Manual of Operations (MOP)
Section 4. Study Visit Schedule and Overview

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4.1 OVERVIEW

Recruitment will take place over a 2-year period. If targets are met within the first 2 years, sites will be notified and recruitment activities will cease. It is anticipated that participants who are randomized early will be followed for approximately 4 years for development of the primary outcome, diabetes. Because D2d is an event-driven trial, follow up periods are estimates and will depend on rates of enrollment and retention. On average, participants will be followed for approximately 3 years. Because of the study design, the exact study end date also cannot be determined in advance. However, after approximately 508 participants have been diagnosed with diabetes, the Coordinating Center (CC) will distribute a formal announcement informing the sites that the required number of outcome events has been reached and the end-of-study visit should be scheduled.

4.2 TIMING OF VISITS

4.2.1 Time of Day

All study visits, except the randomization visit, require the participant to come to the clinical site in the morning after **fasting** overnight for a minimum of 8 hours. Participants must not engage in vigorous exercise for 24 hours before visits.

- ✓ If a participant ate the morning of the visit, the entire visit should be rescheduled. All data entered in EDC for a specific visit must be collected the same date, otherwise, there would be confusion with the visit and blood collection dates and laboratory results would not be uploaded correctly. If there are extenuating circumstances, please contact the Coordinating Center for guidance.
- ✓ If a participant consistently works during an evening or a night shift and typically sleeps into late morning or early afternoon, the visit may be scheduled in the early afternoon. *It is important that all subsequent visits follow this same pattern and be scheduled in the early afternoon.*

4.2.2 Day of the Week

Participants can be seen any day of the week, including weekends. Site should be flexible and try to accommodate the participant by scheduling visits on days that are convenient for the participant with one exception noted below.

⇒ **NOTE:** The refrigerated HbA1c specimen (whole blood) must be shipped within 5 days of collection, and specimens can only be shipped to the Central Lab on Monday, Tuesday and Wednesday. The Coordinating Center will distribute special shipping instructions for weeks that include a holiday. If you have questions regarding ship dates please contact the Coordinating Center (refer to MOP section 9 for contact information).

4.3 VISIT WINDOW

A plus or minus 2-week window is allowed for each scheduled visit to occur. For instance, the M03 visit (month 3) may occur between days 77 and 105 from randomization *(day 0). An effort should be made to schedule the visit in the first two weeks of the window.* That way, if the participant needs to reschedule, there is sufficient time to do so and still stay within the window.

Visits can be scheduled outside of the window for two reasons:

1. If the participant experienced a condition that could affect glucose tolerance (e.g. infection, whole blood transfusion or whole blood donation [see MOP section 11.7 for a list]) in the 8 weeks prior to the scheduled visit.
2. Compelling social circumstances (e.g. participant is on extended vacation).

The reason for the visit occurring outside of the window must be documented in the EDC system. If a visit occurs outside of the visit window, all remaining follow-up visits will remain as previously scheduled. Please see Table 4.2 for time periods allowed for scheduling visits outside of the 2-week window.

Table 4.1 Visit windows

Visit	Target Day*	Visit Window*
Screening (SCR)		-49 to -7
Baseline (BAS)		-21 to -5
Randomization (RAN)	0	0
M03	91	77-105
M06	183	169-197
M09 (phone call)	274	260-288
M12	365	351-379
M15 (phone call)	457	443-471
M18	548	534-562
M21 (phone call)	639	625-653
M24	731	717-745
M27 (phone call)	822	808-836
M30	913	899-927
M33 (phone call)	1004	990-1018
M36	1096	1082-1110
M39 (phone call)	1187	1173-1201
M42	1278	1264-1292
M45 (phone call)	1370	1356-1384
M48	1461	1447-1475
EOS (end of study)	Within 12 weeks of announcement of D2d closeout	
EOSP (phone call)	6 weeks after EOS	4-8 weeks after EOS

*Days from randomization date.

4.4 VISIT REMINDERS

At the first contact, participants will state their preferred method of communication (email, phone, text, social media, etc.) with the research staff. If e-mail (or other electronic method) is agreed upon as the preferred method of communication, participants should be instructed to respond to the message, thereby letting the research staff know that the message was received.

Research staff will email (or call) participants, approximately one week prior to a scheduled visit to remind them of the visit and provide relevant information and instructions:

- Day and time of the visit.
- Procedures planned for the visit (e.g. fasting blood collection, urine collection).
- Need to fast for at least 8 hours overnight.
- Need to abstain from vigorous exercise for 24 hours prior to the visit.
- Need to take the study pill and morning medications on the morning of the visit with water.
- Need to bring bottles with study pills.
- Need to bring all other medications (prescription, over-the-counter and supplements).
- Need to wear comfortable clothes with loose sleeves, as blood will be drawn (all visits except Randomization).
- OGTT-specific instructions (relevant to the baseline, annual, and some confirmatory visits; see MOP sections 9.6.1 and 11).

