Manual of Procedures
Section 18. Primary Outcome Assessment

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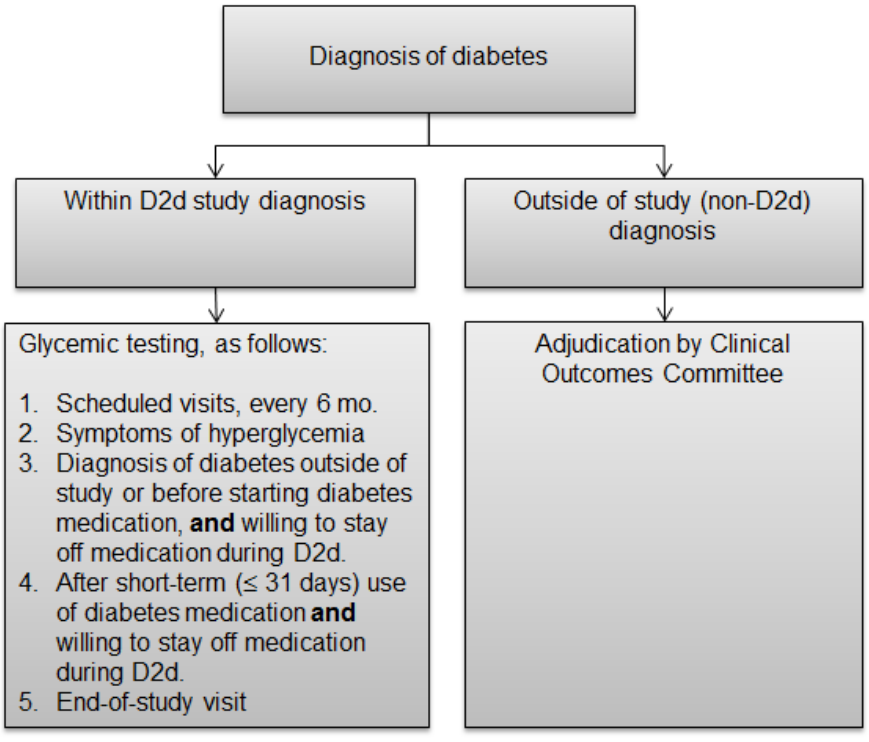
18.1 OVERVIEW OF PRIMARY OUTCOME

The primary outcome of the D2d study is time to progression from pre-diabetes to incident (new-onset) diabetes.

The diagnosis of diabetes is made based on one of the following mechanisms (Figure 18.1):

1. *Within study diagnosis,* based on glycemic criteria from laboratory testing conducted during D2d study visits and analyzed at the Central Laboratory. This mechanism includes glycemic testing during scheduled study visits or unscheduled visits.
2. *Outside of study [non-D2d] diagnosis,* based on clinical and laboratory data that have been collected outside of the D2d study. In this mechanism, which is expected to be uncommon, the independent Clinical Outcomes Committee (COC) confirms the diagnosis of diabetes by an adjudication process.

Figure 18.1. Summary of algorithm for evaluation of diabetes



18.2 LABORATORY DIAGNOSIS OF DIABETES

The diagnosis of diabetes is based on the American Diabetes Association (ADA) glycemic criteria (fasting plasma glucose [FPG] ≥ 126 mg/dL, 2-hour post 75-gram glucose load [2hPG] ≥ 200 mg/dL or hemoglobin A1c [HbA1c] ≥ 6.5%) measured at study visits, according to the algorithms described below. During D2d study visits, blood for plasma glucose (FPG, 2hPG) and whole blood (HbA1c) is drawn locally and shipped to the Central Laboratory for measurement. Results are available to the site typically within 5 business days from day of shipment.

The ADA glycemic criteria will also be followed when the diagnosis of diabetes is confirmed by the adjudication process based on laboratory data collected *outside* of the D2d study.

18.3 DIABETES EVALUATION WITHIN D2d

Glycemic testing for diabetes during the D2d study will be done:

(1) At scheduled visits, every 6 months.
(2) When a participant reports symptoms consistent with hyperglycemia.
(3) When a participant is given a diagnosis of diabetes outside of D2d or prescribed (for any indication) diabetes-specific pharmacotherapy, but – after consultation with her physician – is *willing to not start the medication* and be followed for diabetes within D2d.
(4) When a participant has taken diabetes-specific pharmacotherapy for no more than 31 days but – after consultation with her physician – is *willing to stop the medication* and be followed for diabetes within D2d.
(5) End-of-study visit.

When a participant meets a laboratory criterion for diabetes at a study visit, the site will be notified via the web-based electronic data (EDC) capture system, in which the Central Laboratory enters the results of the glycemic measurements. In many cases, repeat testing will be required to confirm the diagnosis of diabetes (see below for algorithm).

