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 other sections of the MOP. However, several FAQ that recur have been retained.

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

19.4 SCHEDULE

Q1: One of our participants uses e-cigarettes. Should use and frequency of use of e-cigarettes be factored in to responses to the questions about smoking (i.e. "do you currently smoke?" and "on average, how many cigarettes per day have you smoked during the past year?")?

A: **No.** The questions about smoking refer only to use of regular cigarettes. The D2d study does not collect data on electronic cigarettes (or 'vaping'), cigars, pipe smoking, or marijuana use.

19.7 INTERVENTION

Q1: If a participant discontinues study pills by his own choice, namely, not because of a safety issue or adverse event where discontinuation is mandated by the protocol, can he re-start study pills if he changes his mind later?

A: **Absolutely!** Re-starting study pills should be actively encouraged by the sites. The success of D2d depends on participant adherence to the intervention, so instances of study pill discontinuation due to "participant decision" must be minimized. *Site staff should inquire at each visit whether the participant can re-start study pills;* if he is able and willing to do so, it can be done at any time, provided safety local labs are obtained first and results meet protocol safety criteria.

Periodically, the Coordinating Center will review with the sites a list of participants who discontinued study pills for personal reasons, as a reminder to revisit the issue with them.

Q2: If a participant forgets to take a study pill one day, should she be instructed to take two pills the next day?

A: In some instances, this may be appropriate. Before instructing the participant to take two pills if she missed the prior day's dose, the RC should discuss this with the site PI to determine if it is appropriate for the particular participant, as some participants may find it confusing or may be at risk of misinterpreting the instruction. The goal should always be to take one pill every day per protocol.

No more than one day should be made up at a time. So, if a participant forgets to bring his bottle on a weeklong vacation, he should not take 7 pills when he returns home.

Strategies to promote adherence to the daily regime should also be utilized, including:

- Providing participants with a weekly pillbox.
- If the participant takes another daily medication, instruct the participant to take the study pill at the same time.
- Inquire about the participant's daily routine and see if taking the study pill can be tagged onto a routine (e.g. drinking juice with breakfast - take pill with the juice).
- If the participant has a challenge remembering to take the pill in the morning, inquire if it would be easier to remember at a different time of the day.

19.8 CONCOMITANT MEDICATIONS AND SUPPLEMENTS

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.

Please see MOP Section 8 for details.

19.14 SAFETY

Q1: Just to be sure that there is no risk, I want to run safety labs in participants who have permanently discontinued study pills. Can I do that?

A: **No.** Safety labs should not be run outside of protocol. Doing so is inconsistent with GCP. If a site runs labs outside of protocol, results of the tests will not be entered in EDC. If such data is entered, the CC will ask sites to delete them.

Q2: We have a participant (Ms. X) who had a vitamin D level drawn by her PCP and was told it was "higher than the upper limit of normal." What should we do next?

A: The key factors to consider are participant safety and protocol fidelity. Below is the suggested plan of action. Communication with the PCP, preferably verbally, is essential.

Please note that D2d does **not** follow vitamin D level (i.e., 25OHD) because there is no well-established association between a specific threshold and efficacy/toxicity. For safety, D2d follows serum calcium levels and urine calcium creatinine levels. Adverse events (hypercalcemia, hypercalciuria, nephrolithiasis) are rare in D2d and no safety signal has been identified by the Safety and Outcomes Subcommittee or DSMB.

Since Ms. X is still taking study pills it is presumed she had normal serum/urinary calcium levels at prior D2d visits.

1. Please make sure Ms. X is not taking more than one D2d pill/day and not taking out-of-study supplements that contain vitamin D.
2. Please bring Ms. X back for an UNCO visit to run serum calcium (analyzed locally) and urine calcium creatinine level (sent to the central lab), *while on D2d study pill.*
3. If serum calcium or urine calcium creatinine is elevated, the algorithms in the Data Safety Monitoring Plan (MOP section 14) should be followed.
4. If the values are normal, the site investigator or study physician should speak with the PCP and discuss/convey to the PCP that a “high” 25OHD level is not considered unsafe and recommend for Ms. X to continue taking the D2d pill. Reassure PCP and Ms. X that safety variables will be followed and abnormal values will be shared with the PCP.
5. If serum calcium and urine calcium creatinine are normal, but Ms. X and/or PCP are still concerned about the “high” 25OHD level and resistant to continuing study pills as prescribed, the D2d study pill may be reduced to 4 times/week (every other day).

The Site PI may elect to check serum/urine calcium level more often than the protocol calls for, e.g. at the next semi-annual visit.

Q3: I'm worried that a participant will forget to tell me some important information at her visit, and I don't want to miss anything. Can I look at a participant's medical records prior to the visit for any recent labs and to see if she had had any adverse events?

A: **No.** Site staff should not be routinely looking in medical records for participants who return for their visits; however, sites can look at the medical records if there is a specific reason to, based on what a participant told them at their visit. With inactive participants where diabetes adjudication is a possibility, the sites can look at the medical record to seek evidence for diagnosis of diabetes.

19.18 PRIMARY OUTCOME

Q1: A participant has discontinued study pills, but agrees to continue in D2d for study outcomes at regularly scheduled encounters. What do I do differently at any of these visits?

A: If a participant has permanently discontinued study pills, all procedures take place except the following:

- Study pill distribution
- Safety labs:
    - Serum calcium and creatinine will not be collected and sent to the local laboratory.
    - Urine for urine calcium creatinine ratio will not be collected or sent to the Central laboratory.

✓ **Note**: Glycemia testing will continue per the protocol schedule.
✓ **Note:** If the participant is participating in the Biorepository, all repository samples including the urine repository sample be collected per the protocol schedule.

Q2: A participant has been diagnosed with diabetes, but will continue taking study pills and be followed for secondary outcomes at regularly scheduled encounters. What do I do differently at any of these visits?

A: After a participant is diagnosed with diabetes, all visits and procedures will continue to take place. The following will not need to be done:

- Food Frequency Questionnaire
- OGTT will not be done (drinking Trutol, and collecting the 30 and 120 minute samples).

✓ ***Note:*** *Fasting blood and urine samples for glycemia measures (FPG and HbA1c) and safety* ***will*** *continue to be done*.

Q3: A participant has gone through the adjudication process because she was taking metformin for pre-diabetes. The COC determines she did not experience new-onset diabetes based on the records provided to them. Does this participant still have to continue doing OGTTs at her Annual Visits?

A: **Yes**. Because this participant has not yet met the study outcome, she should continue to be followed for incident diabetes and should continue to complete all study procedures, including OGTTs.

Q4: We have an "inactive" participant who has missed several visits and we are unable to contact him. We do have permission to use information from his medical record. Can we use EMR information to complete scheduled encounters as non-visit contacts, and enter these in EDC?

A: **No.** Scheduled encounters (including non-visit contacts that are completed when an in-person visit is absolutely not possible) should not be completed in EDC without direct communication with the participant.

- ✓ **However, EMR can and should be used** (provided permission has been obtained) to determine whether an inactive participant has been diagnosed with diabetes outside of the D2d study and/or has lab results that meet the criteria for diabetes. Sites who have access to and permission to use a participant's medical records should actively check for these each time the participant's next D2d encounter is due. These cases can be submitted for adjudication and, if diabetes is confirmed, the Outcomes form in EDC completed.