⇒ During these reminders, participants will be asked if they have experienced any condition in the prior 8 weeks that may affect glucose tolerance (e.g. infection, whole blood transfusion or whole blood donation) and reschedule the visit if necessary.

✓ Donation of platelets does not require rescheduling the visit.

✓ ***Visits may be postponed for up to 8 weeks if a temporary concomitant condition exists that would affect glucose tolerance*** (e.g. whole blood transfusion, use of glucocorticoids for an extended period)***.*** The reason for the visit occurring outside of the window must be documented in the EDC system. If a visit occurs outside of the visit window, all remaining follow-up visits will remain as previously scheduled.

4.5 SCHEDULED CONTACT IN-BETWEEN VISITS

Interim visit phone contact (M09, M15, etc.) is scheduled between each 6-month follow-up visit commencing after the M06 visit. The objectives of the scheduled phone contacts are to: 1) promote participant retention, 2) assess and encourage compliance with the study pill regime, 3) determine if the participant has had any adverse events, including any visits to his physicians, and 4) remind the participant to contact the study site prior to starting any new medications, especially if she has been diagnosed with diabetes outside of the study or prescribed a diabetes medication (e.g. metformin).

An end-of-study phone contact (EOSP) will take place approximately 6 weeks after the end-of-study visit to determine if the participant has had any adverse events.

See MOP section 13 for a phone contact source document worksheet.

At the screening visit, when complete contact information is collected, participants will be asked for the best time and phone number to be reached by research staff. Alternative phone numbers will be requested including work phone, mobile phone, and phone number of alternative contact (next of kin or emergency contact). If participants express no preference for time of day, phone calls should be first attempted during daytime hours. However, if staff is unable to reach the participant during daytime hours, calls should be made during the early evening. The participant should be asked for any changes in contact information at every visit, especially if the participant has moved, changed jobs, or been difficult to contact.

All attempts to contact participants will be recorded in the contact follow-up log e-CRF in EDC. See hints for contacting participants in MOP section 4.9.4. After contact is made, information obtained during the phone call will be entered into the telephone contact e-CRF (see MOP section 15).

The preferred method of communication for the scheduled contact in-between visits is a phone call. However, occasionally, in lieu of a phone call, scheduled in-between visits contacts may be accomplished by email for participants who are difficult to reach by phone, to meet the same objectives and collect the same information as during the phone call. Participants who report adverse events or other issues will then be contacted by phone. All email communication must be included in the participant's source document.

4.6 SCHEDULED STUDY VISITS

First impressions become lasting impressions, which can influence participant retention and adherence to the study schedule and intervention. Therefore, efforts must be made to promote a pleasant visit experience at the screening and all other visits. Below is a list of items to consider:

- Access to the clinical site:
  - Is the clinical site easy to find? Consider sending the potential participant a map with the clinic location circled. On the study's web site, several sites also provide directions to the clinical site (e.g. http://www.d2dstudy.org/tufts/) or a link for obtaining directions (e.g. http://www.d2dstudy.org/kansas/)
  - Transportation and parking: provide the participant as much information as possible to make arriving at the clinical site as simple as possible.
  - Availability of help: Be available by phone if a participant is lost and needs directions or is running late.
- Prior to the visit
  - Provide the participant with a realistic estimate of how long a visit will take. Do not underestimate visit time.
  - Consider other activities at the clinical site when scheduling participant visits. For example, do not have a participant wait to start the OGTT because the nurse who inserts saline locks is covering inpatient units.
  - Make sure the front desk knows the participant is coming and that she will be fasting and that the visit should begin on time.
- During the visit
  - Be prompt; be at the site before the participant arrives.
  - Provide the participant with an orientation to the clinic, and introduce him to the team members.
  - Remind all staff to be sensitive to the discomfort related to fasting and make sure others do not eat or drink in the participant's presence.
- Between visits
  - Return phone calls as soon as possible, preferably the same day.
  - Work with participants to reschedule appointments.
  - Show support and care by providing additional encouragement and support as needed with between visit follow-up contacts.

Below is a detailed description of each visit. All study visits, except the Randomization visit, are conducted in the morning while the participant is fasting for 8 hours and abstaining from vigorous exercise for 24 hours. Additional details on the measurements and assessments to be made during each visit are found in MOP sections 9, 10, and 11.

