Manual of Operations (MOP)
Section 22. Interim Supplement

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22.1 OVERVIEW

The D2d interim supplement (D2di) is a short-term extension of D2d to allow participants who **return for the last visit** of the D2d study to continue on the assigned study pills and contribute additional data while D2d results are being analyzed and the D2d Research Group and NIH explore the feasibility of a long-term study extension.

At the last scheduled **visit** of D2d, participants will be asked to continue in D2di. Participants will continue on their assigned study pills and will have non-visit contacts (phone or email) at 3 months and 6 months after last D2d scheduled visit to collect (self-reported) outcomes and safety data.

22.2 D2di IRB

Prior to implementing the D2di short-term extension of the D2d study, the protocol and informed consent must be approved by the site IRB.

22.3 D2di INITIATION AND IMPLEMENTATION

22.3.1 Consent Process

After the D2d end-of-study announcement has been made, participants will return for their next scheduled visit, and this will be considered their *last D2d study scheduled visit (LSV)*. At the initiation of the visit, the site PI or RC will inform or remind the participant that it is the D2d study LSV and invite them to participate in the D2di study. The following points may help to build enthusiasm with participants:

- Acknowledge that the completion of D2d is an important accomplishment and thank participants.
- Because participants have done such a great job in D2d, there ***may*** be an opportunity to conduct an extension study.
- In anticipation of this, we are inviting you to participate in D2di, which will bridge the gap between the two studies.

Participants will be informed of the following in relation to the D2di short-term extension:

- Duration will be about 6 months and there are no study visits.
- Participants will continue taking the study pills as originally assigned.
- Participants will communicate (phone or email) with the site in 3 and 6 months to:
    - Answer questions about changes to their health (assessing for adverse events, diabetes outcomes, cancer outcomes).
    - Assess study pill adherence and receive reminders.
- Participation allows participants to stay engaged in the study and with the research team while the D2d study is being completed and a longer extension is being considered.
- Participants will continue to contribute valuable data.

Participants will be asked if they are interested and willing to continue in D2di and will be presented with the Informed Consent Form (ICF) to review. Once all questions have been answered and concerns addressed, the D2d participant will be asked to sign the written ICF.

Documentation of the consent process must be recorded in the D2d LSV source document. It should include who conducted the discussion with the participant, who was present, any concerns expressed by the participant, and how the concerns were answered or resolved.

22.3.2 Next Steps

After the participant has agreed to D2di participation, re-collect and verify that all contact information is correct. Collect:

- Primary and secondary phone numbers
- Email address
- Mailing address
- Secondary contact and confirm that this individual can be contacted if the Research Coordinator is unable to connect with the participant
- Best days/times and method (e.g. phone, email) to complete contact as this is a non-visit study period
- Records release to share information and receive records from the participant's primary care provider's office

Explain to the participant that if she is diagnosed with diabetes during the D2di period, she must contact the Research Coordinator. The Research Coordinator may need to send a records release to be signed by the participant and returned to the study site.

Participants will be given the D2di Participant Drug Information brochure (see appendix) and will be reminded to notify the research coordinator of any changes in their health or medications between non-visit contacts. In addition, they will be reminded to notify the research coordinator if they have a kidney stone, or are told their blood calcium or serum creatinine level is high.

22.3.3 Safety Laboratory Assessment

All D2di participants who **did not** discontinue study pills during the D2d study will continue on their assigned D2d study pills during D2di. Therefore, it is essential that they have current safety laboratory measures.

If the D2d LSV is an **annual visit:**

- Blood and urine will be collected as usual and entered into the EDC Annual visit form. Fasting safety labs will be sent to the local laboratory for analysis.

If the D2d LSV is a **semi-annual visit** and it has **been 183 days or more** since the participant last had serum calcium and serum creatinine (measured locally) and urine calcium creatinine ratio measured (by Central Laboratory), the following must be collected:

- Blood for serum calcium and creatinine should be drawn with the fasting labs and sent to the local laboratory for analysis (per MOP section 9).

