medication**:** ***Enter information regarding Vitamin D dosing*** This should be taken by mouth once a day until your treating physician tells you to stop (this could be up to 3 years or 1095 days). Follow your Medication Calendar that is provided to you by the research nurse.

Things to know about your medication:

1. IF you are currently taking Vitamin D supplements/medication at the time of screening, you will need to discontinue the use of your home supply of Vitamin D and use only the Vitamin D medication/dosing and supply instructed by the study.)
2. You should take your medication at the same time each day.
3. If you miss a dose of your medication, it should be taken as soon as possible on the same day.
4. If it is missed for the entire day, it should not be made up.
5. If a dose is missed, make sure to mark it on your Medication Calendar.

NOTE: After year 3 (1095 days), the investigator will discuss continuation of Vitamin D supplementation recommendations with you. The supply of any recommendations for continued Vitamin D will be at your cost.

Your research nurse is: _____

Contact information: phone _____ pager _

*****We will re-check your Vitamin D level in *insert time point for Vitamin D level check.* Call if you need anything in the meantime.**

After hours, nights, weekends and holidays please call 402-559-5600 and ask for the Oncologist on call.

UNMC Subjects only: * PLEASE CALL YOUR RESEARCH NURSE ABOVE TO LET THEM KNOW THAT YOU RECEIVED YOUR VITAMIN D SUPPLEMENT. *****

Vitamin D Administration Diary → Your prescribed dose is **Enter Dose.**

Name:

MR:

- If you missed a dose please add the comment "missed dose" on the corresponding date.
- If your Study Doctor has asked you to change your dose, please add the new dosage on the corresponding date.
- All completed diaries must be returned to the Study Coordinators at the study site.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Date:__________ **Time of dose:** **__________AM / PM**	**Date:__________** **Time of dose:** **__________AM / PM**	**Date:__________** **Time of dose:** **__________AM / PM**	**Date:__________** **Time of dose:** **__________AM / PM**	**Date:__________** **Time of dose:** **__________AM / PM**	**Date:__________** **Time of dose:** **__________AM / PM**	**Date:__________** **Time of dose:** **__________AM / PM**
Date:__________ **Time of dose:** **__________AM / PM**	**Date:__________** **Time of dose:** **__________AM / PM**	**Date:__________** **Time of dose:** **__________AM / PM**	**Date:__________** **Time of dose:** **__________AM / PM**	**Date:__________** **Time of dose:** **__________AM / PM**	**Date:__________** **Time of dose:** **__________AM / PM**	**Date:__________** **Time of dose:** **__________AM / PM**
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