# STURDY

## **S**tudy **T**o **U**nderstand Fall **R**eduction and Vitamin **D** in **Y**ou

# PROTOCOL

# Version 2.2

# May 5, 2017

# NCT02166333

**SUMMARY OF PROTOCOL VERSIONS AND CHANGES**

Version 1.0
- Original version submitted to DSMB for meeting on December 1, 2014

Version 1.1
- Switched the 3 month post-randomization follow-up to in-person and the 6 month follow-up to a telephone call
- Changed visit codes to match those that will be used for data collection
- For alert values table, clarified that participants who discontinue study pills will still be followed
- Removed row of the alert value table relating to moderately high vitamin D levels & changed the high vitamin D row to be ≥150 ng/ml
- Replaced both calcium safety algorithm figures with updated versions based on University of Maryland's reference ranges and the DSMB recommendations
- Removed mention of the comprehensive metabolic panel (CMP) testing, so that the only laboratory tests done in real-time are serum calcium and vitamin D levels.

Version 1.11
- Made minor corrections.
- Added additional reference related to recommended upper limit of vitamin D intake

Version 1.12
- Replaced the term 'drug' with 'pills'
- Submitted to DSMB and approved
- Original version submitted to IRB

Version 2.0
- Expanded serum vitamin D [25(OH)D] eligible range from 10-25 ng/ml to ≥10 and <30 ng/ml
- Modified supplement (vitamin D and calcium) eligibility to allow for staff judgment, recognizing that many participants take supplements sporadically, vary their dosage accidentally, or cannot describe their intake precisely, which makes it difficult to calculate an accurate average daily dose
- Added exclusion for participants using calcitriol
- Updated calcium eligibility in section 5 (study population and eligibility) to match what is covered in section 11 (safety)
- Clarified the exclusion criteria related to participant moving out of the area within 2 years to only exclude those whose compliance with the study protocol would be affected by such a move
- Clarified that uric acid, struvite, and cysteine stones are not exclusionary but stones made of calcium compounds are exclusionary; in absence of information on type of stone, stones are assumed to be made of calcium compounds
- Replaced the Block Vitamin D and Calcium screener with a vitamin D and calcium food frequency questionnaire
- Removed administration of the vitamin D and calcium food frequency questionnaire from F03
- In follow-up, replaced the three word recall and/or MMSE cognitive assessment with the Mini-Cog®
- Made minor corrections and clarifications

Version 2.1
- Added Appendix I describing the orthostatic hypotension ancillary study protocol

Version 2.2

- Removed mention of the 90-day window between SV and RZ
- Clarification of when participants could be asked to join the orthostatic hypotension ancillary study

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**LIST OF ABBREVIATIONS / GLOSSARY**

| | |
|---|---|
| 1,25(OH)2D | calcitriol |
| 25(OH)D | 25-hydroxyvitamin D |
| BMI | body mass index |
| BV | Baseline Visit |
| CVD | cardiovascular disease |
| D2 | ergocalciferol |
| D3 | cholecalciferol |
| DBP | diastolic blood pressure |
| DCC | Data Coordinating Center |
| DMS | data management system |
| DSMB | Data and Safety Monitoring Board |
| DQQs | data quality queries |
| F## | Follow-up telephone contact or in-person visit at ## months post-randomization |
| FV | Follow-up Visit |
| HIPAA | Health Insurance Portability and Accountability Act |
| HR | heart rate |
| IOM | Institute of Medicine |
| MMSE | Mini-Mental State Exam |
| NHANES | National Health and Nutrition Examination Survey |
| NIA | National Institute on Aging |
| OH | Orthostatic Hypotension |
| PCP | Primary care provider |
| PS | Pre-Screen contact |
| PTH | Parathyroid Hormone |
| RDA | recommended daily allowance |
| RZ | Randomization Visit |
| SPB | systolic blood pressure |
| SPPB | Short Physical Performance Battery |
| STURDY | Study To Understand Fall Reduction and Vitamin D in You |
| SV | Screening Visit |
| TC | Telephone Contact |
| TUG | Timed Up and Go |
| UVB | ultraviolet b |

# 1. ABSTRACT

The public health burden of falls in older persons is substantial. Several lines of evidence suggest that vitamin D supplements might reduce the risk of falls, potentially by 25% or more in persons with low serum 25-hydroxyvitamin D [25(OH)D] levels. However, existing evidence is inconsistent and insufficient to guide policy. The trial is a seamless two-stage, Bayesian response-adaptive, randomized dose-finding trial designed to select the best dose of vitamin D supplementation and to potentially confirm the efficacy of that dose for fall prevention and other related outcomes. Participants will be community-dwelling adults, aged 70+ (~40% black, ~60% women), with a baseline serum 25(OH)D level of ≥10 and <30 ng/ml, who are at high risk for falling.

In Stage 1 of the adaptive design, participants will be randomly assigned to one of four vitamin D3 (cholecalciferol) doses: 200 IU/d, 1000 IU/d, 2000 IU/d, or 4000 IU/d, with assignment probabilities that will vary as falls are reported. Participants will take their assigned pills for two years, or until the study ends, whichever comes first. This stage of the design will select the best dose of vitamin D for prevention of falls, or confirm the futility of distinguishing any differences among the doses for fall prevention. If a best dose is selected, subsequent participants will be randomized in Stage 2 of the trial into the comparison (200 IU/d) or best dose group, and all participants (Stage 1 and Stage 2) will continue to be followed to potentially confirm efficacy. We anticipate enrolling approximately 1,200 participants over the entire length of the project.

The primary outcome is time to first fall (or death) over two years of therapy. Next in importance is the outcome of gait speed from the Short Physical Performance Battery (SPPB). Other outcomes include fall rates, types of falls, SPPB score and its components, grip strength, frailty, 6-minute walk distance, and physical activity assessed by accelerometry. Falls will be ascertained from fall calendars completed daily by participants and from self-report by phone. In-person follow-up visits will occur at 3, 12, and 24 months, with telephone visits occurring at 1, 6, 9, 15, 18, and 21 months after randomization. Subgroups with potential for greater benefit from vitamin D supplementation are blacks, those with baseline 25(OH)D of 10-19 ng/ml, and those with objective evidence of low physical function.

# 2. SPECIFIC AIMS

Falls are preventable events, yet remain the leading cause of injuries and a major cause of hospitalizations in older adults. Several lines of evidence suggest that vitamin D supplementation might reduce the risk of falls. This trial is a seamless, two-stage, Bayesian response-adaptive, randomized dose-finding trial designed to select the best dose of vitamin D supplementation (Stage 1) and potentially confirm the efficacy of that dose for fall prevention (Stage 2). Participants will be community-dwelling adults, ages 70+ (~40% black, ~60% women), who are at increased risk for falling and who have a baseline serum 25-hydroxyvitamin D [25(OH)D] level of ≥10 and <30 ng/ml. Persons taking multivitamin and vitamin D supplements will be eligible if average daily supplement intake of vitamin D is judged by study staff to be consistent with the goal of ≤1000 IU/d, while concurrently meeting the eligibility criteria for serum 25(OH)D.

In Stage 1 of the adaptive design, participants will be randomly assigned to one of four vitamin D3 (cholecalciferol) doses: 200 IU/d, 1000 IU/d, 2000 IU/d, or 4000 IU/d. During Stage 1 and 2, half of participants will be assigned to the 200 IU/d comparison dose. The probabilities of assigning participants to one of the three (>200 IU/d) dose groups will vary monthly according to the calculated Bayesian probability of being the best dose for fall prevention using the cumulative fall rate experience.

If a best dose is selected, Stage 2 will commence. Newly enrolled participants will be randomized with equal probability into either the comparison (200 IU/d) or the best dose group. Prior participants randomized in Stage 1 to the comparator (200 IU/d) and best dose group will remain at their assigned doses, and participants in the other two dose groups will be seamlessly switched to the best dose.

We anticipate enrolling a maximum of 1,200 participants into the STURDY trial. Participants will take study pills for two years (across Stage 1 and Stage 2), or until the study ends, whichever comes first. Participants will be masked to their assigned doses during both Stages. In-person follow-up visits will occur at 3, 12, and 24 months post-randomization.

**Primary outcome:** Time to (a) first fall (defined as any fall, slip, or trip in which the participant loses his or her balance and lands on the floor or ground or at a lower level) or (b) death, whichever comes first. Deaths are expected to be rare compared to falls, but sensitivity analyses of falls and deaths will be done and presented with the primary outcome.

**Secondary outcome:** change in gait speed

## *Primary aims*

1. Use a Bayesian adaptive randomized clinical trial design to select the best of 4 doses of vitamin D supplements (200, 1000, 2000, or 4000 IU/d) for prevention of falls or to confirm the futility of distinguishing any differences among the doses for fall prevention (Stage 1).
2. If a best dose is selected, use a parallel group randomized clinical trial to obtain preliminary estimates of the efficacy of the best dose compared to the 200 IU/d dose for prevention of falls (Stage 2).

## *Other aims*

3. Estimate the effects of vitamin D supplements on the outcomes of:
    a. gait speed
    b. 25(OH)D blood level
    c. physical performance measures (e.g., grip strength and SPPB score)
    d. physical activity level based on accelerometry

    e. other fall outcomes (e.g., multiple falls and fall rates, indoor falls, outdoor falls, injurious falls, falls that result in fractures, and falls that prompt emergency medical care)
    f. other non-fall outcomes (e.g., blood pressure, orthostatic blood pressure, onset of frailty, health-related quality of life)
4. Estimate the shape of the dose-response relationship of vitamin D supplements with the risk of falls and other outcomes.
5. Estimate the shape of the dose-response relationship using other measures of vitamin D status with risk of falls and other outcomes:
    a. achieved 25(OH)D blood level at 3 months
    b. total dietary intake of vitamin D (food, usual supplements, and randomized dose)
6. Explore potential differences in outcomes by subgroups:
    a. key subgroups that may have increased benefit from vitamin D supplementation: blacks, those with baseline 25(OH)D of 10-19 ng/ml, and those with objective evidence of low physical function
    b. other subgrouping variables of interest: baseline supplement use, baseline vitamin D intake, gender, age, body mass index (BMI), medications, and frailty status
7. Explore the extent to which the relationship between vitamin D supplementation and falls is mediated by:
    a. physical activity levels based on accelerometry
    b. physical performance measures
8. Quantify safety concerns related to vitamin D supplementation by examining the frequency of hypercalcemia and acute nephrolithiasis.
9. Establish a well-characterized cohort of individuals at high risk of falls, with an associated biorepository, from which further research questions and creative ancillary studies can be conducted.