4.6.1 Screening Visit [SCR]

Each site will develop its own strategy for determining how participants will be pre-screened and invited to the screening visit (see MOP section 6). The goals of the screening visit are to complete the informed consent process and determine whether the participant meets the screening eligibility criteria. Safety labs (e.g. serum calcium, creatinine) are analyzed at the local site laboratory. Glycemia labs (i.e. FPG, HbA1c) can be analyzed either at the local site laboratory or the Central Laboratory.

⇒ **Sites are strongly encouraged to use the Central Laboratory for the analysis of HbA1c and FPG.**

✓ Please see MOP section 6 for activities that take place during the screening visit.

Volunteers will be invited to the baseline visit, if they meet the following:

1. Fasting Plasma Glucose (FPG) and Hemoglobin A1c (HbA1c) results are within range, as defined by site-specific criteria (see MOP section 6).
2. All non-glycemic inclusion criteria and none of the exclusion criteria.

4.6.2 Baseline Visit [BAS]

The baseline visit must occur after results of the screening laboratory tests (done at the local lab) have been reviewed by the investigator. The goal of the baseline visit is to confirm eligibility based on the glycemic criteria analyzed at the central laboratory and collect baseline data, prior to randomization.

⇒ **The baseline visit should take place ideally within 4 weeks, but no later than 6 weeks, of the screening visit**

Please see section 4.6.2.2 for the option of doing a combined Screening/Baseline visit.

During the baseline visit, the following will occur:

- **Interim medical history and adverse event review.** Inquire if there have been any changes in the participant's health, including any contact with health care system (e.g. physicians, hospitals) since the screening visit. Details should be collected on positive responses including: description of the change in health; reason for contact with the health care system; the status or outcome; and changes made to his treatments.
- **Complete physical examination.** Perform a complete physical examination. This task is completed by staff member qualified to perform a physical examination (e.g. physician investigator, nurse practitioner). Special attention should be paid to findings that might meet an exclusion criterion. Alternatively, the physical examination can be completed at the Randomization visit **before** randomization takes place in SPIRS.
- **Review of concomitant medications and supplements.** Review all prescribed medications, over the counter medications and supplements (see MOP section 8). Note any changes from the screening visit and the reason for the change. Special attention should be paid to dietary supplement use, to ensure that the participant understands the calcium and vitamin D supplements restrictions and the rationale behind the restrictions.
  ⇒ *Please remind the participant to call the Research Coordinator or designee to discuss any changes in medications between study visits.*
- **Physical Measurements (vital signs).** Vital signs (height, weight, blood pressure and heart rate) and waist circumference (see MOP section 11). Please note that waist circumference is measured at the baseline visit only.
- **Questionnaires.** Food Frequency Questionnaire (FFQ) and International Physical Activity Questionnaire (IPAQ) (see MOP section 10).
- **Lifestyle counseling.** All participants will receive information on pre-diabetes and diabetes prevention at baseline (see MOP section 12). Participants will be provided with the National Diabetes and Education Program booklet "Small Steps Big Rewards."

- **Laboratory specimen collection, including OGTT.** Blood and urine are collected and shipped to the Central Laboratory for analysis and storage. See MOP sections 9 and 11 for detailed instructions.
- **Post-visit activities:** Review lab results as soon as they become available and, if participant is eligible, send letter to PCP (see MOP 17, appendix 3a), and schedule randomization visit.

4.6.2.1 Repeating the Baseline Visit

In very specific circumstances, the baseline visit may be repeated. This can be done if one measure is within the eligibility range and a second baseline glycemia measure, is off by a small margin (defined as margin of error for FPG ± 3 mg/dL, HbA1c ± 0.1%, or 2hPG ± 5 mg/dL). The **entire baseline visit** (FPG, HbA1c, 2hPG, and urine calcium creatinine) should be repeated and may be repeated once. Repeat testing should be done within a short period to ensure that the repeat baseline visit remains within the 7-week window between screening and randomization.

⇒ **NOTE:** The site must notify the CC of its intent to repeat a baseline visit at least 2 business days prior to the repeat visit by sending the following information to the CC via email (d2d@tuftsmedicalcenter.org):

Email subject line: D2d (insert site name) repeat baseline visit for (insert enrollment ID)
Email content: Scheduled repeat baseline visit date: (insert date)

At the start of the repeat baseline visit, the participant will be asked if he has had any changes in his health or medication/supplements since the prior baseline visit and the following will be updated:

1. Vital signs, including waist circumference
2. Collection of baseline visit labs, including those for the repository (if Repository Consent provided), per MOP section 9 using a new BAS/Annual collection kit.
3. Physical examination, as needed, if the participant reports changes to health.

