Manual of Operations (MOP)
Section 20. End of Study

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20.1 OVERVIEW

The exact end date for D2d cannot be determined in advance because D2d is an event driven trial; per protocol, the study will initiate end-of-study (EOS) procedures in a timely fashion to ensure the *minimum required number* of diabetes events (n=508) is reached.

⇒ When D2d approaches the minimum required number of diabetes events, the Coordinating Center (CC) will notify the sites to begin implementing the EOS procedures outlined in this MOP section. **The next scheduled visit (i.e., semi-annual or annual) following the notification will serve as the EOS visit.** The timing of the notification will afford ample time for all participants to return for their final scheduled visit and complete the confirmatory (UNCO) testing, if needed.

- Every effort must be made to have all participants return for a final visit no matter their status (active and inactive; whether they have met the diabetes outcome or not; whether they take study pills or not).

20.2 FINAL VISIT TIMING AND SCHEDULING

When D2d is within 2 months of reaching its goal of the minimum required number of diabetes events (based on projections from data from the *prior 6 months*), a study-wide announcement will notify sites that all subsequent scheduled visits (i.e., semi-annual or annual) will be considered the EOS visit.

⇒ All participants must be scheduled for their next (and final) in-person visit within 5 months of the announcement

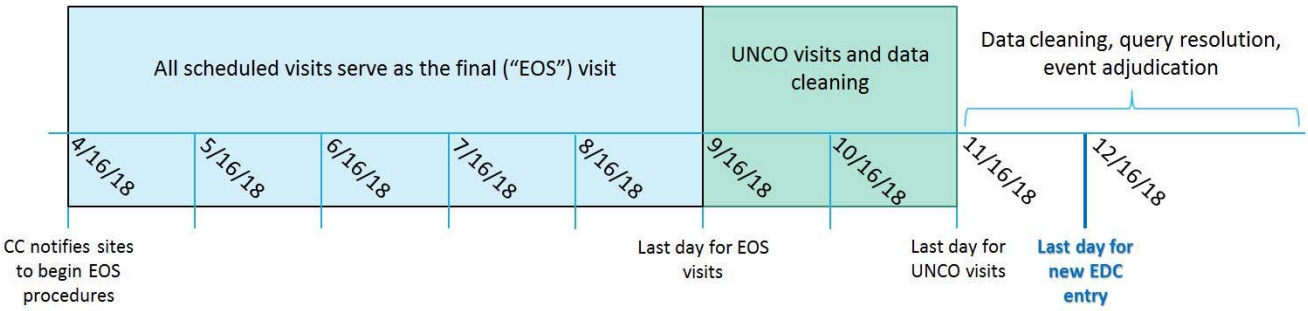
⇒ **IMPORTANT ACTION:** To stay within the timeline, participants who are due for their next in-person visit ~6 months from the announcement *will need to be rescheduled to an earlier time* to ensure timely completion of final/UNCO visits and data entry. For these participants, the interim phone contact should be done earlier to provide an update on end-of-study procedures and re-schedule the next visit, if previously scheduled, to an earlier date. The final visit may fall earlier than the original visit window to allow enough time to receive results from the central laboratory, schedule an UNCO visit (if necessary), and complete data entry promptly.

- The CC will provide a list to each site of all participants' and when their next in-person visit and phone contact (if the phone contact falls prior to the next in-person visit) is due to assist in scheduling and rescheduling participants.

Participants will be informed that their next scheduled visit will serve as the final scheduled visit when scheduling the visit or during the reminder call. Participants will be reminded of the value of their participation and the importance of returning for a final visit.

The last date for ***new*** data entry by sites will be ***exactly 8 months*** after the date the CC notifies the sites to begin implementing the EOS procedures (see figure). Therefore, all visits - including any UNCO visits - must occur as early as possible and sites must enter all data prior to this deadline. The last *date for data to be included in the primary analysis will be* ***exactly 9 months*** after the date the CC notifies the sites to begin implementing the EOS procedures.

Figure 1. Timeline of End-of-Study procedures.



