Manual of Procedures (MOP)
Section 8. Concomitant Medications

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8.1 OVERVIEW

At the screening visit, the participant is instructed to bring all pill bottles and the research coordinator will review the medications with the participant, inquiring what the medication is used for and reconciling with the medical history. At each subsequent visit, the participant will bring a list of her medications and the bottle(s) of any new medications or supplements. The coordinator will review the list of medications/supplements and will ask participants:

- Since your last visit, have you had any changes to the medications or supplements you are taking? Have you started or stopped or had a change in the dose of your medications or supplements?
- Are you now taking or has your doctor prescribed any of these medications or supplements?
    - Vitamin D containing medications, multivitamins or supplements
    - Calcium containing medications, multivitamins or supplements
    - Medications to treat diabetes.

⇒ All changes in medication and supplement use will be recorded, as described in MOP section 8.4 (but not all medications will be entered in the EDC).

8.2 CONCOMITANT SUPPLEMENTS

8.2.1 Vitamin D Supplementation

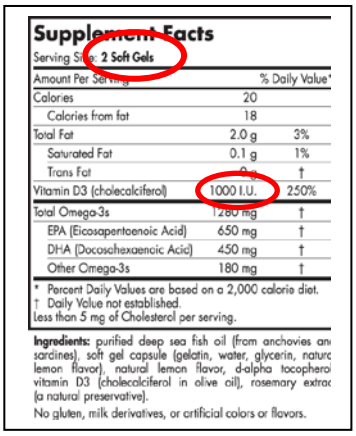
Study personnel will encourage participants to optimize their dietary vitamin D intake and to supplement their dietary intake with vitamin D supplements up to 600 or 800 IU/day (depending on their age), as recommended by the Institute of Medicine.

⇒ Participants will be strongly discouraged from taking vitamin D-containing supplements on their own throughout the trial, beyond what is recommended by the Institute of Medicine for their age group. However, for practical reasons, participants are allowed to take up to 1000 IU/day of vitamin D on their own from all supplemental sources combined (stand-alone vitamin D supplements, multivitamins, medications containing vitamin D [e.g. Fosamax Plus D]), if they wish. The maximum allowable dose of 1000 IU/day was chosen because it is the dosage contained in many commercially available supplements and also the dose most commonly recommended by health care providers.

✓ Therefore, it is critical that study personnel record very carefully the amount of vitamin D in medications and supplements, as described next.

⇒ During the concomitant medication/supplementation review at screening and at each visit, the research coordinator must add up the total dosage of non-dietary vitamin D a participant is taking to make sure the total daily dose does not exceed 1000 IU/day, e.g. 800 IU/day in multivitamin and 2800 IU/week [=400 IU/day] from Fosamax Plus D = 1200 IU/day.

- ✓ Please note participants should be asked if they take any cod liver oil or fish oil supplements and the bottles should be reviewed for the dose of vitamin D. See example below.



Supplement Facts

Serving Size: 2 Soft Gels

Amount Per Serving		% Daily Value*
Calories	20	
Calories from fat	18	
Total Fat	2.0 g	3%
Saturated Fat	0.1 g	1%
Trans Fat	0 g	†
Vitamin D3 (cholecalciferol)	1000 I.U.	250%
Total Omega-3s	1280 mg	†
EPA (Eicosapentaenoic Acid)	650 mg	†
DHA (Docosahexaenoic Acid)	450 mg	†
Other Omega-3s	180 mg	†

* Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.
Less than 5 mg of Cholesterol per serving.

Ingredients: purified deep sea fish oil (from anchovies and sardines), soft gel capsule (gelatin, water, glycerin, natural lemon flavor), natural lemon flavor, d-alpha tocopherol, vitamin D3 (cholecalciferol in olive oil), rosemary extract (a natural preservative).

No gluten, milk derivatives, or artificial colors or flavors.

- ✓ Participants who are unwilling to limit outside-of-study vitamin D supplementation to 1000 IU/day for the duration of the study will be excluded. There is no limit in how much vitamin D participants can take from food or beverage sources (e.g. dairy products).

  NOTE: Site staff should discuss with participants the rationale behind what D2d allows for vitamin D and refer participants to the D2d website for more information. Staff should use the information on the D2d website (d2dstudy.org/about/vitamin-d), and also the appendix "Talking points about vitamin D and calcium" in MOP section 6, as a guide to educate participants and clinicians.