We hypothesize that a best dose of vitamin D (1000 IU/d, 2000 IU/d or 4000 IU/d) will be selected, and that this dose will reduce the risk of falls and will increase gait speed. We further hypothesize that there is an inverse relationship between vitamin D dose and risk of falls and a direct relationship between vitamin D dose and gait speed. If our trial identifies a best dose of vitamin D supplementation, it is possible that a subsequent trial may be necessary to confirm the efficacy of this dose with sufficient power, in which case our trial will provide valuable information related to the design of that trial, including fall rates and variability estimates. If a best dose is not identified, i.e. we confirm the futility of distinguishing any differences among the doses for fall prevention, our study will be a valuable and unique cohort study of individuals at high risk of falls. Irrespective of trial results, our study will have important clinical and public health implications – identifying an effective dose of vitamin D for fall prevention or documenting futility.

# 3. BACKGROUND

## *Falls*

Falls are potentially catastrophic events for older adults and a substantial burden to society, a burden that will only increase as the population ages. Each year, 1 in 3 older adults falls[1] which can cause injury, decreased function, nursing home admission, or mortality.[2-4] An analysis of intentional and unintentional injury by NCHS found that fall rates for those >55 years old increased since 2000 and dramatically increased for those >75 years old.[5] The cost of falls annually in the US is $23.3 billion, with the cost per individual fall being $3,476-$10,749 for an injurious fall and $26,483 per fall requiring hospitalization.[6] The annual rate of falls among seniors is commonly reported as 33% but might be as high as 48%.[2,7]

Risk factors for falls are multiple and interrelated. Non-modifiable risk factors include advanced age,[8] previous falls,[9] and cognitive impairment. Modifiable risk factors include environmental hazards,[10] psychoactive medications,[11-13] and uncorrected vision problems.[14] Slow gait speed is a predictor of falls,[8] as is poor balance, but there is evidence that this may be U-shaped with fast walkers more at risk for outdoor falls.[15] Fall rates in blacks and whites are similar, but the setting of falls differs by race.[7]

The above risk factors are well established, but the extent to which low vitamin D intake or blood levels predict fall risk is less well established. Observational studies suggest that those with lower serum 25(OH)D levels have reduced physical performance and a greater decline in physical function.[16,17] However, evidence from trials is inconsistent. A 2012 Cochrane review concluded that vitamin D supplementation has no beneficial effect for the general population of older adults or those with previous falls but might be beneficial in those with decreased vitamin D levels (relative risk reduction=30%) across the four trials that studied individuals with low vitamin D levels.[18] The most recent meta-analysis by Bolland and colleagues concluded that supplemental vitamin D did not prevent falls.[19] In contrast, a 2013 Workgroup of the American Geriatrics Society recommended a total intake of vitamin D of 4,000 IU/d for all older adults as a means to prevent falls and fractures.[20] This level of intake requires high dose vitamin D supplementation in most individuals.

## *Vitamin D*

Vitamin D has long been known to be vital to bone health.[21] More recent evidence suggests that vitamin D might increase muscle strength, as well as reduce the risk of cancer, infection, and CVD.[21]

**Sources and metabolism of vitamin D**

The major source of vitamin D is endogenous production via the action of the sun's ultraviolet b (UVB) light on 7-dehydrocholesterol precursors in the skin, converting them to D3 (cholecalciferol).[21,22] Exogenous D2 (ergocalciferol) and D3 can also be obtained from the diet as a supplement or from fortified foods. Few foods contain vitamin D, and those that do contain only small amounts. D2 and D3 undergo 25-hydroxylation in the liver to form 25(OH)D, the primary circulating form of vitamin D and the metabolite that best reflects stores of vitamin D (i.e., sufficiency or deficiency states). Binding of the active metabolite [1,25(OH)2D (calcitriol)] to the vitamin D receptor is responsible for all vitamin D's cellular processes.[21,22] The main circulating source of 1,25(OH)2D is from renal 1α-hydroxylation, but many other tissues also express 1α–hydroxylase where locally formed 1,25(OH)2D is thought to have a paracrine/autocrine function.[23] Given tight regulation by intact parathyroid hormone (PTH), levels of 1,25(OH)2D do not correlate well with 25(OH)D levels, and 1,25(OH)2D levels may remain in the normal range even in 25(OH)D deficiency. Thus, 25(OH)D is the preferred biomarker for evaluating vitamin D status.

An important issues relevant to the design of this trial is the distribution of blood levels of 25(OH)D among potential participants in the trial and the routine use of supplements, overall and by gender-racial

groups in our study population. We therefore analyzed data from NHANES (2005-6) to understand the distribution of serum 25(OH)D levels and the use of vitamin D supplement (or multivitamin), overall and by gender-race groups among U.S. adults, ages 70+. See Table 1. Notable findings are (1) overall, 49% of individuals take either a multivitamin or vitamin D [range: 30% in black women to 66% in white women], (2) 58% have a 25(OH)D level between 10 and 25 ng/ml [range: 57% in white men and women to 81% in black women], (3) 41% of supplement users and 63% of persons who do not take supplements have a 25(OH)D levels between 10 and 25 ng/ml. The prevalence of vitamin D use has likely increased. In view of these data, we will enroll those persons on supplements (≤1000 IU/d) as long as their serum 25(OH)D level is within range, and they agree not to change the dose of vitamin D and multivitamin supplements during the trial.

**Table 1: Levels of 25(OH)D and supplement use among persons 70+.**

| 25(OH)D level (ng/ml) | All | Black Men | Black Women | White Men | White Women | Supplement Users | Non-Supplement Users |
|---|---|---|---|---|---|---|---|
| < 10 | 5% | 24% | 15% | 3% | 3% | 1% | 5% |
| **10-19*** | 32% | 55% | 59% | 27% | 31% | 13% | 37% |
| **20-25*** | 26% | 13% | 22% | 30% | 26% | 28% | 26% |
| 26-29 | 17% | 5% | 0% | 18% | 18% | 25% | 15% |
| ≥ 30 | 21% | 4% | 4% | 23% | 22% | 33% | 17% |
| Supplement Use | 49% | 35% | 30% | 52% | 66% | 100% | 0% |

Source: NHANES 2005-6.
*Shaded rows (10-19 and 20-25 ng/ml) indicate eligibility range for STURDY.

**Optimal vitamin D levels and risk factors for deficiency**

Aging is associated with 25(OH)D deficiency because of decreased concentrations of precursors (7-dehydrocholesterol) in the skin.[21] Lower 25(OH)D levels among older individuals may also stem from reduced sunlight exposure as a result of reduced outdoor activity. For those living above 35 degrees latitude (i.e., the state of Maryland), little or no vitamin D can be produced from November to February.[21]

Blacks have lower mean 25(OH) D levels and are at higher risk of 25(OH)D deficiency than whites, but paradoxically have increased bone mass and lower fracture rates.[24] Melanin skin pigmentation absorbs UVB light reducing vitamin D synthesis, and thus race/ethnic groups with darker skin coloring living in the Northern hemisphere are at increased risk for 25(OH)D deficiency. Several explanations may account for this racial disparity, including increased cutaneous melanin content, lower dietary consumption of vitamin D-fortified foods,[25-27] and racial differences in vitamin D metabolism.[28,29] Recently, a paper by Powe and colleagues documented that even though blacks have lower levels of 25(OH)D than whites, black and whites appear to have similar levels of bioavailable vitamin D as a result of lower levels of vitamin D binding protein in blacks.[30]

The optimal vitamin D level is controversial. Many experts believe that an adequate serum 25(OH)D level should be ≥30 ng/ml,[31,32] a level associated with maximal PTH suppression and reduced fracture rates.[21] Other experts claim that a target of ≥30 ng/ml is premature,[33] and note that renal production of $1,25(OH)_2D$ is normal when the substrate 25(OH)D exceeds 15 ng/ml in the absence of kidney disease.[34] While many guidelines suggest repletion in the range of 10-29 ng/ml, there is tremendous uncertainty about the benefits of repleting vitamin D in the range of 20-29 ng/ml, and even debate about repletion in the range of 10-19 ng/ml.[33,34] There is substantial variation in PTH for 25(OH)D levels between 20-30

ng/ml, and plateaus of PTH have been noted with levels as low as 12 or up to 40 ng/ml.[34] At the other extreme, levels of 25(OH)D <10 ng/ml are uniformly considered severely deficient.

In 2011, an Institute of Medicine (IOM) Committee established that the recommended daily allowance (RDA) of vitamin D intake should be 600 IU/d for ages 1-70 years and 800 IU/d for individuals >70 years; an upper limit was set at 4000 IU/d.[35] RDAs were derived assuming minimal sunlight exposure and established at doses for bone effects. The IOM estimated that serum 25(OH)D levels >16 ng/ml and >20 ng/ml should meet the requirements for 50% and 97.5% of the US population, respectively.[35]

## *Effects of vitamin D supplements on serum levels, falls and physical function*

**Vitamin D dose response trials and serum levels**

Dose response studies, particularly those by Wood,[36] Forman,[37] and Gallagher[38,39] provide a basis for estimating the effects of vitamin D supplements on mean serum levels and % above thresholds, at least in adults with 25(OH)D <20 ng/ml (we could not find corresponding data for adults with 25(OH)D between 20-25 ng/ml). Wood reported the effects of placebo, 400 IU/d, and 1000 IU/d on 25(OH)D in women, ages 60-70, with baseline 25(OH)D of 13.5 ng/ml. The mean rise in 25(OH)D was ~0 ng/ml (from placebo), 13.2 ng/ml (from 400 IU/d), and 17.2 ng/ml (from 1000 IU/d). Forman tested 0, 1000, 2000 and 4000 IU/d for 3m in blacks and documented that median levels rose from 15.7 ng/ml at baseline to 29.7 ng/ml (1000 IU/d), 34.8 (2000 IU/d), and 45.9 ng/ml (4000 IU/d). These data are consistent with a curvilinear relationship, but neither study formally tested for deviation from linearity.