20.3 INACTIVE PARTICIPANTS

Every effort should be made to have all "*inactive"* participants return for a final visit. Efforts to contact inactive participants must be documented in the source documents.

For participants who do not return for a final visit or do not have non-visit contact, sites should document in the source documents why the visit was not completed.

⇒ The *"EOS letter to participant no-encounter"* (Appendix 1f) should be sent to these participants after the *"Last day for site EDC entry"* date (see figure 1).

20.4 FINAL VISIT ACTIVITIES & PARTICIPANT NOTIFICATION

The final visit will include **all** activities that occur at the scheduled semi-annual or annual visit (refer to MOP sections 4.6.6 and 4.6.7), including collection of data for non-diabetes outcomes.

20.4.1 Study Pills

The following *modifications* are made in relation to **study pill return and adherence assessment (see Figure 2)**.

Note: if the participant has been inactive and did not have study pills dispensed at the last visit, do not dispense pills at EOS visit. Contact the CC to discuss these cases.

- If the participant has **already met** the diabetes outcome:
  - Participant returns the pill bottle.
  - The research staff (coordinator, nurse, or designee) will count the number of pills remaining and the number will be entered in EDC.
  - No new pills will be dispensed and no additional visits are required to confirm the diagnosis of diabetes. *However, an UNCO visit may be required to confirm an abnormal safety laboratory result.*

- If the participant has **not met** the diabetes outcome:
  - Participant returns the pill bottle.
  - The research staff (coordinator, nurse, or designee) will count the number of pills remaining and the number will be entered in EDC.

- The research staff will assign a new pill bottle and the participant is instructed to continue taking the pills until the research staff reports to her the results of the EOS visit (glycemia and safety testing) and whether an UNCO visit is needed.
- During the visit, site staff discusses with the participant the method of returning study pills if an UNCO visit is not required. Options include: 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, provide him with a pre-paid envelope. *The CC will provide sites with the mailers.*

As done throughout the study, inform the participant that you will communicate with him regarding the results of his lab test (and need for UNCO visit) in approximately one week.

At the conclusion of the visit:

- Thank the participant for her contributions to D2d
- Remind her that one more visit (UNCO) may be required (to confirm diagnosis of diabetes or for safety labs).
- Inform her that the letter with the visit results will describe the next steps, which may include a follow-up D2d study.

20.5 POST FINAL VISIT ACTIVITIES

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

20.5.1 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 stop taking the study pills and return them to the Coordinating Center as previously discussed (either by bringing him back or using the pre-paid envelope).
    - Upon receipt of the pills, the research staff document in the source documents that study pills were returned.
C. Mail "EOS letter to participant" (Appendix 1a-e). The letter will:
    - Inform the participant whether she met the diabetes outcome or not.
    - If applicable, remind participant to return the study pills.
    - Describe next steps.
D. Mail "EOS 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.
    - Describe the **plan** for communication regarding:
        - Participant's glycemic results (HbA1c, FPG, and 2hPG) since joining the study.
        - Participant's study pill assignment (vitamin D or placebo).
        - Summary of overall study results.

20.5.2 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. Remind her to return the study pills at the UNCO visit.
C. At the UNCO visit
   - The research staff will count the number of pills returned and the number will be entered in EDC using an UNCO visit folder.
   - No new pills are dispensed and no additional visits are required.
D. After the UNCO visit:
   - Mail "EOS letter to participant" (Appendix 1a-e, as above).
   - Mail "EOS letter to PCP (Appendix 2a-c, as above).

20.6 COMMUNICATING D2d STUDY PILL ASSIGNMENT AND RESULTS TO PARTICIPANTS

After the D2d study database is locked for the primary endpoint, unmasking of the study pill assignment will occur, and sites will be notified of the participant assignments. Participants, in-turn, should be notified of what they were taking (vitamin D or placebo). The CC will instruct site staff to:

1. Mail **"**EOS letter to participant un-blinding and glycemic results" (*Appendix 3a*). It should be sent to all participants including those who did not return for an EOS visit or withdrew participation. The letter will:
   - Thank participants for their contributions to D2d.
   - Provide participant's glycemic (HbA1c, FPG, and 2hPG) results since joining the study.
   - Disclose study pill assignment (vitamin D or placebo).
   - Include a reminder about the D2d study registry (and include the registry information).