18.3.1 Glycemic testing at scheduled visits

Tests for glycemia are performed without interrupting the assigned study treatment. If a participant is taking a diabetes medication, tests for glycemia are performed after the participant holds the medication the morning of testing.

18.3.1.1 Glycemic testing at annual visits

All three glycemic measures (FPG, 2hPG and HbA1c) will be assessed (see MOP section 9) at scheduled yearly visits (M12, M24, M36 and M48) by conducting a 75-gram OGTT, and the diagnosis of diabetes will be made based on the algorithm shown in Figure 18.2 (same as Protocol - Figure 9.1.1).

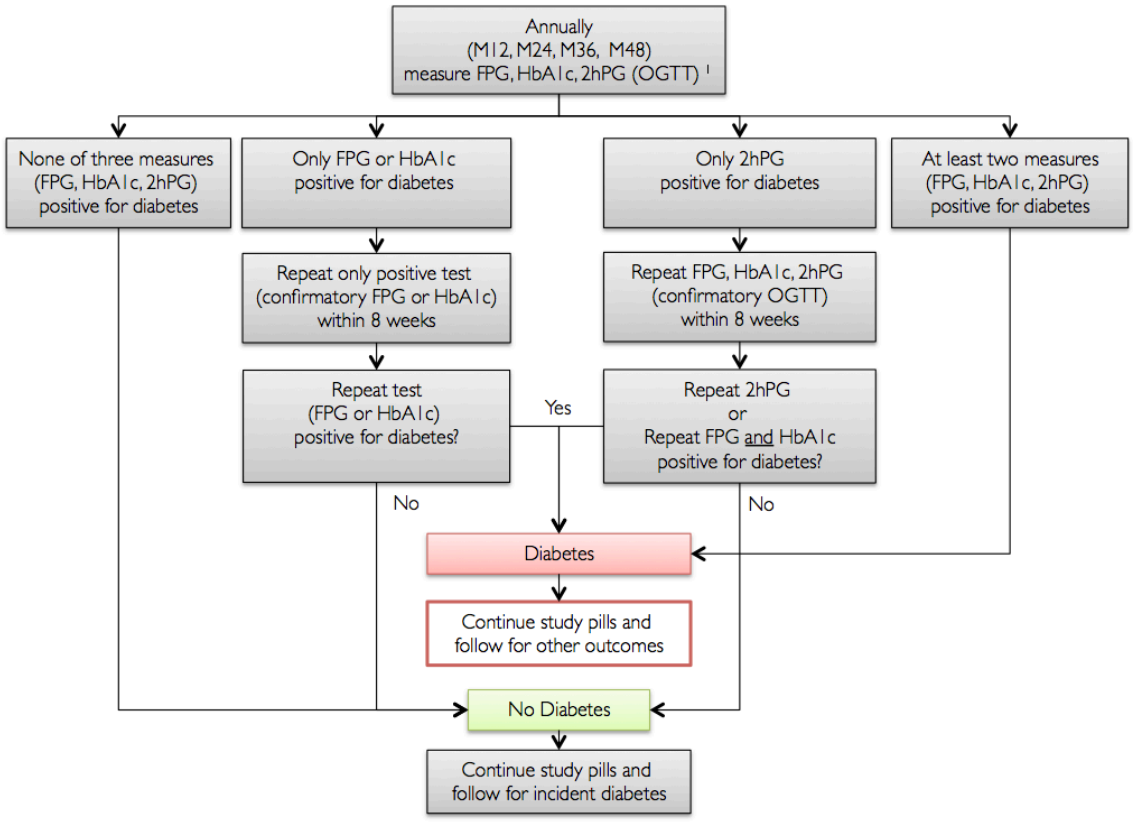
- If all three glycemic measures are negative for diabetes, then the participant does not have diabetes and continues on the assigned treatment and continue to be tested for incident diabetes every 6 months.