✓ The International Physical Activity Questionnaire and the Food Frequency Questionnaire do not need to be repeated.
✓ The physical examination does not need to be repeated unless the participant reports changes to health.

The reason for the repeat baseline visit and information collected during the visit will be documented in the source documents. New data will be entered into the EDC baseline visit eCRF as follows:

1. Visit Date form – change to the new visit date
2. Vital Signs form – replace all vital signs with the new data
3. Central Laboratory form – replace all data
4. Baseline Visit Other Data – make changes as needed
5. **Post-visit activities:** Review lab results as soon as they become available and, if participant is eligible, send letter to PCP (see MOP 17, appendix 3a), and schedule randomization visit.

4.6.2.2 Combined Screening and Baseline Visit

If a potential participant has glycemic tests (FPG and HbA1c) measured outside of D2d at the local laboratory, and the results meet the screening criteria, he may proceed directly to a combined screening/baseline visit, as long as the combined visit occurs within 6 weeks of these tests. During this combined visit, all screening procedures will take place, including other blood tests that have not been done by the local laboratory within the last 6 weeks. Complete the procedures in the order

outlined for each visit such that screening eligibility is ascertained prior to continuing to baseline procedures.

Please see MOP 6 for details.

4.6.3 Diabetes diagnosed at the Screening or Baseline visit

Given their high-risk profile, it is expected that some individuals will be found to have previously unrecognized hyperglycemia in the diabetes range (i.e., HbA1c ≥ 6.5%, FPG ≥ 126 mg/dL and/or 2hPG ≥ 200 mg/dL) at the screening or baseline visits. People who meet the diabetes criteria at the baseline visit are ineligible to participate in D2d and they will receive an informational letter (MOP section 6) indicating the possibility that they may have diabetes and should be seen by their primary care provider to repeat testing for diabetes. Participants will be mailed copies of their laboratory results to share with their primary care provider, but study personnel will not participate in any further evaluation or treatment of participants who are found to have diabetes at baseline.

⇒ Because there is less than perfect correlation between glycemic tests done at the screening (by the local laboratory) and baseline (done by the Central Laboratory) visit, it is recommended that information on glycemic results is shared with participants and their physicians, as follows, to minimize any confusion with trying to reconcile results from the screening and baseline visits.

- ✓ If a participant does not qualify after the screening visit, the glycemic tests at the local laboratory are shared with participants and their providers.
- ✓ If the volunteer completes the baseline visit, only the glycemic tests done at the Central Laboratory are shared with volunteers and their providers.

4.6.4 Randomization Visit [RAN]

The randomization visit should occur as soon as possible, but always within 3 weeks of the baseline visit.

⇒ Prior to the randomization visit, the PI must review and confirm the participant's eligibility by reviewing Screening Inclusion Exclusion Criteria e-CRF and the Baseline Inclusion Exclusion Criteria e-CRF and then **'sign and save'** each form in EDC (see MOP section 15 for detailed instructions).

⇒ The randomization visit is considered Day 0 for the study.

During this short visit, which can occur any time of the day, participants will be randomized and provided with study pills.

- Upon participant's arrival, inquire about any adverse events since the baseline visit.
- Physical examination (if not done earlier) – must be completed **before** randomization in SPIRS.
- After the participant's arrival, the research pharmacist, research coordinator, or designee should log into the Drug Distribution system (SPIRS) and randomize the participant (see MOP section 7).
- A 6-month supply of the assigned study pills will be dispensed to the participant.

- The Participant Information pamphlet is provided to the participant and reviewed by research staff.
- The participant is given a printout of his visit schedule. The participant scheduling tool is available in the appendix.Letter to Randomized Participant (see MOP section 17 for template) is provided to the participant at the randomization visit, as a formal "welcome" to D2d.

⇒ **Post-visit activities:** If the Letter to Physician (see MOP section 17 for template) was not sent prior to randomization then a letter will be sent to the participant's primary care provider (PCP), and other physicians on record post-randomization (MOP section 17, Appendix), informing the clinician of her patient's participation in the study and requesting the clinician to contact the study staff if: (1) she makes the diagnosis of diabetes, (2) prior to starting any diabetes medications, (3) if the participant reports adverse events**. This letter is very important.**

  - The Provider Pamphlet (see MOP section 17) should be sent with the Letter to Physician.

NOTE: The randomization visit may occur off site if it is more convenient for the participant and permitted by the site policies. If the visit occurs off site, a phone call should be conducted within 24 hours prior to the visit to inquire about any adverse events since the baseline visit and to ensure that nothing has changed that would result in the participant not being eligible for randomization. Prior to meeting the participant, the research coordinator should log into SPIRS and randomize the participant (see MOP section 7). All other randomize procedures must be conducted as described above.