- Urine should be collected and sent to the Central Laboratory for analysis (per MOP section 9). A D2d UNCO kit should be used.
  - EDC: An Unscheduled Confirmatory Visit Folder will be opened and completed to document laboratory collection and results [enter reason for visit=D2di participation]

If the D2d LSV is a semi-annual visit and it has been ***less* than 183 days** since the participant last had serum calcium and serum creatinine (measured locally) and urine calcium creatinine ratio (measured by Central Laboratory), the participant is considered up-to-date on safety measures and no safety labs are needed.

Note: If the participant has stopped the study pills during D2d, he may still participate in D2di and no safety labs are needed.

22.3.4 Study Pill Management

Participants will remain on their assigned D2d study pills. At the D2d LSV, participants will have study pills assigned and dispensed per MOP section 20, with the following exceptions:

1. If participant has permanently discontinued study pills (i.e. the Discontinuation of Study Pills form is completed in EDC), study pills will *not* be restarted, regardless of the reason for discontinuation.
2. Participants who met the D2d diabetes outcome **will** have study pills dispensed at the D2d LSV.
3. Before participants are dispensed study pills, safety laboratory tests should be done in participants who **have not had** safety laboratory testing for *183 days or more* (as above 22.3.1).

Study pill return: After the last encounter during D2di, the participant will be asked to return the remaining study pills. Participants may return the pills in-person or by mail. If he is not sure whether he can return in-person or he prefers to mail them, the site will mail him a pre-paid envelope. The CC will provide sites with the pre-paid envelopes.

22.3.5 Study Encounters

Timing
D2di participants will have phone or email encounters 3 and 6 months after the LSV (when the ICF was signed). A scheduling tool for projecting the target dates for these D2di encounters may be found in the appendix. As with D2d, a plus or minus 2-week window is allowed for each scheduled encounter to occur. For instance, the M03 D2di contact may occur between days 77 and 105 from the LSV *(day 0). Contact attempts should be initiated in the first two weeks of the window.* That way, if the participant is hard to contact, there is sufficient time to complete the encounter and still stay within the window. However, if the participant is not reached during this window, contact attempts should continue.

Activities
At each follow-up contact, participants will be asked questions per MOP sections 4.5 and 21.2. The Research Coordinator will record the information on the source documents and in EDC. If the participant responds positively to any of the questions, additional information will be obtained and

records obtained, as needed, per MOP (Outcome, MOP 18.6; Serious Adverse Event reporting, MOP 14; Non-Diabetes Outcome, MOP 21).

22.3.6 Safety Monitoring

If a participant self-reports having any of the following the study pills will be discontinued:

- kidney stone
- high blood calcium
- high blood creatinine
- high urine calcium creatinine ratio
- low glomerular filtration rate (GFR)

22.3.7 Diabetes Outcome Assessment

Diabetes outcome data will be collected and ascertained by adjudication (see MOP sections 18.5 and 18.6). Note that procedures outlined in MOP sections 18.3.2-6 *will **not** be followed* during D2di.

22.3.8 D2di Participation Flowcharts

The following two figures illustrate the flow of participation in D2di depending upon if the participant's D2d LSV is a Semi-annual or an Annual visit.