- If two or all three of the glycemic measures are positive for diabetes, the participant is considered to have reached the diabetes outcome and no confirmatory testing is required.
- If only FPG or only HbA1c is positive for diabetes, then a confirmatory visit to repeat *only the same glycemic test that was positive* will be completed within 8 weeks. If the repeat measure is also positive for diabetes, then the participant is considered to have reached the diabetes outcome.
    - Example: *HbA1c = 6.5%*, FPG = 119 mg/dL and 2hPG = 178 mg/dL at the scheduled annual follow-up visit; *HbA1c = 6.6%* at the confirmatory visit. Participant is diagnosed with diabetes.
- If only the 2hPG is positive for diabetes, then a confirmatory visit *with an OGTT* to repeat all three glycemic measures is completed within 8 weeks. If the repeat 2hPG is positive for diabetes, then the participant is considered to have reached the diabetes outcome. If the repeat 2hPG is negative for diabetes but *both* repeat HbA1c and FPG are positive for diabetes, then the participant is considered to have reached the diabetes outcome. Otherwise, the participant does not have diabetes and continues on the assigned treatment and continues to be tested for incident diabetes every 6 months, per protocol.
    - Example: HbA1c = 6.4%, FPG = 122 mg/dL and *2hPG = 204 mg/dL* at the scheduled annual follow-up visit; *HbA1c = 6.6%, FPG 128 mg/dL* and 2hPG = 189 mg/dL at the confirmatory visit. Participant is diagnosed with diabetes.
- If confirmatory testing is not completed within 12 weeks of the positive test, the participant is considered to have not reached the diabetes outcome and will be tested again for incident diabetes at the next scheduled visit.

⇒ *NOTE ON CONFIRMATORY TESTING:* To lessen the chance that participants would dramatically alter their lifestyle after a positive glycemic test on initial testing or be unduly alarmed, the following will be done:

1. Study personnel will emphasize to participants that an initial positive test for diabetes may often not be verified at confirmatory testing and that, rarely, repeat testing may be required for quality control purposes.
2. Confirmatory testing should be completed within a short period of time (e.g. within 1-2 weeks).

Figure 18.2. Flow diagram of evaluation for diabetes at the annual visit



[1] During the annual OGTT, the following will also be drawn: insulin at 0, 30 and 120 minutes and glucose at 30 minutes

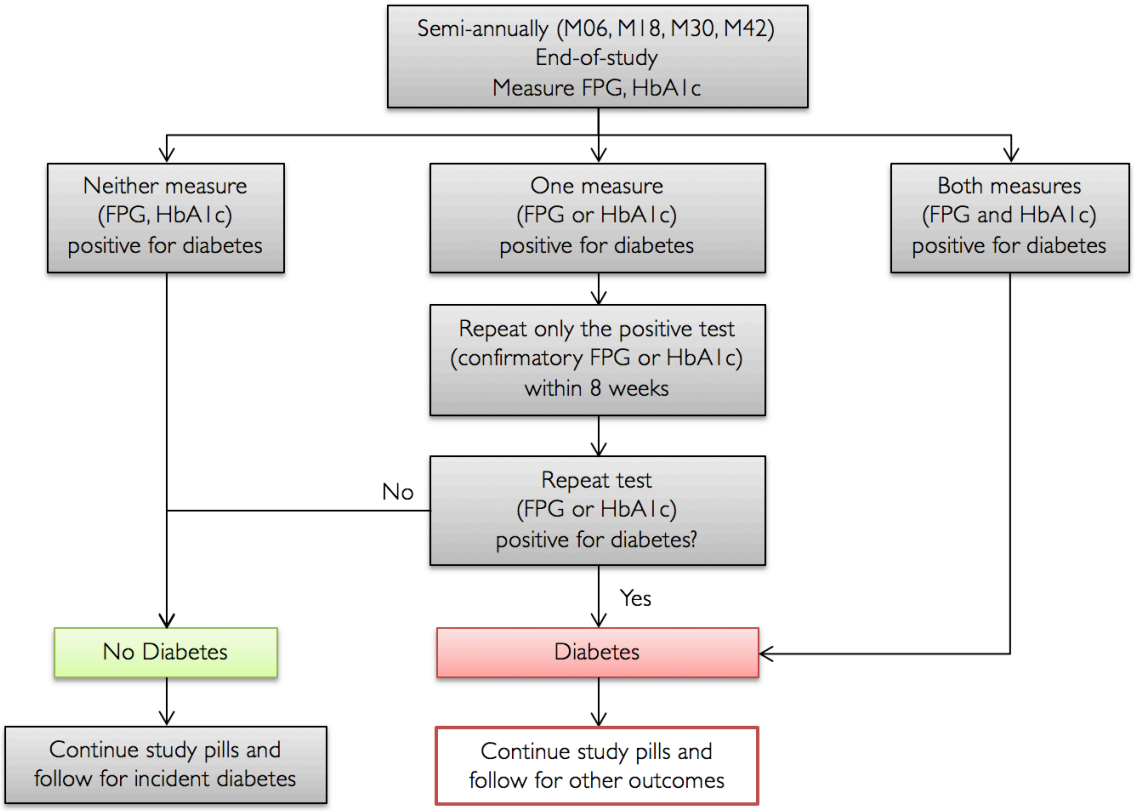
18.3.1.2 Glycemic testing at semi-annual visits

Fasting plasma glucose and HbA1c will be assessed (see MOP 9) at scheduled semi-annual visits (M06, M18, M30, M42) and the diagnosis of diabetes will be made based on the algorithm shown in Figure 18.3 (same as Protocol - Figure 9.1.2).