4.6.5 Month 3 Visit [M03]

The M03 visit is scheduled 3 months after the randomization visit. The goals of this visit are to encourage participant compliance and perform safety assessments. During this visit, the following will occur:

- **Interim medical history and adverse event review.** See MOP section 4.6.2
- **Symptom-directed physical examination.** If, during the medical history, the participant reports any changes in their health, investigator judgment should be used to determine if a physical exam directed by the reported symptoms is needed.
- **Review of concomitant medications and supplements.** See MOP sections 4.6.2 and 8.
- **Physical Measurements (vital signs).** Vital signs (height, weight, blood pressure and heart rate) (see MOP Section 11). Waist circumference will not be measured at M03 visit.
- **Laboratory specimen collection.** Blood (analyzed locally) and urine (sent to the Central Laboratory) will be collected for analysis and storage. See MOP section 9 for detailed instructions.
- **Post-visit activities:** Review lab results as soon as they become available and, if indicated, schedule a confirmatory visit (see MOP section 14, Appendix for safety algorithms).

4.6.6 Semi-Annual Visits [M06, M18, M30 and M42]

Semi-annual visits are scheduled at 6, 18, 30 and 42 months after the randomization visit. The goals of these visits are to encourage participant compliance, perform safety assessments, and provide the participant with a new 6-month supply of study pills. The following will occur during these visits:

- **Interim medical history and adverse event review.** See MOP section 4.6.2

- **Symptom-directed physical examination.** See MOP section 4.6.5.
- **Review of concomitant medications.** See MOP sections 4.6.2 and 8.
- **Physical Measurements (vital signs).** Vital signs (height, weight, blood pressure and heart rate) (see MOP section 11). Waist circumference will not be measured at these visits.
- **Laboratory specimen collection.** Blood is collected and shipped to the Central Laboratory for analysis (and storage during M06 visit only). See MOP section 9 for details.
- **Study pill return, adherence assessment and distribution.** See MOP section 7.
    - Participant will return pill bottles.
    - The research staff (pharmacist, coordinator, nurse, or designee) will count the number of pills remaining. The number will be entered into EDC system, which will calculate adherence (based on the number of pills dispensed and the number of days since the last dispensing).
    - A 6-month supply of the assigned study pills will be dispensed to the participant with a new copy of the Participant Information pamphlet, which contains information about the date and time of the next visit and contact information about the site. The research pharmacist, research coordinator, or designee will log into SPIRS and determine which bottle of pills should be dispensed to the participant.
- **Post-visit activities:** Review lab results as soon as they become available and, if indicated, schedule a confirmatory visit (see algorithm in MOP 18). Send follow up letter to participant's PCP indicating that testing was either positive or negative for diabetes (see MOP section 17, Appendix) and, if negative, reminding them of the importance of not starting diabetes medication prior to the diagnosis of diabetes being made within the study.

4.6.7 Annual Visits [M12, M24, M36 and M48]

Annual visits are scheduled at 12, 24, 36, and 48 months after the randomization visit. The goals of these visits are to encourage participant compliance, perform safety assessments, assess study outcome measures, and provide the participant with a new 6-month supply of study pills. The following will occur during these visits:

- **Interim medical history and adverse event review.** See MOP section 4.6.2
- **Symptom-directed physical examination.** See MOP section 4.6.5.
- **Review of concomitant medications.** See MOP sections 4.6.2 and 8.
- **Physical Measurements (vital signs).** Vital signs (height, weight, blood pressure and heart rate) (see MOP section 11). Waist circumference will not be measured at these visits.
- **Laboratory specimen collection, including OGTT.** Blood is collected and analyzed locally. Blood and urine are collected and shipped to the Central Laboratory for analysis and storage. See MOP section 9 for detailed instructions.
    - ✓ PLEASE NOTE: If participant has previously met the diabetes outcome, an OGTT is not required. All other procedures including fasting A1c and glucose are to be completed.
- **Questionnaires:** FFQ at M12 and M36 for those who have not been diagnosed with diabetes and IPAQ at each annual visit (see MOP section 10).
- **Study pill return, adherence assessment and distribution.** See MOP sections 4.6.6 and 7.
- **Post-visit activities:** Review lab results as soon as they become available and, if indicated, schedule a confirmatory visit (see algorithms in MOP section 18 and MOP section 14, Appendix).