- ✓ For a participant who is taking > 1000 units/day and ≤ 2000 units/day and is willing to reduce the dose to no greater than 1000 units/day for the duration of the study, the baseline visit should be scheduled such that, *at the baseline visit*, the person has been taking *≤1000 IU/day for at least **8** weeks.*

- ✓ For a participant who is taking > 2000 IU per day and is willing to reduce the dose to no greater than 1000 IU for the duration of the study, the baseline visit should be scheduled such that, *at the baseline visit,* the person has been taking *≤1000 IU/day for at least **12** weeks.*

- ✓ *If during the trial, a participant reports that his physician instructed him to take more than 1000 IU/day of vitamin D from supplements, the physician will be contacted and informed that the participant is in the D2d study and supplementation higher than 1000 IU/day is discouraged, as it is often not indicated. If the physician prescribes the higher dose of vitamin D anyway, the participant will continue in D2d and continue taking study pills. Prescribed high-dose supplemental vitamin D (e.g. 50,000 IU once a week for 8 weeks) is entered into the Concomitant Medication e-CRF.*

8.2.2 Calcium Supplementation

Study personnel will encourage participants to optimize their dietary calcium intake and to supplement their dietary intake with calcium supplements up to 600 mg/day.

⇒ Participants will be discouraged from taking calcium-containing supplements on their own throughout the trial, beyond 600 mg/day. The Institute of Medicine recommends total calcium intake of 1000-1200 mg/day from either food or supplements; however, there is concern that high calcium intakes from supplements may be associated with adverse cardiovascular effects and the current recommendation is to optimize calcium intake through diet with supplementation only as needed to reach the recommended total intake.

⇒ During the concomitant medication/supplementation review at each visit, the research coordinator (or designee) must add up the total dosage of non-dietary calcium a participant is taking to make sure the total daily dose does not exceed 600 mg/day.

✓ During screening, potential participants who are taking more than 600 mg/day of calcium from supplements and are unwilling to lower their intake to less than 600 mg/day during the study will be excluded. There is no limit in how much calcium participants can take from food or beverage sources (e.g. dairy products).

✓ **NOTE:** Site staff should discuss with participants the rationale behind what D2d allows for calcium and refer participants to the D2d website for more information. Staff should use the information on the D2d website (d2dstudy.org/about/vitamin-d), and also the appendix "Talking points about vitamin D and calcium" in MOP section 6, as a guide to educate participants and clinicians.

✓ A participant who is taking more than 600 mg/day of supplemental calcium at the screening visit but is willing to lower her supplemental intake to less than 600 mg/day for the entire study, will be instructed to do so and return for the Baseline visit no earlier than one week.

✓ If during the trial, a participant reports that his physician instructed him to take more than 600 mg/day of calcium from supplements, the physician will be contacted and informed that the participant is in the D2d study and supplementation with calcium higher than 600 mg/day is discouraged, as it is often not indicated. If the physician prescribes the higher dose of calcium anyway, the participant will continue in the study.

8.2.3 Other Supplements

Participants are allowed to take additional vitamins or supplements that *do not contain vitamin D or calcium*. All supplement use (with or without calcium or vitamin D, including fish oils) will be recorded in the source documents, to aid the research staff in calculating amount of supplemental calcium or vitamin D. Supplements do not need to be recorded on the concomitant medication e-CRF. The only exception to this is if a participant takes a **Niacin** supplement *specifically under the direction of her physician to treat high cholesterol* (e.g. not part of a multivitamin or combination supplement), the information should be recorded on the concomitant medication form in EDC (see MOP section 8.5.2).

8.3 CONCOMITANT MEDICATIONS

All concomitant medications a participant takes during the study will be recorded in source documentation.

- ✓ *Given the low benefit-to-burden ratio of recording all medication information in EDC, only specific medications of interest to the study will be entered into EDC (see MOP section 8.5.2).*

At screening (or pre-screening), research staff will review all medications (those taken on a regular schedule and those taken as-needed) and reconcile the medications with the D2d study excluded medications list (see MOP section 8.5 and MOP section 18 Appendix**).**

- ✓ **The site physician must review the participant's concomitant medication list prior to randomization**.

Participants who take any of the excluded medications, either regularly or as-needed, will not be randomized.

If, during the trial, a medication from the D2d excluded medications list is prescribed by a physician, the physician will be contacted and informed that the participant is in the D2d study and the medication is an exclusionary medication. If the physician prescribes the medication anyway, the participant will continue in the study.

8.4 EXCLUSIONARY MEDICATIONS TO PARTICIPATION

8.4.1 Anti-hyperglycemic Medications

See list in MOP section 18 Appendix.