2. Mail **"**EOS cover letter to PCP" (*Appendix 3b).* This letter should be sent to the PCPs of all participants including those who did not return for an EOS visit. The participant's **"**EOS letter to participant un-blinding and glycemic results" should be included with this letter.

Note: the CC will provide site staff with an Excel file listing each participant that provides the participants' study pill assignments and all glycemia testing results. The site should have prepared a database of participant IDs, names, and contact information (see sample in Appendix 3c).

20.7 DATA ENTRY

It is essential that all data collected at the final encounter (EOS visit and UNCO, if needed) be entered *as soon as possible after the encounter is completed.* Detailed information on how to complete the data entry is below.

20.7.1 Study Pill EDC documentation

Use the following scenarios for guidance, contacting the Coordinating Center with any questions.

20.7.1.1 Participant completes EOS visit

20.7.1.1.a Scenario: participant is on study pills, but has already met the diabetes outcome at the time of the EOS visit

Study Pill Distribution eCRF is completed as normal, except for the following:

Note: pills are not *dispensed in this scenario*

Data field	Data entry
Was a bottle of study pills assigned at this visit?	Select "No"
If No, explain:	Enter "EOS visit"

Study Pill Discontinuation eCRF

- Enter the Study Pill Discontinuation date as the EOS visit date.
  - Select "Completed study per protocol."

20.7.1.1.b Scenario: participant is on study pills and has not met the diabetes outcome at the time of the EOS visit and requires and returns for a Confirmatory Visit

Study Pill Distribution eCRF at the scheduled visit is completed as normal

Note: pills are *dispensed in this scenario*

Study Pill Return – documented in the UNCO folder – completed as normal with pill count

Data field	Data entry
Was a bottle of study pills assigned at this visit?	Select "No"
If No, explain:	Enter "EOS"

Study Pill Discontinuation eCRF

Enter the Study Pill Discontinuation date as the UNCO visit date.

- Select "Completed study per protocol."

20.7.1.1.c Scenario: participant is on study pills and has not met the diabetes outcome at the time of the EOS visit and does not require a Confirmatory Visit

Study Pill Distribution eCRF at the scheduled visit is completed as normal

Note: pills are *dispensed in this scenario*

Study Pill Discontinuation eCRF

- After review of the results and determination that an UNCO is not required, the participant is contacted to inform him of the results and ask him to stop taking the study pills. The Study Pill Discontinuation date is the date the coordinator completed this contact.
  - Select "Completed study per protocol."

20.7.1.2 Participant does not complete EOS visit

- Enter the Study Pill Discontinuation date as the date of the last scheduled encounter as described in 20.7.2. This will be the same date as the Study Completion date.
  - Select "End of Study not done"

20.7.2 Study Completion e-CRF

The Study Completion e-CRF will be completed after all laboratory result e-mails have been received and data entered into the visit e-CRF as detailed below. The "study completion" date is the date of the *last encounter* (EOS or UNCO).

Date of study completion or early withdrawal:

For participants who have an EOS encounter, enter the "study completion date" as:

- The date of the EOS visit (scheduled visit or non-visit contact for participants absolutely unable to come for a last visit) or
- The date of the post-EOS UNCO visit, if completed.

For participants who do not have an EOS encounter, enter the "study completion date" as:

- The date consent was withdrawn,
- The date of death, or
- The date of *last* contact when participant data was entered into EDC. Specifically:
    - In-person visit [scheduled or UNCO]
    - Non-visit contact
    - Scheduled interim phone call
    - Non-scheduled contact [i.e., reporting of AE]

Did participant complete the study per protocol?

Yes = All participants who have a study visit or non-visit contact completed after the CC notifies sites to begin EOS procedures or died prior the last scheduled study visit (see Figure 1).