Send follow up letter to participant's PCP indicating that testing was either positive or negative for diabetes (MOP section 17, Appendix) and, if negative, reminding them of the importance of not starting diabetes medication prior to the diabetes diagnosis being made within the study.

4.6.8 End-of-study Visit [EOS]

The end-of-study visit is scheduled within 12 weeks of the announcement of study closeout. The goals of this visit are to perform safety assessments, assess study outcome measures, and complete closeout activities. The following will occur during this visit

- **Complete medical history and adverse event review.**
- **Complete physical examination.** See MOP section 4.6.2.
- **Review of concomitant medications.** See MOP sections 4.6.2 and 8.
- **Physical Measurements (vital signs).** Vital signs (height, weight, blood pressure and heart rate) (see MOP section 11). Waist circumference will not be measured at this visit.
- **Laboratory specimen collection.** Blood is collected and analyzed locally. Blood and urine are collected and shipped to the Central Laboratory for analysis and storage. See MOP section 9 for detailed instructions.
- **Study pill return and adherence assessment.** See MOP sections 4.6.6 and 7.

4.7 UNSCHEDULED STUDY VISITS

4.7.1 Visit for symptoms consistent with hyperglycemia

At any time when a participant reports symptoms consistent with hyperglycemia, a visit should be scheduled to evaluate glycemia. The visit should be scheduled as soon as possible, preferably within a week of the participant notifying the site.

The following will occur during this visit:

- **Interim medical history and adverse event review.** See MOP section 4.6.2
- **Symptom-directed physical examination.** See MOP section 4.6.5.
- **Review of concomitant medications.** See MOP sections 4.6.2 and 8.
- **Physical Measurements (vital signs).** Vital signs (height, weight, blood pressure and heart rate) (see MOP section 11). Waist circumference will not be measured at these visits.
- **Laboratory specimen collection.** Blood is collected (for FPG and HbA1c only) and shipped to the Central Laboratory for analysis. See MOP section 9 for details.
- **Post-visit activities:** Review lab results as soon as they become available and, if indicated, schedule a confirmatory visit (see algorithm in MOP section 18). Send follow up letter to participant's PCP indicating that testing was either positive or negative for diabetes (MOP section 17, Appendix) and, if negative, reminding them of the importance of not starting diabetes medication prior to the diabetes diagnosis being made within the study.

4.7.2 Visit for diagnosis of diabetes made outside of the D2d study or use of diabetes medication

Prior to conducting an UNCO visit, the study staff must review the procedures in MOP section 18 (Primary Outcome). If glycemic testing is required, an unscheduled confirmatory visit should be scheduled as soon as possible, preferably within a week of the participant notifying the site.

The following will occur during this Unscheduled/Confirmatory visit:

- **Completion of the** Non-D2d Diabetes Diagnosis/Medication Worksheet, See MOP section 18.
- **Interim medical history and adverse event review.** See MOP section 4.6.2
- **Symptom-directed physical examination.** See MOP section 4.6.5.
- **Review of concomitant medications.** See MOP sections 4.6.2 and 8.
- **Physical Measurements (vital signs).** Vital signs (height, weight, blood pressure and heart rate) (see MOP section 11). Waist circumference will not be measured at these visits.
- **Laboratory specimen collection.** Blood is collected and shipped to the Central Laboratory for analysis. See MOP section 9 for details.
- **Post-visit activities:** Review lab results as soon as they become available, and if indicated, schedule a confirmatory visit (see algorithm in MOP section 18). The site PI or study physician should communicate with the participant's PCP and /or prescriber provider indicating that testing was either positive or negative for diabetes and, if negative, discuss with them the importance of not starting diabetes medication prior to the diagnosis being made within the study.

4.7.3 Confirmatory Visit

A confirmatory visit is scheduled if at any visit, a participant meets glycemia criteria for diabetes that requires confirmation (see protocol figures 9.1.1 and 9.1.2). The confirmatory visit will be scheduled within 8 weeks of initial "trigger" visit.

⇒ It is important to emphasize to the participant that being called back for additional testing *does not necessarily mean that they should be concerned about a possible diagnosis of diabetes* and they should avoid making drastic changes to their diet or physical activity level before the confirmatory visit.

The following will occur during this Unscheduled/Confirmatory visit:

- **Adverse event review.**
- **Review of concomitant medications.** See MOP sections 4.6.2 and 8.
- **Laboratory specimen collection, which may include OGTT**: Laboratory testing depends upon the conditions that triggered the confirmatory visit (see protocol figures 9.1.1 and 9.1.2).

4.7.4 Diagnosis of Diabetes Communication

If a participant meets the D2d glycemia criteria for diabetes, then the information needs to be communicated to the participant either via a phone call or visit (to be decided between the participant and site staff).