Gallagher reported the effects of 0, 400, 800, 1600, 3200, 4000 and 4800 IU/d over 12m separately in white and black older women with baseline 25(OH)D<20 ng/ml and formally tested for differences by race. The initial report in white women reported a curvilinear relationship. The subsequent report which compared blacks and whites documented a linear relationship and no significant race effect, at least when BMI was in their models. Mean rise in 25(OH)D per 1000 IU/d increment in dose was 5.2ng/ml in adults with BMI<30 and 4.1ng/ml in those with BMI>30. A dose of 800 IU/d was estimated to increase 25(OH)D to >20ng/ml in 97.5% of black women. Overall, these reports document a progressive dose response relationship of vitamin D with serum levels across the range of doses proposed in this trial (200-4000 IU/d), with no evidence of toxic levels even at the highest dose. In a subsequent report, Gallagher and colleagues documented that there was no relationship of vitamin D dose with hypercalcemia.[40]

**Effects of vitamin D supplements on falls and physical function**

At least 20 trials of vitamin D supplementation to prevent falls have been performed.[19] However, there is significant heterogeneity in outcomes, as well as substantial heterogeneity in study methods, including the quality of outcome ascertainment. The most noteworthy trials are:

- Pfeifer[41]: 800 IU/d of vitamin D with 1,200 of calcium, compared to calcium supplementation alone, significantly reduced the risk of falls by 27% over 12m in European seniors, with further benefit over 8 additional months after the vitamin D supplements were stopped.
- Bischoff-Ferrari[42]: 700 IU/d reduced the risk of falls in women by 46% but not in men (7%, NS).
- Sanders[43]: an annual dose of 500,000 IU increased risk of falls by 15% (p=0.03). The relevance of this trial is unclear, given the non-physiologic approach to vitamin D administration.
- Broe[44]: in the only available dose response trial (200-800 IU/d), the 800 IU/d dose reduced the risk of falls by 28%; however, this study was limited to nursing home residents.

Vitamin D may reduce the risk of falls in older adults through an improvement in skeletal muscle function.[45,46] Binding of the vitamin D receptor in muscle modulates transcription of genes which effect calcium and phosphate uptake and downstream impacts proliferation and differentiation of muscle cells.[45] Vitamin D doses of 800-1000 IU/d are associated with increased quadriceps strength, decreased body sway, and improvements on tests of physical performance.[41,47] Improvements in muscle strength, and

subsequent gait stability, may contribute to the association of vitamin D therapy with reduction in falls. Alternatively, if increased gait stability and muscle strength lead to increased physical activity, then the paradoxical findings of Sanders and colleagues[43] in which vitamin D increased the risk of falls might result from increased physical activity. Further, there are plausible differences in vitamin D efficacy by subgroups. Those with low 25(OH) D levels, blacks (because of their low 25(OH)D levels),[24] those with low physical activity[42] and older adults with low muscle strength and mobility[47] may benefit more from vitamin D supplementation than other subgroups.

**Vitamin D with or without calcium**

Prior clinical trials of vitamin D with fall outcomes have been heterogeneous in regards to whether vitamin D treatment was combined with calcium supplements or not. A meta-analysis of 25 trials found that vitamin D with calcium compared to calcium alone reduced falls by 16% but did not find a significant reduction in falls for studies that tested vitamin D alone vs. placebo, or vitamin D with or without calcium vs. placebo.[48] Furthermore, the authors of this meta-analysis highlighted that methodologic issues in analyzing data from the same trials gave differing results. There are also recent safety concerns regarding calcium supplements of potential cardiovascular risks,[49] as well as concerns for hypercalcuria/hypercalcemia.[40] A trial of vitamin D monotherapy would more appropriately be able to evaluate the independent efficacy of vitamin D for fall reduction without the confounding effect (benefit or harm) from concomitant calcium supplementation.

## *Significance*

For seniors, the consequences of falling can be devastating. From a societal perspective, the public health burden of falls is enormous with annual health care costs attributed to falls exceeding $20 billion. Available evidence suggests that supplemental vitamin D, a simple well-tolerated intervention, might be beneficial, reducing the risk of falls by 25% or more. Critical questions remain:

- What is the most effective dose of vitamin D to prevent falls? Is more vitamin D better? To date, most trials have tested doses within a constricted range, typically ≤1000 IU/d. Doses up to 5000 IU/d appear safe, but evidence from trials is sparse at this higher range, especially using daily pills, as opposed to intermittent high dose supplementation, which has been associated, paradoxically, with an increased risk of falls.
- What are the effects in key subgroups, particularly blacks? Despite ample documentation that blacks have lower levels than whites, there is virtually no evidence from outcome trials that supplemental vitamin D is beneficial in blacks.

Our trial is designed to address these evidence gaps and simultaneously expand our knowledge of the impact of vitamin D supplements/intake and 25(OH)D levels on gait speed, other dimensions of physical function, physical activity, and frailty.

# 4. DESIGN

## *Principal research objective*

To conduct a seamless, two-stage, Bayesian response-adaptive, randomized trial to select the best dose of vitamin D for the prevention of falls in community-dwelling adults, ages 70+, who are at increased risk of falling and who have a serum 25-hydroxyvitamin D (25(OH)D) level of ≥10 and <30 ng/ml. In Stage 1 of the trial, participants will be randomly assigned to one of four vitamin D3 (cholecalciferol) doses: 200 IU/d (comparator), 1000 IU/d, 2000 IU/d, or 4000 IU/d, with assignment probabilities that will vary as falls are reported and entered into the database. This design will select the best dose of vitamin D for prevention of falls, or confirm the futility of distinguishing any differences among the doses for fall prevention. If a best dose is selected, participants from Stage 1 of the trial in the comparator (200 IU/d) and best dose groups will remain at their assigned doses, and participants in the other two dose groups will be dose-adjusted to the best dose. Subsequent participants enrolled during Stage 2 of the trial will be randomized to either the comparator or best dose group. In both Stage 1 and 2, all participants will take study pills and be followed for outcomes for two years or until the end of the study, whichever comes first. Follow-up visits will occur at 3, 12, and 24 months post-randomization.

# 5. STUDY POPULATION AND ELIGIBILITY

The study population will consist of approximately 1,200 adults, ages 70 and older, who are at high risk for falling. To enhance the generalizability of this trial, we have few exclusion criteria. Eligibility will be determined over a series of contacts, including phone-based contacts and in-person visits. Table 2 lists eligibility criteria.

**Table 2: Eligibility Criteria.**

| **Inclusion Criteria** |
|---|
| ▪ Age 70 and older<br>▪ Non-institutionalized<br>▪ High risk for falling, defined by a 'yes' response to at least one of the following:<br>  ▪ Have you fallen and hurt yourself in the past year?<br>  ▪ Have you fallen 2 or more times in the past year?<br>  ▪ Are you afraid that you might fall because of balance or walking problems?<br>  ▪ Do you have difficulty maintaining your balance when bathing, dressing, or getting in and out of a chair?<br>  ▪ Do you use a cane, walker, or other device when walking inside or outside your home?<br>▪ Serum vitamin D [25(OH)D] level ≥10 and <30 ng/ml (≥25 and <75 nmol/L)<br>▪ Able to provide informed consent<br>▪ Able to walk (with or without assistive device)<br>▪ Willing to accept randomization to each vitamin D dose<br>▪ One of the following:<br>  ▪ No vitamin D supplementation at screening<br>  ▪ Average daily vitamin D supplementation judged by study staff as being consistent with the goal of ≤1000 IU/d at screening and willing to continue the dose unchanged throughout the trial<br>▪ One of the following:<br>  ▪ No calcium supplementation at screening<br>  ▪ Average daily calcium supplementation judged by study staff as being consistent with the goal of ≤1200 mg/d at screening and willing to continue the dose unchanged throughout the trial |
| **Exclusion Criteria** |
| ▪ Cognitive impairment, defined as Mini-Mental State Exam (MMSE) score <24<br>▪ Hypercalcemia, serum $Ca^{2+}$ ≥11.0 mg/dl or >10.5 mg/dl (confirmed)<br>▪ Hypocalcemia, serum $Ca^{2+}$ <8.5 mg/dl<br>▪ Kidney, ureteral, or bladder stones made of calcium compounds (≥2 in lifetime, or 1 in the last 2 years); in the absence of information on type of stone, stones will be assumed to be made of calcium compounds<br>▪ Planning to move out of area within 2 years, where plans would prevent compliance with the study protocol<br>▪ Disease or condition expected to cause death or to prevent compliance with the study protocol in the next 2 years<br>▪ Participation in another trial of vitamin D or falls, or any trial that might affect the risk of falls<br>▪ Lactose allergy (lactose intolerance is okay)<br>▪ Use of any form of oral or injected calcitriol (brand names: Rocaltrol®, Calcijex®, and Zemplar®; generic names: calcitriol, paricalcitol, doxycalcitriol, 22-oxacalcitriol) |

# 6. RECRUITMENT

**Field centers**

The trial will be conducted at two well-established field centers in Central Maryland, namely, the ProHealth clinical research unit in West Baltimore and the Comstock Center in Hagerstown, Maryland.

*The ProHealth Clinical Research Unit* is a dedicated research facility that has been the site for numerous NIH-sponsored trials, including the NIA-sponsored TONE trial. This participant-friendly 15,000 $ft^2$ off-campus, clinical research unit is located in the Woodlawn suburb of Baltimore and is convenient to participants from Baltimore City, Baltimore County, Anne Arundel County, and Howard County. The facility has 9 exam rooms and 2 phlebotomy stations and space for up to 50 staff. Available equipment includes five -70$^o$ freezers and refrigerated centrifuges.

*The George W. Comstock Center for Public Health Research and Prevention* is an off-campus dedicated research facility that has been the site for several major NIH-supported cohort studies and trials, including the NHLBI-sponsored ARIC study. The facility is centrally located within the county seat (Hagerstown) of Washington County and is convenient to local travel routes and interstates, and served by public transportation (bus). It is also convenient to residents of Frederick County. The Comstock Center is housed in a handicapped accessible stand-alone facility with ample free parking. The 9,500 $ft^2$ facility has 12+ examination rooms, phlebotomy stations, and blood processing rooms with several -70$^o$ freezers.