No = If participant does not have an EOS encounter (visit or non-visit contact) after the CC notifies sites to begin EOS procedures (see Figure 1).

If no, select the primary reason for withdrawal:

Select from the drop-down menu:

Withdrew consent prior to baseline: Do not select as this option is not applicable
Withdrew consent prior to randomization: Do not select as this option is not applicable
Withdrew consent after randomization: Select if the participant withdrew consent
Adverse event: Select **only** if the investigator determines that due to an adverse event, it is not in the best interest of the participant to continue in the study.
Did not complete End of Study encounter: Select if all other options do not apply.

20.7.3 Other Scenarios

If there are other scenarios not covered in sections 20.7.1 and 20.7.2, please contact the Coordinating Center for guidance.

20.8 ADDITIONAL EOS DATA COLLECTION

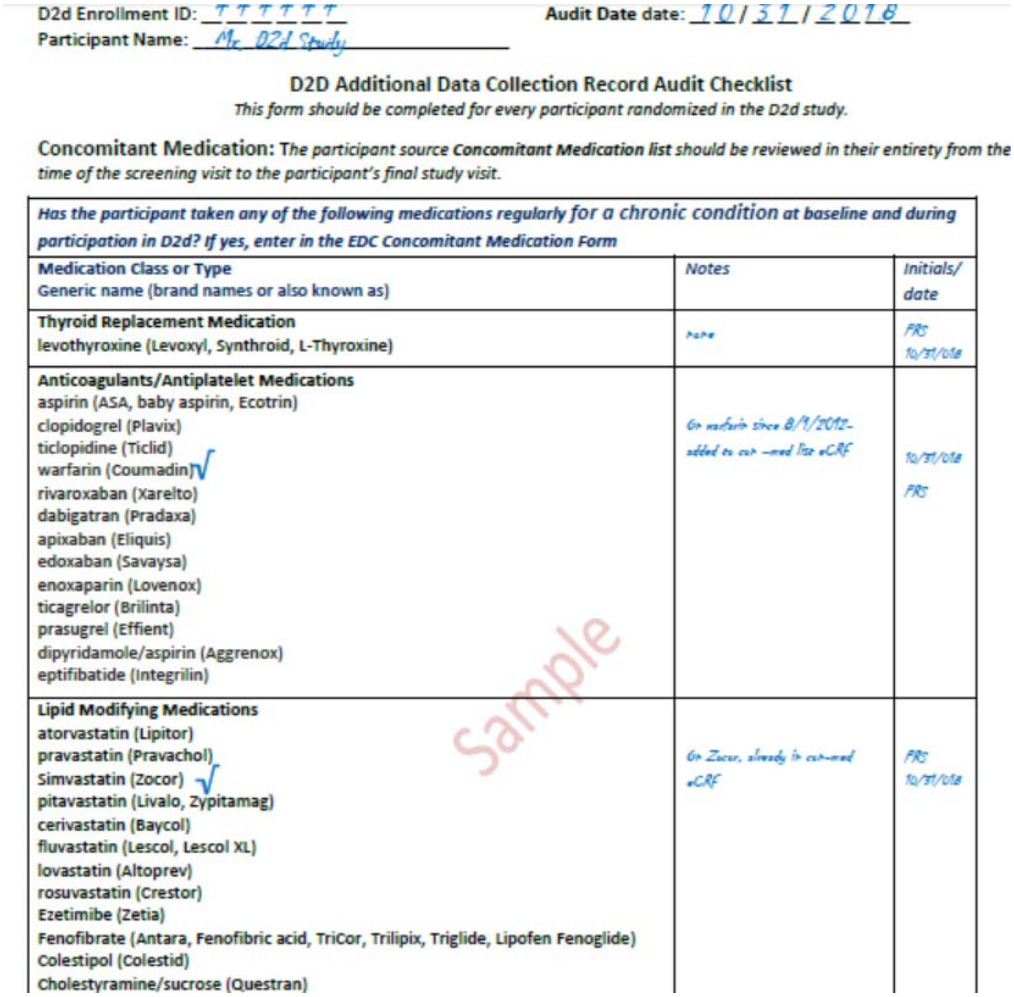
As the only large US-based prediabetes cohort enrolled following current American Diabetes Association prediabetes criteria, it is important for the D2d Study to ensure the data collected is thorough and will be able to answer relevant questions beyond the primary outcome. There is particular interest in cardiovascular outcomes. Therefore, the Steering Committee has decided it is necessary to collect additional concomitant medications, especially those related to thyroid function and cardiovascular actions or indications.