The following will occur during this phone call or visit:

- Laboratory results are shared with the participant and the significance discussed.
- Participant will be instructed to see her primary healthcare provider for management of her diabetes (diabetes will not be managed within the study).
- Participant will be provided with a letter outlining the laboratory results and instructing her to see her primary healthcare provider (see MOP section 20).
- A letter will be sent to the participants primary healthcare provider (see MOP section 17).
- The importance of continued participation in the study will be stressed.

4.7.5 Visit for abnormal safety laboratory result

Abnormal results of a follow-up safety test (e.g. calcium, serum creatinine [e-GFR calculated in EDC] from the local laboratory, or urine calcium creatinine from the Central Laboratory) per the Data Safety Monitoring Plan (DSMP) (see MOP 14, appendix 1 DSMP figures 2, 3, and 4), may require an unscheduled visit to re-evaluate the safety measure. The visit should be scheduled in the time frame described in the DSMP.

The following will occur during this Unscheduled/Confirmatory visit:

- **Laboratory specimen collection.** Blood or urine is collected and either sent locally (serum calcium and serum creatinine) or shipped to the Central Laboratory for analysis (urine calcium creatinine ratio). See MOP section 9 for details.
- Any other procedures that are indicated based on participant report.
- **Post-visit activities:** Review lab results as soon as they become available and follow safety algorithms in MOP section 14, Appendix.

4.7.6 Visit to follow-up on report of Adverse Event

The site investigator may deem it necessary for the participant to return for an Unscheduled/Confirmatory visit to evaluate an adverse event reported between scheduled visits. The activities required during the visit will be dependent upon the event and the investigator's judgment.

4.8 SEQUENCE OF VISIT ACTIVITIES

At each visit, multiple tasks must be accomplished. Some tasks need to be performed in a certain order so that the tasks are completed without interference or the introduction of factors that may alter the results. Stress is one factor that can alter the results of OGTT, the study's primary outcome measure. Therefore, efforts should be made to minimize stress during the OGTT procedure. The following study activities may be perceived as stressful to the participant: blood draws, phlebotomy, saline lock insertions, blood pressure measurement, weight measurement.

The following order is suggested for completion of visit activities (not all activities occur at all visits).

- Written informed consent (screening visit or at other visits if ICF changes)
- Medical history/interim history
- Non-study medication review
- Vital signs and waist circumference
- Urine specimen collection*
- Fasting specimen collection
- OGTT
- Physical examination**
- Questionnaires***
- Lifestyle counseling***
- Study pill count***
- Study pill teaching***
- Study pill distribution***

* If the participant is to unable to void prior to the start of the OGTT, the urine collection may be done during or after the OGTT.
** The complete physical examination should be done before or after the OGTT, to minimize its influence on the OGTT measurements. Symptom-directed physical examination may be done during the OGTT.
*** These activities can be done during the OGTT

4.9 MISSED VISITS

4.9.1 Contacting Participant after Missed Visit

Beginning with the Screening visit, if a participant does not come to a scheduled visit, research staff should call the participant that same day to reschedule the visit. In a non-judgmental manner, staff will inform the participant that he missed the visit and that the staff would like to reschedule the visit. Staff will thank the participant for his willingness to participate in the study and stress that all study visits are important to accomplish the study goals.

Staff will try to determine if the reason for missing the visit will make it difficult for the participant to attend future visits (e.g. lack of transportation, childcare responsibilities on certain days). Staff will work with the participant to remedy any attendance obstacles (for instance, schedule the visit on a day of the week convenient to the participant, arrange transportation).

4.9.2 Timing of Rescheduled Visits

Efforts should be made to reschedule visits within the visit window. However, if this cannot be accomplished, it is acceptable to schedule the visit outside of the window following the guidelines in the table below.

