Manual of Procedures
Section 19. Frequently Asked Questions

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PLEASE NOTE: Most, but not all of, the answers to previous versions of MOP 19 have been incorporated in the MOP. However, several FAQ and answers have been retained in this document.

Sections are numbered to correspond to the relevant MOP section. The answers to these questions will eventually be incorporated in the MOP.

19.6 Screening & Inclusion – Exclusion Criteria

Q1: Many participants who qualify otherwise do not want to stop their high dose vitamin D or calcium supplements to meet the study's criteria. How should I handle this?

A: The maximum vitamin D (no more than 1000 IU/day) and calcium (no more than 600 mg/day) intake from supplements allowed for all D2d participants is based on the best evidence available and consensus among experts in vitamin D and calcium. There is no limit in how much vitamin D or calcium participants can take from food or beverage sources (e.g. dairy products). Sites should discuss with participants the rationale behind what the D2d study allows and refer participants to the D2d website for more information. Staff should use the information on the D2d website (d2dstudy.org/about/vitamin-d) as a guide to educate participants and clinicians. The CC has also developed a more extensive "Talking points about vitamin D and calcium," which is found in the appendix of MOP 6.

Q2a: A potential participant reports that she was diagnosed with type 2 diabetes about 9 months ago. At that time, her hemoglobin A1c was 7.6%; however, she changed her lifestyle, lost weight and last month her A1c was 6.3%. Should I screen her?

Q2b: Another participant was diagnosed with type 2 diabetes 3 years ago. At that time, his hemoglobin A1c was 9.1% and was on insulin and metformin. He has been on no diabetes medications for the 16 months and his A1c was 6.1% last month. Should I screen him?

A: **Yes**, both participants may be considered for a screening visit. D2d excludes people with diabetes at present (based on glycemic criteria or current use of medications) or if they have not been on diabetes pharmacotherapy within the past year. Past diabetes, by itself, is not exclusion.

Q3: One of our research call lists has several people with rheumatoid arthritis on the list and many are on prednisone and have been for several years. Can these people be enrolled?

A: **No**, participants who take glucocorticoids on a regular basis for treatment of their underlying condition (e.g. rheumatoid arthritis) are excluded. However, persons with adrenal insufficiency treated with physiologic doses of glucocorticoids who are otherwise stable are *not* excluded.

Q4: We have a patient who had a tubular adenoma of the colon in 2010. It was removed and subsequent colonoscopies have been clear. He was told he didn't need another colonoscopy until 2015. Should he be enrolled?

A: **The participant should be excluded**. As the protocol is currently written, participants with a history of cancer of less than 5 years are excluded.

Q5: A male participant reports starting testosterone replacement 10 weeks ago. The protocol states women taking menopausal hormone replacement therapy must be on a stable dose for 12 weeks prior to the baseline visit. Does the same time frame apply for men taking hormone replacement therapy?

A: **No.** There are no protocol restrictions for testosterone replacement therapy.

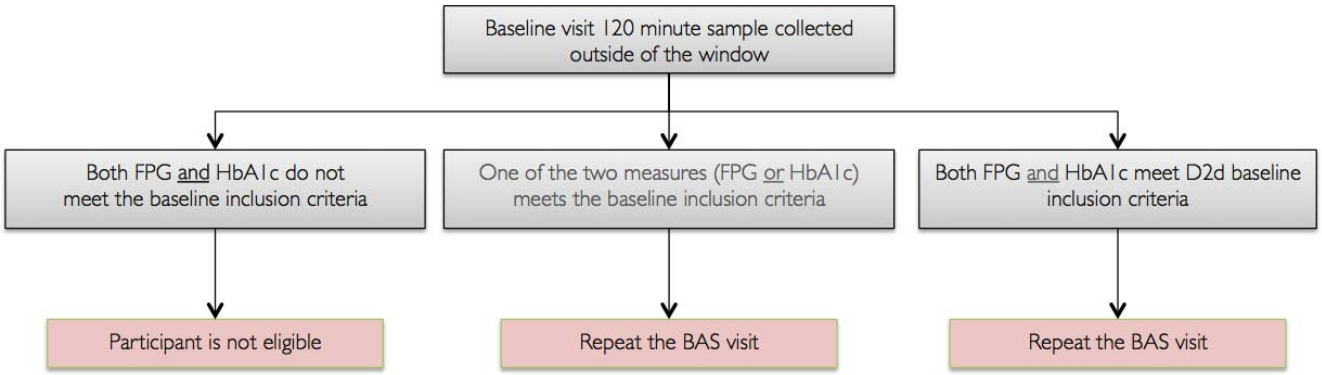
Q6: *If a participant has a history of non-calcium (e.g., uric acid) kidney stones within the past 3 years, can she be enrolled?*

If a person currently has a known kidney stone that has been present for many years, based on radiology studies, and has not been causing him any symptoms, can he be enrolled?