Figure 1. D2d LSV, Semi-Annual

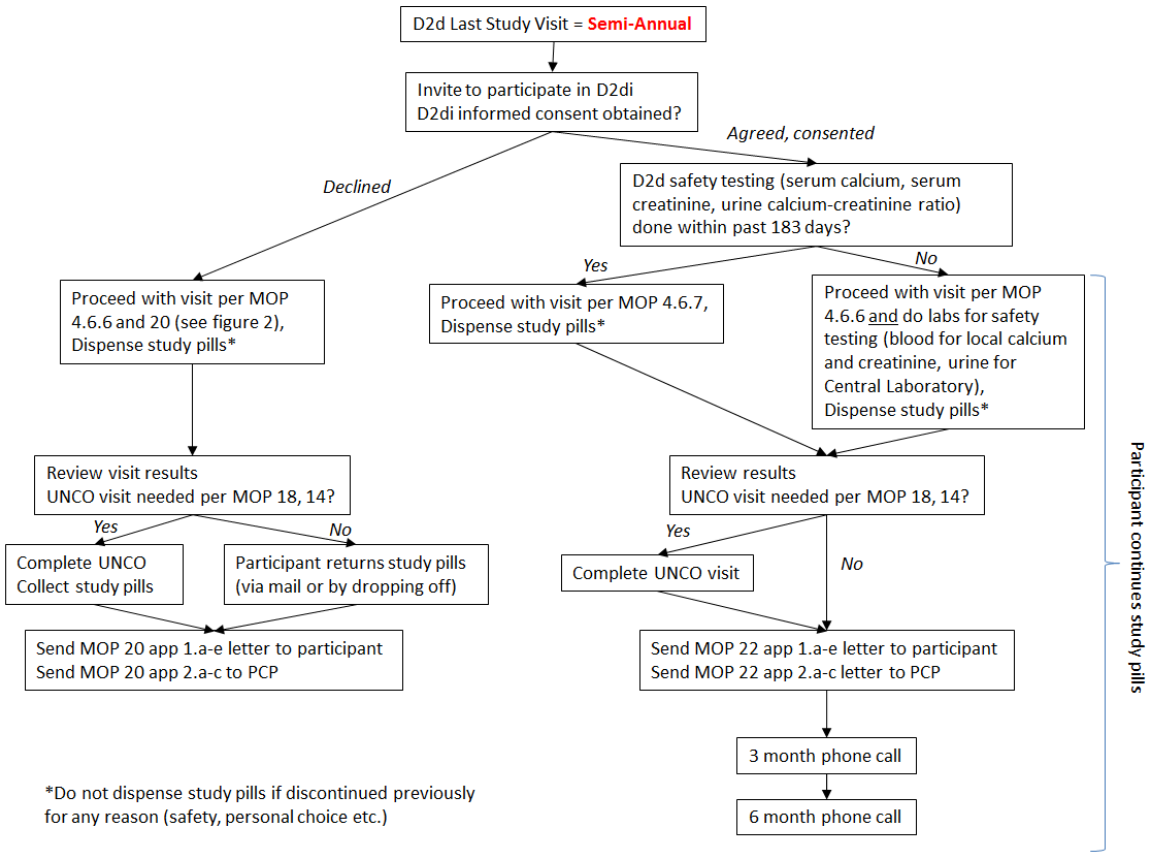
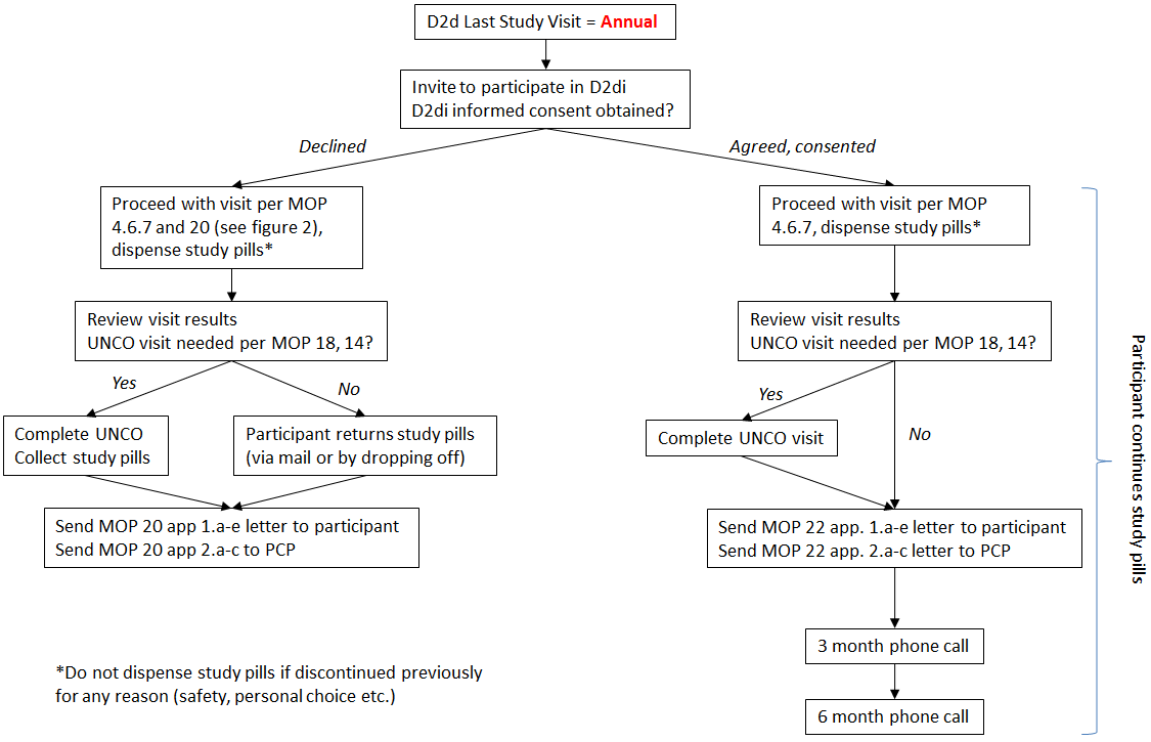