8.4.2 Glucocorticoid (IV or oral) Medications

Hydrocortisone
Methylprednisolone
Prednisone
Dexamethadasone

PLEASE NOTE:

- ✓ Persons with adrenal insufficiency treated with physiologic doses of glucocorticoids who are otherwise stable are *not* excluded.
- ✓ Inhaled glucocorticoids are not exclusions.
- ✓ Recent short-term use of glucocorticoids (including injections into a joint or epidural space), are not exclusions; however, visits should be timed appropriately (see below)

8.4.3 Calcium / Vitamin D

Ergocalciferol or cholecalciferol higher than 1000 IU/day
Calcitriol
Paracalcitol

8.4.4 Weight-loss Medications

Lorcaserin (Belviq)
Naltrexone Hydrochloride + Bupropion Hydrochloride (Contrave)
Orlistat (Alli, Xenical)
Phentermine (Suprenza, Adipex)
Phentermine/topiramate (Qsymia)
Liraglutide (Saxenda)
Diethylpropion

8.4.5 Medications that interfere with the absorption or metabolism of vitamin D

8.4.5.1 Phosphate Binders

Aluminum hydroxide (Alternagel, Amphojel, Alu-tab)
Calcium acetate (PhosLo)
Sevelamer (Renagel)

8.4.5.2 Bile Sequestrants

Cholestyramine (Locholest, Prevalite, Questran)
Colesevelam (WelChol)

8.4.5.3 Other

Rifampin

8.5 MEDICATIONS WITH RESTRICTIONS AT RANDOMIZATION

8.5.1 Anticonvulsants

The following anticonvulsants can interfere with the absorption vitamin D and therefore the participant must be on a stable dose for the 6 months prior to screening:

Carbamazepine (Tegretol)
Oxcarvazepine (Trileptal)
Phenobarbital
Phenytoin (Dilantin, Phenytex)

Primidone (Mysoline)
Topiramate (Topamax, Qudexy XR, Trokendi XR)
Valproate, Valproic Acid (Depakote, Depakene, Depacon, Stravzor)

8.5.2 Thiazide diuretics

Thiazide diuretics (see list 8.6.2.1) at doses greater than 37.5 mg per day may increase the risk of nephrolithiasis in people taking Vitamin D. Therefore, the maximum combined dosage allowed for study inclusion is 37.5 mg/day.

8.6 MEDICATIONS RESTRICTIONS DURING THE STUDY

8.6.1 Use of glucocorticoids during study

8.6.1.1 Oral Steroid

A short-term (defined as less than 10 days) course of glucocorticoids or corticosteroids may be prescribed for a variety of conditions (e.g. asthma). During treatment with these medications, glycemia measures may become temporarily elevated. Study visits should be scheduled or postponed so that participants are scheduled for a visit requiring glycemic measures at least one week after the last glucocorticoid dose.

8.6.1.2 Steroid injection into joint, tendon, or epidural space

Participant may receive and injection of a steroid into a joint, tendon, epidural space or other specific location to treat inflammation and pain. Glycemia measures may become temporarily elevated after an injection therefore study visits should be scheduled or postponed to at least one week after an injection.

8.6.2 Use of weight-loss medications during study

The use of weight-loss medications during study participation is not encouraged. If a participant insists on starting a weight-loss medication *and* is approaching a routine study visit, an effort should be made to schedule the next D2d regular visit before (or as soon as possible after) the participant starts the weight loss medication for collection of un-confounded data. Full participation in the study will continue.

8.6.3 Participant starts on diabetes medication during study

During initial conversations, potential participants should be informed that, for D2d to succeed, diabetes medications should not be started prior to the diagnosis of diabetes, according to study criteria, which are consistent with the American Diabetes Association criteria for diabetes. This should be reinforced at each encounter with the participant.

If a health care provider *prescribes diabetes-specific pharmacotherapy (for any indication),* whether or not the participant plans to initiate the pharmacotherapy, the site PI (or study physician) should **promptly initiate contact with the PCP (or prescribing clinician)** and participant *to review the D2d protocol and the need for protocol-specific glycemic testing.* ***See MOP section 18.3.3.***

8.7 DOCUMENTATION OF MEDICATIONS AND SUPPLEMENTS

8.7.1 Source Documentation

For each medication or supplement the participant reports taking (or has taken since the last contact), the following will be recorded in the *source documents*:

- Name of medication or supplement (generic name)
- Indication
- Start date
- Ongoing (yes/no)
- End date
- Dose and units
- Frequency
- Route of administration

At each visit, the medication/supplement list will be reviewed. New medications/supplements will be added and updates will be made.