A: **No.** The exclusion criteria *"history (past 3 years) of hyperparathyroidism, symptomatic or asymptomatic (i.e. radiographic) nephrolithiasis or hypercalcemia"* does not specify the type of stone. Therefore all kidney stones are exclusionary.

Q7: *During the baseline OGTT, I collected the 120-minute specimen outside of the time window. What should I do?*

A: If the 120-minute specimen is not collected within the 110-130 minute period, the specimen should not be processed and not sent to the Central Laboratory. The fasting plasma glucose, the 30-minute sample and the HbA1c should be sent to the Central Laboratory. The sites will follow the algorithm below to determine if the participant should return for a repeat baseline visit.



19.7 Intervention / Concomitant Medication

Q1: A randomized participant called me to report that he was prescribed a course of high dose vitamin D by his primary care physician (e.g. 50,000 IU once a week for 8 weeks). What should we do with this participant?

A: It is critically important that study staff remind the participant and alert the primary care physician of the requirement of D2d that participants should not be on doses of vitamin D that exceed (on average) 1000 IU/day.

Site staff should discuss with participant and his primary care physician 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.

It is ultimately the decision of the primary care physician to prescribe high dose vitamin D. *If the randomized participant is prescribed high-dose vitamin D, it will be given without study pill interruption. The participant continues in the study and continues to take the study pills and returns for scheduled follow-up visits. Per the intent to treat principle, the study pill is never stopped, except for an adverse event related to the study pill, during pregnancy or at participant's request (the latter is strongly discouraged).*

⇒ **When high-dose vitamin D is given to participants, the CC should be alerted.**

At the next visit, the study staff should enter the participant's **current** vitamin D supplement dosage in the *Other Visit Data* e-CRF. High dose Vitamin D **prescribed** by a physician should be entered in the concomitant medication form with the dosage, start and stop dates.

During the study, site staff stays in constant and close communication with the participants' physicians to educate them about the study design to ensure that they communicate with study staff before the patient receives a high dose vitamin D, outside of D2d.

19.8 Concomitant Medications

Q1: If a person is taking gabapentin (Neurontin) for a non-seizure disorder (e.g. neuropathy), do they need to be on a stable dose for 6 months?

A: **Yes.** Protocol exclusion criterion 14 requires participants to be on stable doses of anticonvulsants for 6 months prior to screening. The indication for treatment does not matter.

19.17 Retention

Q1: A participant reports that she stopped taking the study pills and, after much discussion, she adamantly refuses to continue them. Should I discontinue her participation in the study?

A: **No.** Participants continue in the study regardless of compliance with study pills. Participants can go "off study" (i.e., discontinue from D2d) only for withdrawal of consent, which is defined as no longer wishing to participate in **all aspects** of the trial. Withdrawal of consent needs to be documented.

Unless a participant goes "off study", she will be asked to return for all scheduled follow-up evaluations, to collect outcome and safety data, even after she has reached the primary endpoint. Participants should be reminded at every visit that their participation is always important, even if they are not taking the study pills as instructed.

Even if a participant cannot return to study visits (e.g., if she is homebound), participation can continue by obtaining information over the phone and via medical records.

Q2: I have a participant that is moving to Africa for 2 years. He would like to continue participating but does not plan to return for her visits during the two years. What should we do?

A: Per intention-to-treat principle, he continues to participate in the study, but will need to stop the study pills, if he cannot return for scheduled safety assessments. During the two years, phone or e-mail contact should be scheduled every 3 months to determine if he is diagnosed with diabetes or anything else has changed. Upon returning to the US, his full participation should resume.

Q3: I have a participant that is moving to another state. Can he continue his participation at another site closer to where he will be living?

A: Possibly. Please contact the Coordinating Center as soon as possible after you learn of his move to review the required logistics.