In the past, sites were instructed to enter into EDC *only* medications prescribed for one of the following indications: hypertension, hyperlipidemia, osteoporosis, weight loss, and diabetes. **We are now requesting that use of any of the medications listed in appendix 4, regardless of indication, be added to the EDC Concomitant Medication e-CRF.** We expect this information to be easily retrievable from each participant's Concomitant Medications/Supplements Source Document which has been kept up-to-date throughout their participation.

Note: Only medications taken during the period from Screening to the Study Completion should be entered into EDC.

The following tools have been developed to assist you in completing this audit of the records:

Appendix 4, Additional Data Record Audit Form: This form should be used to document completion of the audit and entry of the medications into Concomitant Medication e-CRF.



D2d Enrollment ID: TTTTTT Audit Date date: 10/31/2018
Participant Name: Mr. D2d Study

D2D Additional Data Collection Record Audit Checklist

This form should be completed for every participant randomized in the D2d study.

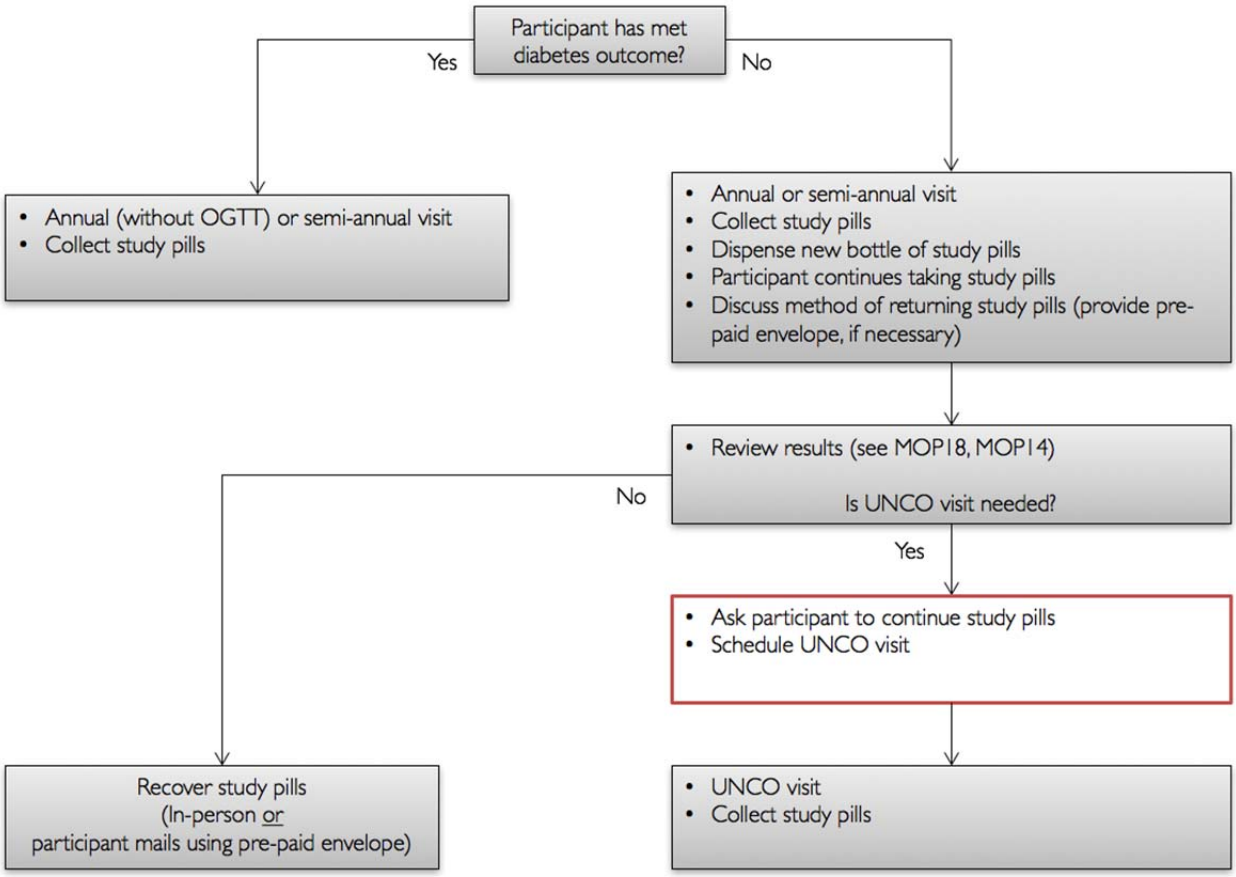
Concomitant Medication: *The participant source **Concomitant Medication list** should be reviewed in their entirety from the time of the screening visit to the participant's final study visit.*