**Recruitment strategies**

Both field centers will implement a variety of strategies to achieve their recruitment targets, i.e. ~800 participants at ProHealth and ~400 participants at the Comstock Center. Our experience is that multiple strategies are typically required. Accordingly, we intend to implement the most promising strategies and implement secondary/backup strategies, if needed. A particularly promising recruitment source are senior centers and assisted living communities which provide the opportunity for on-site screening. Mass mailing of brochures to older persons also has considerable appeal. In addition, we will consider print stories and advertisements in local newspapers, screening events at fairs, distribution of brochures and flyers in public locations and health care facilities, and targeted mailings to persons who have sought medical care for falls. If necessary, we will apply for a HIPAA waiver.

**Recruitment of women and minorities**

Given the demographic characteristics of individuals residing in central Maryland, we anticipate that ~ 60% of participants will be women and ~40% will be African-American.

# 7. DATA COLLECTION AND MEASUREMENTS

## *Data collection contact schedule*

Eligibility, baseline, and follow-up data will be collected by phone, through mailings, and at in-person visits. In-person data collection visits will be primarily be conducted at the ProHealth Clinical Research Unit in Woodlawn, MD or the Comstock Center in Hagerstown, MD. However, we will also screen participants and potentially conduct visits at senior centers and other places where older persons congregate. In some situations and with participant consent, we will also collect data in other locations (e.g., the participant's home or work), when they cannot go to our clinical locations, often because of illness, immobility, moving out of the immediate area, or change in schedule. In general, we try to be as flexible as possible to meet the needs of our participants. For example, we might divide or bundle data collection across visits. See Table 3 for an overview of proposed data collection items by contact. Some items might be dropped based upon participant burden, scientific considerations, available resources, and the results of field testing. The primary data collection points for participant-level data are as follows:

***Pre-Screen Contact (PS)*** – A brief questionnaire will be administered by phone or in person to identify potentially eligible participants quickly and efficiently.

***Screening Visit (SV)*** – This in-person visit will include written informed consent for screening, questions about eligibility and demographics, cognitive screening, and blood collection to measure 25(OH)D and calcium levels to determine eligibility.

***Baseline Visit (BV)*** – After confirming eligibility, including 25(OH)D and calcium levels, participants will be asked to provide written informed consent for enrollment in the trial, complete questionnaires and physical assessments, and provide blood and urine for banking. Those who are interested and are eligible after the baseline visit will be asked to complete a run-in (RI) period of approximately 10 days or more, taking placebo pills and completing the fall calendar to demonstrate ability to adhere to study protocols.

***Randomization (RZ)*** - After confirming all eligibility criteria, and re-affirming consent orally, treatment will be assigned using an internet-based system. Participants will be given study pills and instructions on taking pills, keeping the fall calendar, and reporting falls and safety issues.

***Telephone Contacts (TC) –*** Routinely scheduled telephone calls will be conducted to achieve regular contact every 3 months with participants. The purpose of these calls is to maintain rapport and to promote adherence with pill taking and completion of the fall calendar. These contacts will occur at 1, 6, 9, 15, 18, and 21 months post-randomization. In addition, we will contact participants by phone when they report a fall.

***Follow-Up Visits (FV)*** – Persons will have in-person visits at 3, 12, and 24 months after randomization, which will include questionnaires, physical assessments, blood draws for testing and banking, and urine collection for banking.

**Table 3: Data Collection Schedule.**

| | Pre-Randomization | | | RZ | Year 1 | | | | | Year 2 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Months from randomization | -2+ | -2+ | -1 | 0 | 1 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 |
| [C]linic, [T]elephone, or [E]ither | E | C | C | C | T | C | T | T | C | T | T | T | C |
| Visit | PS | SV[+] | BV[+] | RZ | F01 | F03 | F06 | F09 | F12 | F15 | F18 | F21 | F24 |
| Consent | O | W | W | O | . | . | . | . | . | . | . | . | . |
| Prescreen questionnaire | X | . | . | . | . | . | . | . | . | . | . | . | . |
| Registration (demographics, eligibility) | . | X | . | . | . | . | . | . | . | . | . | . | . |
| Participant location and proxy info | . | X | U | U | U | U | U | U | U | U | U | U | U |
| SSN (for W4, CMS, SSDI) | . | . | X | . | . | . | . | . | . | . | . | . | . |
| Medical records release | . | . | X | . | . | . | . | . | X | . | . | . | X |
| Blood draw[*] | . | X | X | . | . | X | . | . | X | . | . | . | X |
| Urine collection (stored) | . | . | X | . | . | X | . | . | X | . | . | . | X |
| Medical history including AE history | . | VS | B | VS | S | L | S | S | L | S | S | S | L |
| Cognitive testing[$] | . | X | . | . | . | X | . | . | X | . | . | . | X |
| Physical measurements[#] | . | . | X | . | . | X | . | . | X | . | . | . | X |
| SPPB | . | . | X | . | . | X | . | . | X | . | . | . | X |
| Timed Up and Go (TUG) Test | . | . | X | . | . | X | . | . | X | . | . | . | X |
| Accelerometry | . | . | X | . | . | X | . | . | X | . | . | . | X |
| 6-minute walk | . | . | X | . | . | X | . | . | X | . | . | . | X |
| Grip strength | . | . | X | . | . | X | . | . | X | . | . | . | X |
| Physical function questionnaire | . | . | X | . | . | X | . | . | X | . | . | . | X |
| Physical activity questionnaire | . | . | X | . | . | X | . | . | X | . | . | . | X |
| Vitamin D and calcium food frequency questionnaire | . | . | X | . | . | . | . | . | . | . | . | . | . |
| SF-12 | . | . | X | . | . | X | . | . | . | . | . | . | . |
| Adherence reminders | . | . | X | X | X | X | X | X | X | X | X | X | X |
| Fall calendar | . | . | RI[^] | X | X | X | X | X | X | X | X | X | X |
| Pill dispensing/return | . | . | RI[^] | X | . | X | M | M | X | M | M | M | X |

Abbreviations: O=oral; W=written; U=update; B=baseline; VS=very short; S=short; L=long; RI=run-in; M=mail; AE=adverse event

[+]physical assessments and questionnaires can be completed at either SV or BV, as long as they are completed prior to RZ

[*]real-time 25(OH)D and calcium; stored blood

[$]MMSE at screening visit; Mini-Cog® at FVs

[#]height (baseline only), weight, and blood pressure, including orthostatic BP

^at the end of the baseline visit, participants will be given placebo pills and instructed to take one daily and complete the pill/fall calendar for a period of approx. 10 days to 1 month, which they will return at the randomization visit

## *Measurements*

The following sections describe the specific measurements to be collected from participants, in accordance with the above Data Collection Schedule.

**For the primary outcome:**

*Falls ascertainment*. In this trial, a fall is defined as any fall, slip, or trip in which the participant loses his or her balance and lands on the floor or ground or at a lower level. Starting with the BV and continuing through F24 or the end of the study, whichever comes first, participants will be asked to keep a falls calendar, the gold standard.[18,50] The calendar is similar to traditional calendars with monthly pages. The field centers will provide each participant with a blank falls calendar and a postage-paid envelope for each month that the participant is in the study, with instructions to mail back the completed calendar just after each month ends. Participants will be instructed to mark at the end of each day (or in the morning of each subsequent day) whether they fell, with instructions to notify the field center after any fall (after seeking medical attention, if needed).

A standardized follow-up interview will be administered to obtain details about when the fall occurred, the circumstances of the fall and any resulting injuries and treatment. If a fall is marked on a received calendar and the fall has not previously been reported to the center, the participant will be called by an interviewer who will administer the fall follow-up interview. If a calendar is not received by mail as expected, an interviewer will call to inquire about their status and remind the participant to mail the calendar. If a previously unreported fall is reported during a missing calendar inquiry call or during one of the routine trimonthly TCs, the caller will administer the fall follow-up interview.

**For the secondary outcome:**

*Short Physical Performance Battery (SPPB), including gait speed*. We will assess functional limitations using the SPPB, an objective assessment developed at the NIA. The SPPB includes timed tests for usual gait speed, balance, and the ability to rise from a chair. A usual-paced 4-meter walk is timed to assess gait speed. For balance, the participants are asked to maintain their feet in side-by-side, semi-tandem, and tandem positions for 10 seconds each. Finally, participants are asked to stand up and sit down five times as quickly as possible. Each test is scored from 0 to 4 using cut points from a large population-based study. The final SPPB score is calculated as the sum of the three tests with a range between 0 and 12, with higher scores reflecting better physical performance. Each component, including gait speed, will be outcomes of the trial.

**Other data collected:**

*Prescreen questionnaire*. A brief pre-screen questionnaire to assess basic eligibility will be administered by phone or in-person.

*Medical history*. Prior to randomization (at SV or BV), we will collect medical history, including fall history and fall risk factors, general medical history, and medication and supplement use. At each subsequent contact (including RZ, TCs, and FVs), a medical history and events update will be administered.

*Participant location and proxy info*. Detailed contact information for participant and proxy, if applicable, will be obtained at SV and reconfirmed or updated at each study contact (FVs and TCs).

*Medical records release*. Signed medical record release form will be obtained at BV and updated at each visit. Additionally, SSN will be collected at BV.

*Specimen collection*. Non-fasting blood will be drawn at SV, BV, and each FV. At SV and each FV, one serum aliquot will be shipped to the University of Maryland Core Laboratory for a) calcium and b) vitamin D levels (see below). At SV, additional serum aliquots will be stored. At BV and each FV, serum, plasma, whole blood, and a spot urine will be collected and stored in aliquots. At BV, blood will

also be collected for DNA (buffy coat). All specimens will be stored at -70°C. Potential assays, supported by ancillary studies, include PTH, FGF-23, inflammatory markers, and markers of kidney function. Of substantial interest are assays of vitamin D binding protein that will allow us to estimate bioavailable 25(OH)D.

*Vitamin D assays*. Field centers will ship or deliver the frozen serum aliquots designated for vitamin D and calcium eligibility or safety assay on a weekly basis. The Lab will analyze batches weekly. Serum 25(OH)D2, 25(OH)D3, and C-3 epimers will be measured using HPLC/tandem mass spectrometry. Mass spectrometry is considered the "gold standard" for the 25(OH)D assay. Calibration will be confirmed with the National Institute of Standards and Technology's (NIST) SRM 2972 and SRM 972a. Total imprecision CVs for 25(OH)D3 and 25(OH)D2 are 12% for level of 5 ng/ml and 8% at levels of 10 ng/mL or greater. A lower limit of detection for both analytes is 2 ng/ml.