8.7.2 Electronic Data Capture (EDC) System

✓ Given the high burden of recording all medication information in EDC, only specific FDA approved medications that are prescribed for the following indications will be recorded on the Concomitant Medication e-CRF:

- Hypertension (see below for list of medications)
- Osteoporosis/Osteopenia (see below for list of medications)
- Weight-loss (see below for list of medications)
- Cholesterol or lipid lowering (see below for list of medications)
- Diabetes (see section MOP section 18 Appendix for a list of medications)
- Short course high doses of vitamin D (e.g. 50,000 IU per week)

➢ In addition, *regular* use of aspirin will be recorded on the Concomitant Medication e-CRF. *Regular use* is when aspirin is taken on a set schedule, e.g. every day or every other day, whether prescribed by a provider or not. If a participant takes aspirin occasionally (prn) for pain or fever, that is not considered regular use.

Participant source document concomitant medication list(s) should be reviewed from the start of each participant's participation to the present and aspirin must be recorded retroactively and updated going forward as with the other medications entered into EDC.

Below is a list of commonly prescribed medications approved for these indications.

Please note: new medications approved by the FDA may not be included on this list. If you are unsure of the approved indication of a medication, the information can be found in drug reference books, and on the FDA website: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name. At the FDA website, you can search for the drug by generic name and then will select the link the link “Label information,” review the most up-to-date label for the “Indications and Usage” section. This section will include a list of the approved indications.

8.7.2.1 Hypertension Medications

Thiazide and Thiazide-like Diuretics:
Chlorothiazide (Diuril)
Chlorthalidone
Hydrochlorothiazide (Microzide)
Indapamide
Metolazone (Zaroxolyn)

Other Diuretics:
Bumetanide
Ethacrynic Acid (Edecrin)
Furosemide (Lasix)
Torsemide (Demadex)
Spironolactone (Aldactone)

Angiotensin converting enzyme inhibitors (ACE Inhibitors):
Benazepril (Lotensin)
Captopril (Capoten)
Enalapril (Vasotec)
Fosinopril
Lisinopril (Prinivil, Zestril)
Quinapril (Accupril)
Ramipril (Altace)

Angiotension II receptor blockers:
Candesartan (Atacand)
Eprosartan (Teveten)
Irbesartan (Avapro)
Losartan (Cozaar)
Telmisartan (Micardis)
Valsartan (Diovan)

Beta blockers:
Atenolol (Tenormin)
Metoprolol succinate (Toprol-XL)
Metoprolol tartrate (Lopressor)
Timolol
Nadolol (Corgard)
Pindolol (Visken)
Propranolol (Inderal)

Calcium channel blockers:
Amlodipine (Norvasc)
Isradipine
Nicardipine (Cardene)

Nifedipine (Procardia)
Felodipine (Plendil)
Diltiazem (Cardizem, Dilacor)
Verapamil (Calan)

Alpha blockers:
Prazosin Hydrochloride
Terazosin Hydrochloride Doxazosin Mesylate(Cardura)

8.7.2.2 Osteoporosis/Osteopenia Medications

Bishposphonates
- Alendronate (Fosamax)
- Risedronate (Actonel, Atelvia)
- Ibandronate (Boniva)
- Zolendronic acid (Reclast, Zometa)
- Etidronate (Dridronel)
- Tiludronate (Skelid)

Recombinant human PTH (Forteo)
Denosumab (Prolia)
Tiludronate (Skelid)
Raloxifene (Evista)
Calcitonin

8.7.2.3 Weight-loss Medications

Lorcaserin (Belviq)
Naltrexone Hydrochloride + Bupropion Hydrochloride (Contrave)
Orlistat (Alli, Xenical)
Phentermine
Phentermine/topiramate (Qsymia)
Liraglutide (Saxenda)
Diethylpropion

8.7.2.4 Cholesterol or Lipid Lowering

Statins:
Lovastatin (Altoprev)
Rosuvastatitn (Crestor)
Fluvastatin (Lescol)
Atorvastatin (Lipitor)
Lovastatin (Mevacor)
Pravastatin (Pravachol)
Simvastatin (Zocor)

Bile acid binding resins:

Colestipol (Colestid)
Cholestyramine/sucrose (Questran)
Colesevelam (Welchol)

Cholesterol absorption Inhibitors:
Exetimibe (Zetia)

Fibrates:
Fenfibrate (Lofibra)
Gemofibrozil (Lopid)
Fenofribrate (TriCor)

PCSK9 Inhibitors:
Alirocumab (Praluent)
Evolocumab (Repatha)

Niacin:
Niaspan
Niacin (single component over the counter supplement)

Omega 3 fatty acids:
Lavaza (a prescription omega-3 fatty acid supplement)
Vascepa