Has the participant taken any of the following medications regularly for a chronic condition at baseline and during participation in D2d? If yes, enter in the EDC Concomitant Medication Form		
Medication Class or Type Generic name (brand names or also known as)	*Notes*	*Initials/ date*
Thyroid Replacement Medication levothyroxine (Levoxyl, Synthroid, L-Thyroxine)	none	FRS 10/31/018
Anticoagulants/Antiplatelet Medications aspirin (ASA, baby aspirin, Ecotrin) clopidogrel (Plavix) ticlopidine (Ticlid) warfarin (Coumadin) √ rivaroxaban (Xarelto) dabigatran (Pradaxa) apixaban (Eliquis) edoxaban (Savaysa) enoxaparin (Lovenox) ticagrelor (Brilinta) prasugrel (Effient) dipyridamole/aspirin (Aggrenox) eptifibatide (Integrilin)	Gr warfarin since 8/1/2012- added to cur -med list eCRF	10/31/018 FRS
Lipid Modifying Medications atorvastatin (Lipitor) pravastatin (Pravachol) Simvastatin (Zocor) √ pitavastatin (Livalo, Zypitamag) cerivastatin (Baycol) fluvastatin (Lescol, Lescol XL) lovastatin (Altoprev) rosuvastatin (Crestor) Ezetimibe (Zetia) Fenofibrate (Antara, Fenofibric acid, TriCor, Trilipix, Triglide, Lipofen Fenoglide) Colestipol (Colestid) Cholestyramine/sucrose (Questran)	Gr Zocor, already in cur-med eCRF	FRS 10/31/018

Sample

Appendix 5, Excel File of Medications of Interest: This Excel file may be saved on your computer and used during the source document review to search from the medications of interest by generic or brand name.

Figure 2. End-of-Study (EOS) Algorithm. This algorithm will be followed at the last scheduled semi-annual or annual visit, which will also serve as the final ("EOS") visit.



20.9 APPENDICES

Appendix 1a EOS Letter to Participant No Diabetes Annual Visit

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

Appendix 1c EOS Letter to Participant New Diabetes Annual Visit

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

Appendix 1e EOS Letter to Participant Prior Diabetes

Appendix 1f EOS Letter to Participant No Encounter

Appendix 2a EOS Letter to PCP No Diabetes

Appendix 2b EOS Letter to PCP New Diabetes

Appendix 2c EOS Letter to Participant Prior Diabetes

Appendix 3a EOS Letter to Participant Un-blinding and Glycemia Results

Appendix 3b EOS Cover Letter to PCP

Appendix 3c Sample Participant Contact Information Excel File

Appendix 4 Additional Data Record Audit Form (example and blank form)

Appendix 5 Excel File of Medications of Interest