*Physical measurements.* Height will be obtained at BV using a stadiometer. Weight will be obtained at BV and each FV using a calibrated scale. Sitting and standing BP will be obtained by trained certified observers using the OMRON 907 device which records BP using an oscillometric technique.[51]

*Frailty components*. We will assess frailty and frailty risk using procedures developed at Hopkins.[52] Five frailty components will be assessed: 1) gait speed, 2) grip strength, 3) low physical activity, 4) feelings of fatigue or exhaustion, and 5) unintentional weight loss. *Gait speed* will be measured as part of the SPPB and will consist of the time in seconds it takes the participant to walk 4 meters at their usual pace. *Grip strength* will be assessed for each hand in kilograms of force using a hand dynamometer. *Low activity* will be assessed using questions modified from the Minnesota Leisure Time Activities Questionnaire. *Fatigue or exhaustion* will be measured using four questions inquiring about feeling tired, weak, needing to exert unusual effort, or inability to initiate activities. *Unintentional weight loss* will be determined at baseline by asking participants what their weight was a year previously and how their weight has changed in the past year. Those reporting that they lost weight are asked if the weight loss was intentional. During follow-up, actual weight change from baseline will be assessed starting with the 12-month assessment (F12). All participants are asked if they have lost any weight intentionally since the prior visit. If a participant surpasses pre-determined thresholds on ≥3 of the 5 components or phenotypic criteria, then that participant is considered to be frail. A pre-frail stage is present when thresholds are surpassed in 1 or 2 components.

*6-minute walk*. Cardiorespiratory fitness and endurance walking ability will be assessed using the 6-minute walk test, a self-paced endurance walking test and a validated measure of cardiorespiratory fitness in older adults. The test will be performed on a 10-meter course in a corridor marked by cones at both ends. A trained technician will administer the test using a stopwatch. Participant instructions are to "cover as much ground as possible over 6 minutes at a pace you can sustain for the 6 minutes." Standardized encouragement will be given after each minute, along with the number of minutes remaining. A tally will be made for each lap completed. Total distance will be recorded at the end of 6 minutes.

*Timed Up and Go (TUG) test.* The TUG test is used often used in the clinical settings to determine older adults who are at high risk for falling. The test instructs participants who are sitting in a standard arm chair to stand up from the chair, walk at their normal pace to a line 3 meters away, turn, walk back to the chair at their normal pace, and sit down again.

*Accelerometry*. Free-living physical activity will be assessed using the Actigraph Link activity monitor positioned on the non-dominant wrist. Accelerometry counts will be measured at a sampling frequency of 80 hertz for 7 days in the free-living environment. Participants will be asked to wear the monitor at all times. At the end of the 7-day period, monitors will be returned to the research staff via express mail. Data will be downloaded using commercial software (Actilife) to derive activity counts/min and raw acceleration data (g's) will be stored for future analyses.

*Physical function*. Structured interview questions will be used to collect information on whether participants have difficulty or need assistance from others to perform instrumental (e.g., shopping, preparing meals, housework, managing medications, transportation) and basic (e.g., using the toilet, bathing, dressing, eating) activities of daily living.

*Vitamin D and calcium intake*. We recognize the limitations of available tools to measure vitamin D sources (i.e., diet, supplements, and sunlight). We will assess vitamin D and calcium intake in two ways: 1) Participants will be asked to bring all medications, including supplements, to each in-person visit. Medications and supplements containing vitamin D or calcium will be recorded, along with amount taken and frequency, so that we can estimate average daily intake. 2) At BV, each participant will complete a vitamin D and calcium food frequency questionnaire. There is no validated questionnaire that assesses sunlight.[53]

*Cognitive testing*. The Mini-Mental State Exam (MMSE)[54] is a commonly used 30-item screening tool for assessing general cognitive functioning and screening for possible dementia. Scores range from 0 to 30, with lower scores indicating greater cognitive impairment. The MMSE will be administered pre-randomization (SV or BV), and screenees who score below 24 on the MMSE will be excluded from participation in the trial. The Mini-Cog®[55] will be administered at each FV.

*SF-12*. Health-related quality of life and general self-rated health status (excellent, very good, good, fair, poor) will be assessed using the 12-item short form of the SF-36.[56] The SF-12 is widely used in clinical and epidemiological research and provides summary measures of physical and mental health functioning.

*Adherence*. Study staff will remind participants about the importance of pill adherence during each TC and FV. Various tools will be used to promote adherence, e.g. pill organizers, calendars, and phone call reminders, with engagement of care providers when appropriate. Pills will be distributed in person or by mail every 3 months.

# 8. QUALITY ASSURANCE AND QUALITY CONTROL

The investigative teams at the DCC and two field centers understand the critical importance of collecting complete, high-quality data and developing procedures to accomplish this important objective. Core activities include:

- Standardization - maintaining common study documents (protocol, MOP, case report forms) with special efforts to minimize version control issues.
- Training – developing training procedures led by experienced investigators and senior staff, developing and implementing certification procedures and performance metrics, and conducting annual training.
- Robust data systems – implementing web-based data entry system with duplicate data entry; using off-site data storage with automated back-up systems; programming data queries to check logic and consistency of data between forms and over time; implementing replicate programing for major papers.
- Site visits – conducting site visits has an important role in promoting best practices, identifying operational problems not evident in trial reports, and maintaining a culture that promotes high quality.
- Performance monitoring with feedback – tracking enrollment and follow-up (observed/expected, overall and by key subgroups); monitoring missed visits, data completeness, protocol deviations, and data entry errors; distributing feedback through routine trial monitoring reports for the field centers, Steering Committee and DSMB. These reports, together with constructive feedback, have an important role in identifying and resolving issues expeditiously.

# 9. RANDOMIZATION AND MASKING

## *Randomization*

The Data Coordinating Center (DCC) will generate random treatment assignments using a Bayesian response-adaptive randomization scheme. Treatments will be assigned using an online program accessible to the clinical centers through the data system. After the entry of specified pre-randomization data, and confirmation of eligibility, each enrolled participant's assignment will released. The clinical center will be directed to issue the masked vitamin D bottle as indicated. The data system will also check for and prevent duplicate assignments (same participant randomized more than once). Documentation of all these processes will be retained at the DCC and shall be accessible only to authorized personnel.

The procedures related to randomization of participants at the clinical centers will be as follows:

- Eligibility and baseline data will be collected and entered into the database at the clinical centers
- The data system will confirm eligibility and then issue treatment assignment as described above
- The data system will automatically store the date and time of assignment, the identity of the clinical center staff person making the assignment, the participant's ID, and the treatment assignment identifier to be issued
- Randomization materials, including a visit schedule and allowable time windows for visits, will be generated for the clinical center

## *Masking*

Treatment assignments will be masked to the participants and the personnel of the clinical centers, but not to a restricted set of personnel at the DCC. The vitamin D manufacturer will produce matching vitamin D pills for the 4 doses so that the different doses are indistinguishable to participants and study personnel.

Participants and study personnel will not be unmasked until follow-up and all data collection are completed. Emergency unmasking before the end of the treatment period is expected to be rare. Clinical centers may request an emergency unmasking through the study website.

# 10. INTERVENTIONS

## *Form of vitamin D*

The trial will test the effects of vitamin D in the form of vitamin D3 (cholecalciferol), rather than vitamin D2 (ergocalciferol). We will provide daily doses, rather than intermittent high doses (e.g. yearly 500,000 IU), which are non-physiologic and which have been associated with adverse outcomes.[43] Our rationale for using D3 is as follows:

- vitamin D3 is the only form synthesized by humans and the form obtained from usual dietary sources.[57]
- vitamin D3 is more effective at raising and maintaining serum 25(OH)D levels.[58] Vitamin D2 and its metabolites bind less tightly to the vitamin D binding proteins and vitamin D receptors in the body; therefore, D2 does not circulate as long. Hence, vitamin D2 has a shorter half-life than vitamin D3.[59,60]
- shelf-stability of vitamin D3 is greater than D2, and is more likely to remain active for a longer period of time and when exposed to extremes of temperature, humidity, and storage
- vitamin D3 has been the most utilized form of vitamin D in clinical trials, including the ongoing VITAL trial.[61] Hence, there is a greater body of experience, as well as greater opportunity to compare and facilitate analyses across studies.

## *Doses*

Our intent is to test the effects of vitamin D3 doses across a broad range of doses which are safe, non-toxic, and potentially beneficial. Below (Table 4) is our rationale for each of the 4 doses to be tested:

**Table 4: Cholecalciferol Doses and Rationale.**

| Dose | Rationale |
|---|---|
| 200 IU/d | Estimates of mean dietary intake and supplement use in the study population were critical to selecting the lowest dose, which per the RFA should "provide reasonable assurance that total vitamin D intake (diet and supplement) is not less than the RDA for the age group," which is 800 IU/d for individuals ages 70 and older.<br><br>200 IU/d (mean dietary intake) + 525 IU/d (avg. background supplementation (75% taking vitamin D x avg dose of 700 IU/d)) + 200 IU/d (lowest dose) ≈ 925 IU/d (> RDA)<br><br>Mean dietary intake was estimated from NHANES 2005-6 data, and the average dose was assumed as the average of the most common multivitamin dose (400 IU/d) and the maximum allowable supplement dose (1000 IU/d). |
| 1000 IU/d | This is close to the dose used in the trials which documented a benefit of supplemental vitamin D on falls (800 IU/d)[41,44] and muscle strength (1,000 IU/d).[47] |
| 2000 IU/d | This is the dose used in the ongoing VITAL trial.[61] |
| 4000 IU/d | This corresponds to the Upper Limit for total vitamin D intake set by the IOM and is well below the 'maintenance tolerable upper limit' of 10,000 IU/d , recommended by the Endocrine Society Clinical Practice Guideline.[62] It is also just below the most common dose, 5000 IU/d, now consumed by individuals taking supplemental vitamin D (personal communication, Greg Faull). This dose is also well below the levels that might lead to vitamin D toxicity. |

## *Pills*

Placebo pills during run-in and vitamin D3 tablets (200, 1000, 2000 and 4000 IU tablets), all identical, will be manufactured by Continental Vitamin Company (CVC, Vernon, CA). The pills are small, ~5mm diameter and ~3mm high. They can be swallowed or consumed sublingual, thereby facilitating pill-taking and adherence. Vitamin D3 content of the pills will be measured periodically and independently to confirm dosage.