Figure 2. D2d LSV, Annual



22.4 POST D2d LAST SCHEDULED VISIT ACTIVITIES

As soon as possible after the D2d LSV, review the lab test results and communicate the following to the participant (document all communication, including attempts):

22.4.1 Scenario 1: Participant does not need to return for an UNCO visit

A. Notify participant of glycemia results, per usual procedures.
B. Instruct him to continue taking the study pills.
C. Mail "D2di letter to participant" (MOP 22 Appendix 1a-e). The letter will:
    - Inform the participant whether she met the diabetes outcome or not.
    - Describe next steps of the D2di study.
D. Mail "D2di letter to PCP" (Appendix 2a-c). The letter will:
    - Inform the PCP if the participant met the diabetes outcome or not.
    - Thank the PCP for partnering with D2d and let her know that the participant is continuing for an additional 6 months in D2di.
    - Describe the **plan** for communication regarding:
        - Participant's glycemic results (HbA1c, FPG, 2hPG) since joining the D2d study.
        - Participant's study pill assignment (vitamin D or placebo).
        - Summary of overall study results.

22.4.2 Scenario 2: Participant needs to return for an UNCO visit

Reasons: for safety [see MOP section 14] or glycemic testing [see MOP section 18]

A. Notify participant of the need to return for an UNCO visit, per usual procedures.
B. Schedule UNCO as soon as possible and instruct her to continue taking study pills.
C. At the UNCO visit, the research staff will remind the participant to continue taking the D2d study pills and that you will speak in approximately 3 months (from date of D2d LSV)
D. After the UNCO visit:
    - Mail "D2di letter to participant" (Appendix 1a-e, as above).
    - Mail "D2di letter to PCP" (Appendix 2a-c, as above).

22.5 DATA ENTRY

Section to be updated when EDC system finalized.

22.6 APPENDICES

Appendix 1a D2di LSV Letter to Participant No Diabetes Annual Visit

Appendix 1b D2di LSV Letter to Participant No Diabetes Semi-annual Visit

Appendix 1c D2di LSV Letter to Participant New Diabetes Annual Visit

Appendix 1d D2di LSV Letter to Participant New Diabetes Semi-annual Visit

Appendix 1e D2di LSV Letter to Participant Prior Diabetes

Appendix 2a D2di LSV Letter to PCP No Diabetes

Appendix 2b D2di LSV Letter to PCP New Diabetes

Appendix 2c D2di LSV Letter to PCP Prior Diabetes

Appendix 3 D2di Participant Drug Information Brochure

Appendix 4 D2di Scheduling tool