Table 4.2

Missed visit	Rescheduling Guideline
Baseline [BAS]	• Preferably, scheduling for the Screening and Baseline visits should be done at the same time to ensure that these two visits fall as close to each other as possible, ideally, within 4 weeks of each other. If the baseline visit does not occur within 4 weeks of the Screening visit, an additional 2 weeks for scheduling are permitted. • If > 6 weeks have passed since Screening visit, all screening labs (including HbA1c and FPG) need to be repeated and the medical history and concomitant medications must be updated to determine eligibility.
Randomization [RAN]	• If > 3 weeks have passed since Baseline visit, repeat Baseline visit. • If > 7 weeks have passed since Screening visit, do a combined Screening/Baseline visit.
Month 3 [M03]	• The visit can be rescheduled up until month 4. • If > 4 months have passed since the Randomization visit, do not reschedule the visit; collect the 3-month-specific laboratory data (serum calcium, creatinine, urine calcium-creatinine ratio) at M06.
Semi-annual [M06, M18, M32, M42]	• If the visit can be scheduled within 3 months of the scheduled semi-annual visit date, conduct the full semi-annual visit and dispense study pills. • If less than 3 months remain until the next annual visit, skip the semi-annual visit and proceed with the annual visit. The semi-annual visit will be considered missed.
Annual [M12, M24, M36, M48]	• If the visit can be scheduled within 3 months of the scheduled annual visit date, conduct the full annual visit and dispense study pills. • If less than 3 months remain until the next semi-annual visit, skip the annual visit and proceed with the semi-annual visit. The annual visit will be considered missed. NOTE: the annual visit safety measures (serum calcium and creatinine and urine calcium creatinine ratio) should be collected at this visit.
Multiple missed visits	• Participants who miss > 1 visit and wish to resume participation need to be scheduled to come in for the scheduled study visit that is closest to the date the participant re-appeared. For example, if a participant returns in month 25, then the M24 annual visit is conducted. If a participant returns in month 29, then the M30 semi-annual visit is conducted. NOTE: safety measures (serum calcium and creatinine and urine calcium creatinine ratio) should be collected at the visit.

4.9.3 Repeated Missed Visits

If a participant misses a visit and fails to return for the re-scheduled visit, multiple additional attempts to reschedule the visit should be made. If the participant fails to keep 3 appointments for a visit, the Letter to Participant Missed Follow-up Visit should be sent to the participant via certified mail (see MOP section 17). The letter stresses the important role the participant plays in the research and that the site staff are eager to discuss follow-up with the participant. Phone contact should be attempted one week after the letter was sent. If the participant granted permission for the research staff to share information with the primary care provider (PCP), the PCP can be sent a letter providing an update on the participant's status and encouraging continued participation (see MOP section 17).

As the date of the next scheduled visit approaches (e.g. participant missed the semi-annual visit, and the date of the annual visit is approaching), attempts to contact the participant to schedule the visit will be undertaken beginning 4 weeks prior to the visit. Attempts should include phone calls to the participant, email, and contacting the next of kin/emergency contact as well as sending a letter (see MOP section 4.9.4). All attempts to contact a participant will be documented in the EDC contact follow-up log. Attempts to contact the participant should be repeated every 6 months, before each scheduled visit, until the study end.

4.9.4 Hints for Contacting Participants

To prevent and/or address difficulties with contacting participants, staff should consider the following:

- At the beginning of each contact with a participant (phone or in person), confirm that the contact information on record is correct and inquire if there are any changes that need to be made.
- Inquire whether participants have any plans to move or change jobs, and encourage the participant to call the research coordinator with any updates.
- Contact the participant by using the different numbers and contact names provided. Note: always remain respectful of the participant's privacy when leaving messages.
- Call the participant at different times of the day, especially the evening if they work during the day.
- Call the participant from different phone numbers, especially if the number is blocked on caller-id. Consider calling from a private phone instead of using a phone from a medical center.
- Send the participant an e-mail.
- Engage the participant's healthcare provider (if permission was granted), by sending a Status letter (see MOP section 17).
- Consider utilizing the internet or medical center registration system to find the participant.

4.9.5 Lost to Follow Up

⇒ *While the study is ongoing, participants are never considered to be lost to follow-up.*

As noted in MOP section 4.9.3, attempts to contact the participant will continue until the study end or until the participant has requested withdrawal from study participation.

4.9.6 Withdrawal from the study (going “off study”)

Participants can go “off study” only for withdrawal of consent, which is defined as no longer wishing to participate in all aspects of the trial. The site investigator may also withdraw participants for a safety reason, but that will be a rare occurrence.

If a participant does not return for study visits but is willing to respond to questions over the phone and/or release medical records, information on the participant’s status (alive, dead) and diagnosis of diabetes or other outcomes will continue to be obtained. Refer to MOP section 17.5 for details.

4.9.7 Documentation

All attempts at contacting participants, including rescheduling efforts should be documented in the participant contact follow-up log in EDC. If the site chooses to not utilize the EDC contact follow-up log, then documentation must be kept in the source documents. Copies of letters sent to participants and participant healthcare providers will be included as source documents.

4.10 TOOLS TO HELP WITH SITE MANAGEMENT

4.10.1 Follow Up Due Report

The CC will generate a report that lists all participants at the site with a follow-up due in the next three weeks or an overdue visit.

4.11 APPENDICES

Appendix 1 Participant Schedule