## *Distribution and adherence*

Pill bottles will be distributed every 3 months via mail or at in-person visits. Adherence will be actively promoted at all participant contacts, starting with the baseline visit. A run-in period will precede randomization in order to give screenees an understanding of study procedures (primarily pill-taking and fall reporting procedures) and to identify participants with potential adherence problems. Throughout the study, participants will be encouraged to use pill organizers and other reminder tools. Caregivers will be engaged, as necessary, to promote adherence.

# 11. SAFETY

## *Safety monitoring*

The study will monitor participant safety. One aspect of safety monitoring is to evaluate screenees to determine whether it is safe for them to participate. Key safety related eligibility criteria are the exclusion of persons with (a) a baseline 25(OH)D level of <10 ng/ml, (b) a confirmed baseline serum calcium level of ≥10.6 mg/dl, or (c) kidney, bladder, or ureteral stones made of calcium compounds (≥2 in lifetime, or ≥1 in the last 2 years).

A second aspect is monitoring enrolled participants for safety issues potentially related to the study. Surveillance for serious adverse events, other relevant clinical events, and laboratory abnormalities will occur by questionnaire and by laboratory tests at follow-up contacts. If a participant develops a medical problem, the safety of continuing or resuming the study will be ascertained by the participant's PCP in collaboration with a study clinician.

Third, we may become aware of medical problems including abnormal laboratory tests and physical measurements that are unrelated to the study. Results of routine clinical labs and physical measures obtained as part of study visits will be provided to the participant, who will be encouraged to share the results with his or her PCP. For alert values, the participant will be contacted, and study staff will request permission to share the results directly with the participant's PCP.

Each clinical center will have a designated study clinician(s) who will review medical eligibility criteria, clinical measures, and laboratory reports. This individual also will serve as the primary contact for staff, participants, and their PCPs regarding medical issues. The study clinician will also be responsible for reviewing and reporting SAEs for the site. This person or persons will have appropriate back-up during vacations or other absences to provide 24/7 medical safety coverage for the duration of the study. A separate 'safety officer' will advise the coordinating center.

## *Potential risks*

This study should not involve any major risk to screenees and trial participants. However, there are some potential risks associated with participation in this study, which are as follows:

1. Participants may be uncomfortable with certain questions on the questionnaires.
2. Bruising and a rare chance of local infection from venipuncture to collect blood samples could occur.
3. There might be loss of confidentiality and privacy.
4. Serum vitamin D level, i.e. 25(OH)D, might drop below 10 ng/ml after enrollment. However, serum vitamin D levels will be measured at 3, 12, and 24 months post-randomization for safety.
5. Serum 25(OH)D levels will increase. Given the eligibility criteria of enrolling only deficient subjects, it is unlikely that even the highest vitamin D dose will raise vitamin D levels into a potentially toxic range (>150 ng/ml).
6. Vitamin D supplements might increase serum calcium levels and increase the risk of kidney stones. However, a recent report of a dose-response trial, Gallagher and colleagues did not detect any increased risk of hypercalcemia with high dose vitamin D.[40] Still, our protocol has several features which should further reduce this risk. First, we will exclude potential participants with elevated serum calcium levels ≥10.6 and/or those who are taking an estimated average of supplemental calcium >1200 mg/day. Second, we will monitor serum calcium levels at 3, 12, and 24 months post-randomization.

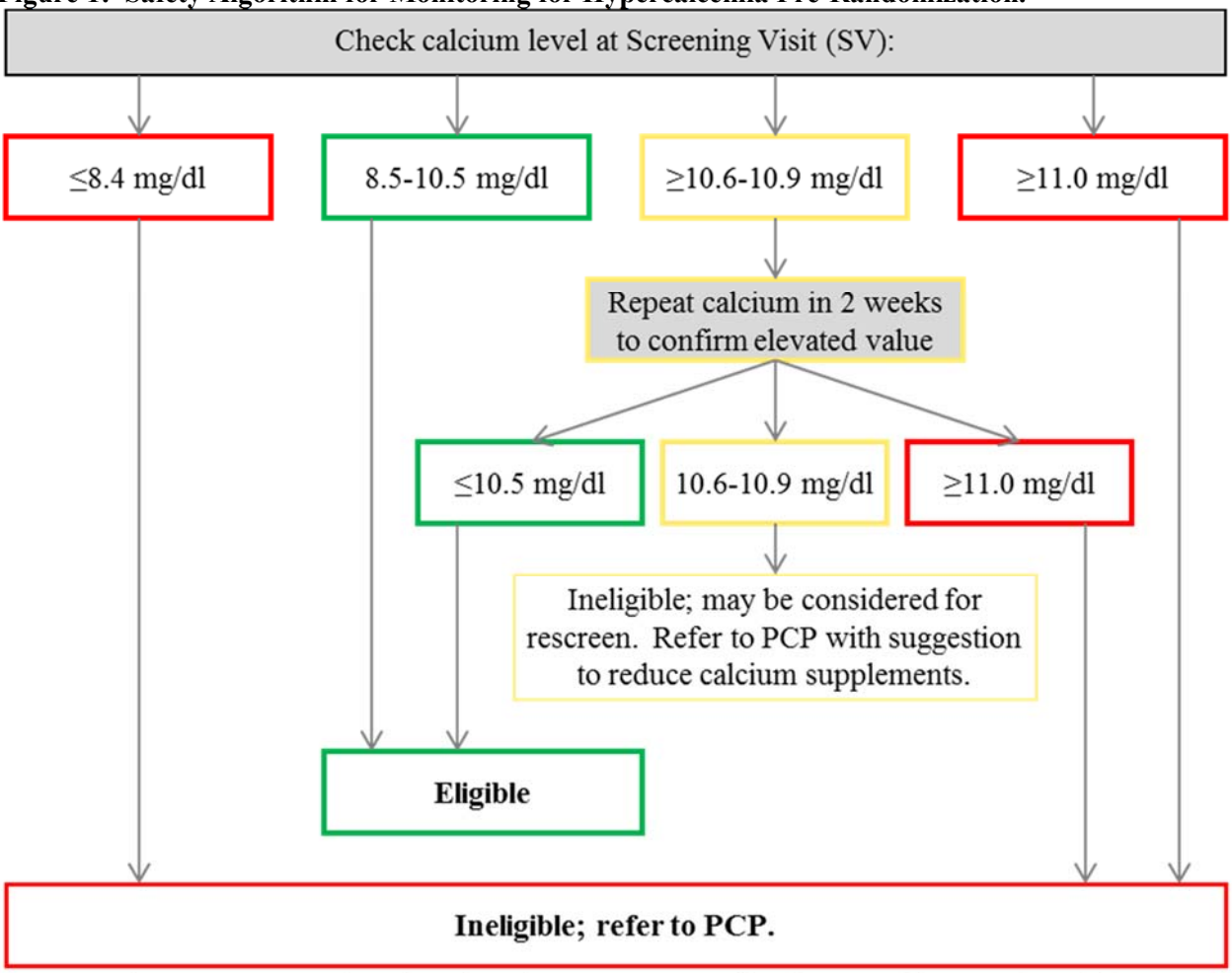
Alert values

Table 5 lists the alert values and subsequent actions that will occur. When alert values occur, the participant and study clinician at the field center will be notified; the participant's PCP will also be notified if the participant has given permission for this notification.

**Table 5: Alert Values and Actions.**

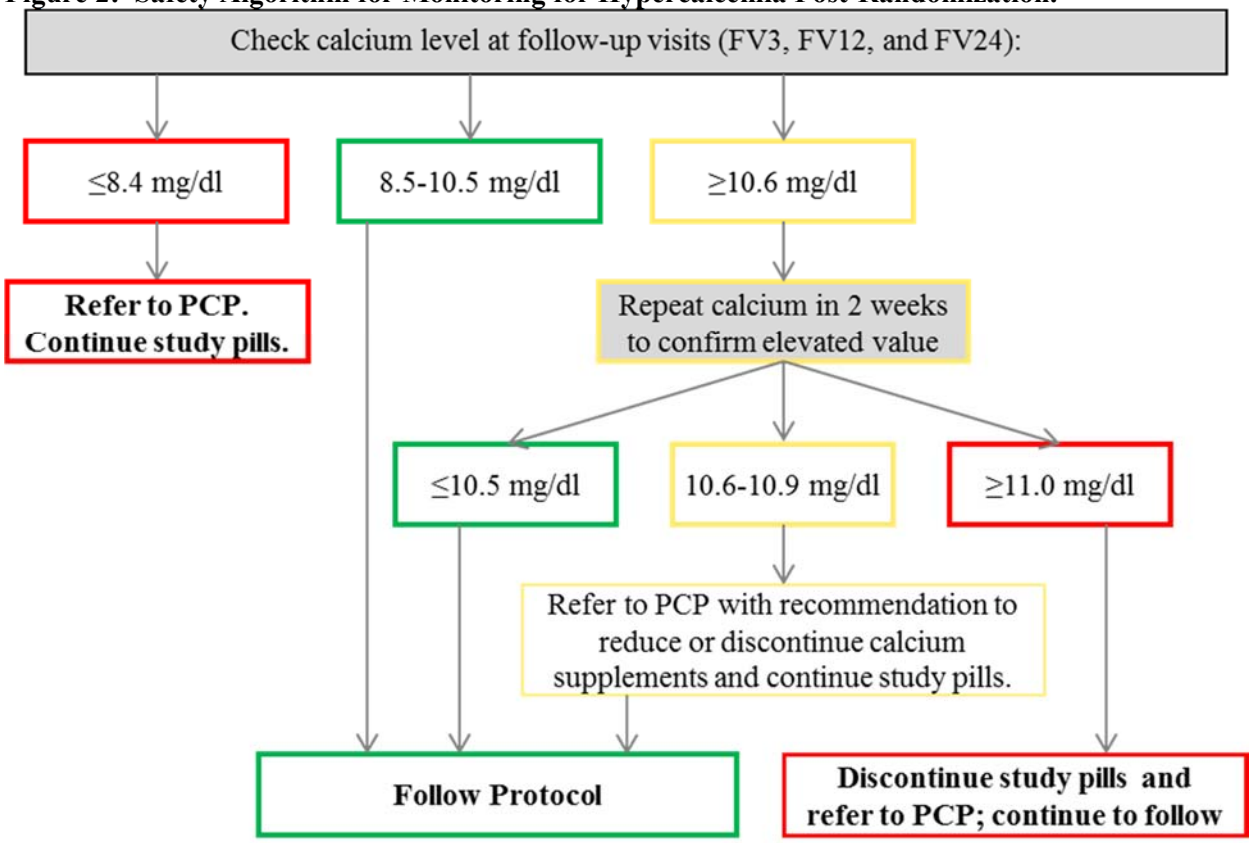
| ***Issue*** | ***If detected Pre-Randomization*** | ***If detected Post-Randomization*** |
|---|---|---|
| **Serum Calcium** | See Figure 1 (pre-randomization calcium algorithm figure) | See Figure 2 (follow-up calcium algorithm figure) |
| **Serum Vitamin D [25(OH)D] Level** | | |
| Low (<10 ng/ml) | Excluded | Unlikely given screening process and provision of at least 200 IU/d. Refer to PCP |
| High (≥150 ng/ml) | Individuals with a 25(OH)D ≥30 ng/ml will be excluded | Discontinue study pills and refer to PCP. Continue follow-up. |
| **Other** | | |
| Kidney stones | Exclude if lifetime hx of ≥ 2 episodes of kidney, bladder, or ureteral stones made of calcium compounds OR 1 episode in last year | Discontinue study pills. Continue follow-up. |

**Figure 1: Safety Algorithm for Monitoring for Hypercalcemia Pre-Randomization.**




**Note:** The cut points used are based on the LLN – 1 SD (for the CV of the assay) and the ULN + 1 SD (for the CV of the assay) at the lab analyzing the samples. If the lab used or the reference ranges change, we will revise the algorithm to reflect the appropriate ULN/LLN +/- 1 SD.

**Figure 2: Safety Algorithm for Monitoring for Hypercalcemia Post-Randomization.**




**Note:** The cut points used are based on the LLN – 1 SD (for the CV of assay) and the ULN + 1 SD (for the CV of assay) at the lab analyzing the samples. If the lab used or the reference ranges change, we will revise the algorithm to reflect the appropriate ULN/LLN +/- 1 SD.

## *Adverse event surveillance and reporting procedures*

The OHRP defines an adverse event as "Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, … symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research." The National Institute on Aging defines serious adverse event as any adverse event that:

- Results in death,
- Is life-threatening or places the participant at immediate risk of death from the event as it occurred,
- Requires or prolongs hospitalization,
- Causes persistent or significant disability or incapacity,
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards.

Surveillance for SAEs and other relevant clinical events that may be associated with study participation will occur at in-person and telephone visits. In addition to the fixed time points, participants may report events in other settings, e.g. phone contacts. A study clinician will review completed forms, will classify the event according to several dimensions (expectedness, relatedness to participation in STURDY, and type), and will take appropriate action.

In view of the study population and the 2 year duration of follow-up, medical events unrelated to participation in STURDY are expected to occur, including the development of cancer, heart disease, stroke, cognitive decline, and the development or worsening of other chronic conditions; increased symptoms from a chronic condition; surgeries and procedures; musculoskeletal problems; and accidents.

All serious adverse events and all unanticipated problems will be reported individually to the DCC (STURDY will have a specific form for such reports), and these reports will be forwarded to the DSMB, the NIA, the Study Chair and the Steering Committee within 7 days of when the clinic learned of the event.

Other adverse events will be reported to STURDY on an interim event form or a regular interview form and, in general, will be reported in aggregate form to the DSMB at the time of regular data reports. However, clinics will have the option of bringing any event to the immediate attention of the DCC (via faxing the report form to the DCC which will forward all such forms to the Safety Officer) for review and discussion by the Steering Committee and for consideration of immediate reporting to the DSMB. Similarly, the DCC will have the option of bringing any event to the attention of the Steering Committee.

# 12. ANALYSIS

## *Bayesian adaptive trial design*

We will conduct a seamless two-stage, Bayesian adaptive, randomized trial for dose-ranging and efficacy confirmation of vitamin D for the prevention of falls in community-dwelling adults, ages 70+, who are at increased risk of falling. Stage 1 of this design will select the "best" dose of vitamin D for prevention of falls from the following doses:, 1000 IU/d, 2000 IU/d, and 4000 IU/d for comparison to the 200 IU/d dose (comparator). If a best dose is selected, Stage 2 will test the efficacy of the chosen dose versus comparator.

## *Analysis plan*

A separate complete statistical analysis plan has been prepared, which provides more detail; here is a summary. The data management team will conduct all analysis of study data. A trial statistician will be assigned to all approved papers. Working with the lead investigator, the statistician will develop an appropriate analysis plan. Formal written analysis requests will be reviewed for clarity before work is begun. This procedure minimizes rework and thus, makes most efficient use of staff resources.

Our primary and, where possible, secondary analyses will be conducted according to the intention-to-treat principle with all participants randomized counted in the group to which they were randomized. We define our ITT primary outcome measure as time to a composite of first fall, death, or completely lost to follow-up. Sensitivity analyses of each component of the primary outcome will be done and presented in the primary paper together with the primary outcome measure. Standard methods will be used to examine data for outliers, and the distributional assumptions of the models will be confirmed.

**Stage 1 – Dose Finding**: The Bayesian response adaptive design for Stage 1 will assign participants to dose 200 IU with a fixed 50% probability and doses 1000 IU, 2000 IU, or 4000 IU with varying probability using a response-adaptive randomization scheme. Stage 1 will start with a "burn-in" period in which probabilities of assignment to the 1000, 2000 and 4000 IU dose groups will remain equal across groups. This allows dose adaption probabilities to become more stable. We found that, with 4 groups, stabilization is sufficient after approximately 1/10 (20 participants per group) of the maximum of 1200 have been randomized. More precisely, we will define the "burn-in" period as the time from randomization of the 1$^{st}$ participant to the time when the 100$^{th}$ randomized participant has been followed for 6 months. At that time (the end of the burn-in period), all available first fall data on all randomized participants will be used to adjust the dose group assignment probabilities. Thereafter, assignment probabilities will be updated periodically, using all the accumulated falls data, until either a best dose is selected or the futility of selecting a best dose is determined.

These assignment probabilities will be calculated using Bayes' Theorem, given the prior distribution of mean time to fall and the cumulative fall data observed as of the time of the probability update. Calculations will follow common practice as implemented in Cytel's Compass 2.0 commercial design software and the public domain ARand software from Berry et al. We chose the distribution of the Bayesian priors based on previous literature,[41,42,44,63-70] as suggested in Berry et al. The adaptive design assumptions and methods are detailed in a separate Statistical Design and Analysis Plan document, which will have restricted access limited to the biostatistical unit for STURDY and, confidentially, the DSMB and NIA staff as appropriate.

We expect to find a best dose and terminate Stage 1 using considerably fewer than 1200 participants and therefore we expect to proceed to Stage 2 (efficacy). However, we recognize the worst case is possible: the dose finding continues until the end of the STURDY trial with no Stage 2 data collected. The clinical staff will not know when the switch from Stage 1 to Stage 2 occurs, since the content of the vitamin D

capsule can be tailored to any dose without changing the size of the pill. Interactions with the manufacturer will be managed by the biostatistical unit and not shared with the clinical staff during the trial.

**Stage 2 – Efficacy**: If an early winner is declared, then both the control (200 IU/d) and "best" dose group will continue seamlessly into Stage 2 with continued recruitment and continued follow-up for all primary and secondary outcomes. The remaining two non-"best" dose groups will be dose-adjusted (up or down) to the "best" dose, with falls occurring after the dose-adjustment counted in the primary analysis with time to first fall for efficacy measured from the point of dose-adjustment as the zero time point.

Our null hypothesis that there is no effect of treatment for any of the three doses >200 IU versus comparator (200 IU) on time to first fall will be tested by pooling all participants in the >200 IU doses and comparing the pooled data with those in the comparator dose using the log-rank test for time to first fall, based on all participant data at completion of the study.

## *Power and sample size*

**Stage 1**: Assuming a maximum sample size of 1200 participants and using other assumptions as described in the separate Statistical Design and Analysis Plan, we performed simulations of trial scenarios with varying dose-response assumptions. The number of months needed to arrive at a decision and end Stage 1 is variable. Different scenarios, including average times to finding a best dose for a range of assumptions about the shape of the dose-response relationship, are described in the separate Statistical Design and Analysis Plan. These shapes include flat, linear increasing, linear decreasing, U-shaped, inverse U-shape, and custom shapes. The Bayesian Adaptive Design performs well under all of these scenarios with high probabilities of picking the best dose or finding the futility of picking a best dose.

**Stage 2**: As discussed above, the sample size needed for Stage 1 will be variable. After Stage 1 is complete, newly enrolled participants will be randomized in a 1:1 ratio to either the "best" dose or the comparator dose (200 IU). New participants will be enrolled until a total of 1200 participants (Stage 1 and Stage 2) have been randomized. Existing participants in the 200 IU (comparator) and the "best" group will continue in their assigned group. Existing participants in the other dose groups will be re-assigned to the "best" group for Stage 2 follow-up. The primary outcome variable is time to first fall in the comparator (200 IU) group compared to time to first fall in the "best" dose group (data from the group identified as best in Stage 1 will be combined with data from the participants randomized to that dose in Stage 2, and with data from the participants originally assigned to the two non-"best" doses who are dose adjusted up to the best dose in Stage 2). The primary Stage 2 analysis will be a two-sided log-rank test with 1200 subjects; with 600 controls vs. 600 in the "best" dose group we would achieve 92% power, assuming Type I error=0.05, hazard ratio=0.75, 10% dropouts, and assuming participants enrolled in the first 2 years are closed out after 2 years (varying follow-up from 6 months to 2 years).

## *Interim monitoring*

The NIA has appointed a multidisciplinary DSMB that will be responsible for the protection of the safety of participants enrolled in the trial. The DSMB will adopt a charter describing its responsibilities and operating characteristics. The DSMB will review the accumulating data on the primary outcome composite (falls + deaths + completely lost to follow-up) measure, time to first fall. . At each interim analysis, the DSMB will make recommendations to the NIA about continuing, modifying, or stopping the trial. The DSMB will meet periodically to review interim reports and analyses derived from the accumulating data or related findings from sources external to the trial that may be needed to make recommendations to the NIA regarding: 1) overall efficacy and benefit/risk ratio, 2) efficacy and benefit/risk ratios within defined subsets of participants, and 3) overall and clinic-specific performance and data quality.

## *Missing data*

We will employ recommended strategies to prevent missing data, based on published research.[71-74] However, prevention is far superior to a statistical cure, and every effort will be made to collect outcome data on all participants.

# 13. DATA MANAGEMENT

Data will be collected from three main sources: 1) data collected by trial staff on trial case report forms for later entry into the data management system (DMS); 2) data entered by participants and/or trial staff directly into the DMS; and 3) data generated by ancillary facilities, such as laboratories, and sent to the DCC electronically. The DMS will be accessible only via the secure website and only to authorized personnel. Data entered into the DMS will be subject to intra- and inter-item checks, such as range checks, logic checks, and consistency checks. All data collected on paper case report forms will be checked by a second research assistant before data entry, and all such forms will be maintained for later random audits (in which selected case report forms will be compared with the DMS data). Any data items that are missing will be explicitly marked as such using functions in the DMS, although certain key values will not be allowed to be marked 'missing'. The DCC will identify questionable values and report them as Data Quality Queries (DQQs) to the clinical sites for resolution. Data entry staff will perform data entry as soon as possible after data have been collected.

## *Data confidentiality and integrity*

The investigative team, including staff at all levels of the study (clinical sites, DCC, laboratory sites, etc.) will be apprised of the need to maintain strict controls to ensure data integrity. All staff with access to any portion of the study data will receive training in the importance of maintaining participant confidentiality; this training will include mandatory training modules on HIPAA (Health Insurance Portability and Accountability Act). All data collected and stored electronically will be password protected and saved on secure servers. All study-related computers will be located behind appropriate firewalls and will maintain automated virus update mechanisms. Hard copies of data collection forms will be stored in secure areas (locked offices or cabinets). All staff will sign statements attesting to their understanding of and willingness to abide by policies designed to protect the integrity of the study data. General access to the data entry website is password protected, with an additional requirement that users enter an individual username and password to gain access to the DMS. DMS data will be backed up locally once per day, and off-site three-times per day via automated download processes. Data backups will be checked periodically to ensure proper backup functioning.

## *Analysis guide*

To facilitate data analysis requests, the data management team will create a detailed analysis guide for the study investigators. This guide provides detailed, organized documentation of all study variables along with a process that allows researchers to request analyses in a clear, concise fashion. A summary data set including the most frequently used variables will be provided. Copies of every data form used in the study will also be provided along with a description of the variable naming scheme used in the data system.

## *Trial-wide data release.*

The data management/analysis team will prepare and distribute a limited access dataset to the NIA project office for public use with the analysis guide. The data release documentation provides detailed, organized documentation of study variables and clear instructions on how to install and access the data.

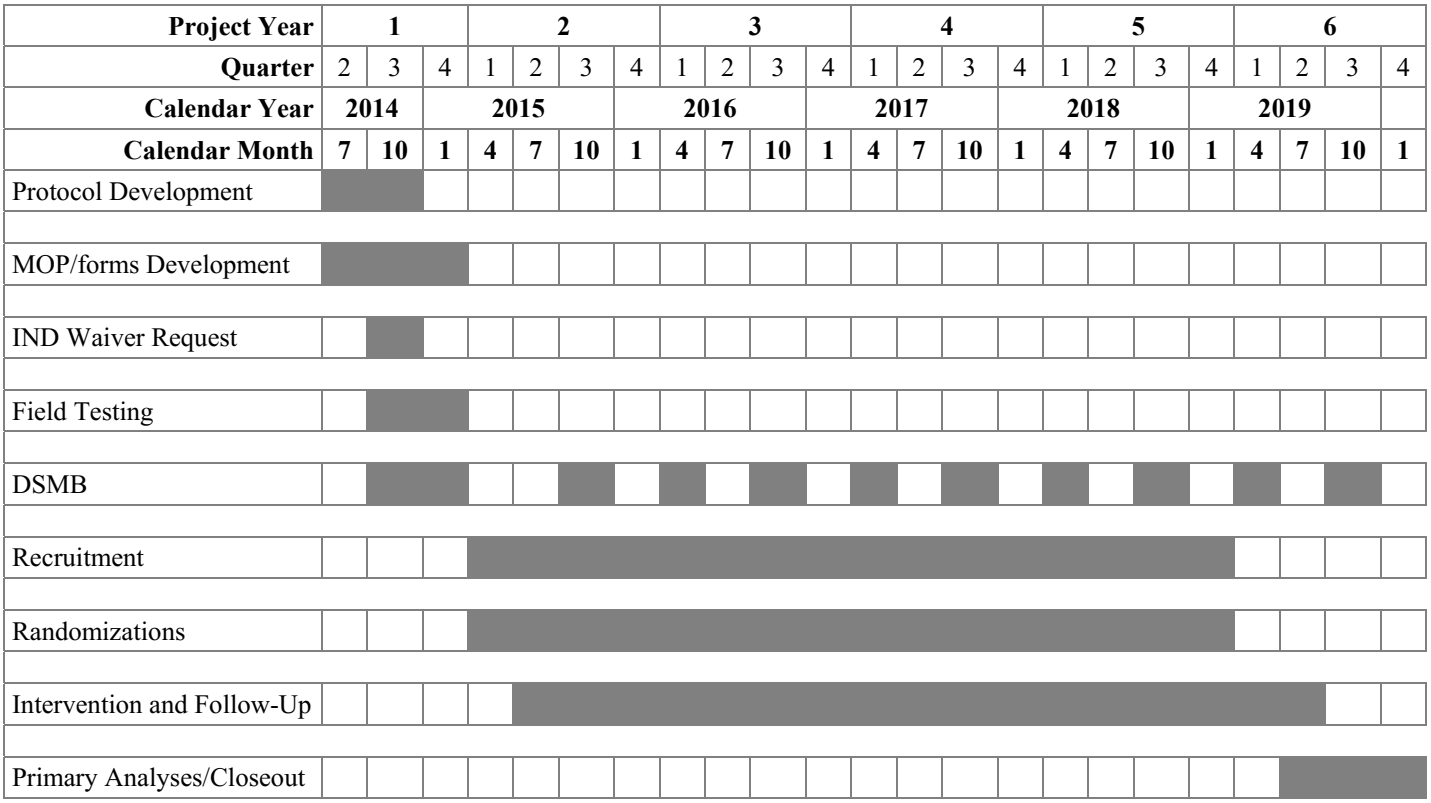
# 14. TIMELINE

The trial consists of three main phases: planning, implementation (recruitment, intervention, and data collection), and data analysis. Planning for the trial commenced in July 2014. Recruitment will commence in spring 2015 and should last approximately 3-4 years, with randomizations occurring ~1 month behind recruitment. Participants will be followed for 2 years, or until the end of the follow-up period around fall 2019, whichever comes first (with a minimum follow-up of 6 months). Remaining time will be devoted to data analyses, presentation/publication, closeout, and dissemination activities.

**Figure 3: General Timeline of STURDY Clinical Trial.**

**Project Start Date:** **7/1/2014**

**Project End Date:** **5/31/2020**



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# 16. APPENDIX I: ORTHOSTATIC HYPOTENSION ANCILLARY PROTOCOL

## *Background*

Orthostatic hypotension (OH) is a common medical condition in older adults, associated with higher risk of falls, cardiovascular disease, stroke, and death. STURDY affords a unique opportunity to study OH and its symptoms in greater detail in a population of older adults (ages 70 years and older) over a follow-up period of two years.

## *Aims*

1. To characterize orthostatic hypotension in participants of STURDY
2. To determine the association of orthostatic hypotension with subsequent falls
3. To evaluate whether vitamin D reduces OH symptoms

## *Participants*

The STURDY main trial consent will include an optional component where STURDY participants can choose whether to participate in the OH ancillary protocol. Newly screened and enrolled participants will provide consent at the Baseline Visit (BV). Participants who have already provided consent for STURDY will be given the option at their next in-person visit (RZ, F03, F12, or F24) to participate in the ancillary study by signing the optional consent statement.

## *Data collection schedule*

Newly enrolled participants:

- Randomization Visit (RZ): OH blood pressure assessment and OH symptom questionnaire
- Follow-up Visits (F03, F12, and F24): OH blood pressure assessment and OH symptom questionnaire

Participants already randomized in STURDY, newly consenting to the OH protocol:

- Next in-person follow-up visit (F03, F12, or F24): OH blood pressure assessment and OH symptom questionnaire
- Subsequent Follow-up Visits (F12, F24): OH blood pressure assessment and OH symptom questionnaire

Some items or visits may be dropped from the data collection schedule based upon participant burden, scientific considerations, and available resources.

## *Procedures*

*OH Symptom Questionnaire*

- Participants will be administered a 20-item questionnaire about symptoms experienced upon standing and other symptoms related to low blood pressure

*OH Assessment*

- Participants will lie for 5 minutes in the supine position. After 5 minutes of rest, 3 assessments of systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) will be taken using an Omron 907.
- Participants will be asked to stand. The duration for standing will be recording. Immediately after standing, a second set of 3 assessments will occur (SBP, DBP, and HR).
- Participants will be asked a question about dizziness/light-headedness experienced while standing ("As you stand, on a scale from 0 to 10, with 0 being no symptoms and 10 being the worst

possible, please rate if you feel ‘dizziness, lightheadedness, feeling faint, or feeling like you might black out’.”)

- Starting at 3 minutes after standing, participants will undergo a final set of 3 assessments (SBP, DBP, and HR).
- All assessments are time stamped via a GoPro clamped onto the Omron device, and the triplicate assessments will be separated by 2-3 seconds each.
- Media file containing the recorded orthostatic assessments will be stored on a secured computer and extracted by a data manager at a later time.

## *Safety*

If at any time, the participant feels dizzy or uncomfortable, s/he is instructed to lean against the table, and then study staff should help the participant into a chair in the room.