- If both glycemic measures are negative for diabetes, then the participant does not have diabetes and continues on the assigned treatment and continues to be tested for incident diabetes every 6 months.
- If both glycemic measures are positive for diabetes, the participant is considered to have reached the diabetes outcome and no confirmatory testing is required.
- If only one of two glycemic measures (FPG or HbA1c) is positive for diabetes, then a confirmatory visit to repeat *only the same glycemic test that was positive* will be completed within 8 weeks. If the repeat measure is also positive for diabetes, then the participant is considered to have reached the diabetes outcome. Otherwise, the participant does not have diabetes and continues on the assigned treatment and continues to be tested for incident diabetes every 6 months, per protocol.
    - Example: HbA1c = 6.3% and *FPG = 127 mg/dL* at the scheduled semi-annual follow-up visit; *FPG = 129 mg/dL* at the confirmatory visit. Participant is diagnosed with diabetes.

- If confirmatory testing is not completed within 12 weeks of the positive test, the participant is considered to have not reached the diabetes outcome and will be tested again for incident diabetes at the next scheduled visit.

Figure 18.3. Flow diagram of evaluation for diabetes at the semi-annual and end-of-study visits



18.3.2 Glycemic testing for symptoms consistent with hyperglycemia

At any time when a participant reports symptoms consistent with hyperglycemia (see below), an Unscheduled\Confirmatory (UNCO) visit should be scheduled as soon as possible to measure FPG and HbA1c. During UNCO, a similar algorithm as the semi-annual visit is followed to interpret the glycemic results, as shown in Figure 18.4.2.

Symptoms of hyperglycemia include:

- Blurry vision
- Excessive thirst
- Excessive hunger
- Frequent urination
- Extreme fatigue
- Unexplained weight loss
- Frequent infections

18.3.3 Glycemic testing for diagnosis of diabetes made outside of study or before starting diabetes-specific medication (for any reason).

If a health care provider makes the diagnosis of diabetes outside of the D2d study or *prescribes diabetes-specific pharmacotherapy (for any indication),* whether or not the participant plans to initiate the pharmacotherapy, the site PI (or study physician) should **promptly initiate contact with the PCP (or prescribing clinician)** and participant *to review the D2d protocol and the need for protocol-specific glycemic testing.*

The discussion should emphasize that the primary outcome of D2d is the development of diabetes, and thus it is critical that any diagnosis of diabetes be *in adherence with the study protocol* (i.e., by glycemic testing analyzed by the Central Lab). The site PI should determine whether the PCP is willing to withhold starting diabetes-specific pharmacotherapy, and also not initiate pharmacotherapy for pre-diabetes or other diagnoses (e.g., metabolic syndrome), *and allow follow-up for diabetes progression within D2d, as per protocol. In the discussion, the value of glycemic testing within D2d in assessing diabetes progression should be emphasized.*

Note: Diabetes-specific pharmacotherapy is defined as any FDA-approved medication for diabetes (e.g., metformin, Victoza [liraglutide]) and any other medication that contains an active substance approved for diabetes (e.g. Saxenda [liraglutide]) *even if the indication for usage was not diabetes*. For example, a participant may plan to initiate metformin for polycystic ovarian syndrome (PCOS), colesevelam for hypercholesterolemia, acarbose for post-prandial hypoglycemia, etc. A participant may also plan to initiate a medication that contains an active substance approved for diabetes (e.g. Saxenda [liraglutide]) for weight loss.

Note: Medications with approved indication for weight loss (e.g., Qsymia) are not considered diabetes-specific pharmacotherapy. *However*, if the participant is approaching a routine study visit, an effort should be made to schedule the next D2d regular visit before (or as soon as possible after) the participant starts the weight loss medication for collection of un-confounded data.

1. *If the PCP and participant agree to withhold diabetes medication, the participant continues in the protocol without interruption* with D2d-specific glycemic testing done at a D2d visit outside of the study schedule (UNCO) or at the next scheduled D2d visit (e.g. M06, M12), if the next visit scheduled visit is approaching. Site staff – in consultation with the Coordinating Center – will determine whether the participant undergoes an UNCO or waits for the next scheduled D2d visit. During UNCO, a similar algorithm as the semi-annual visit is followed to interpret the glycemic results, as shown in Figure 18.4.1 and 18.4.2

2. If the PCP (or participant) is determined to start diabetes-specific pharmacotherapy regardless of the results of D2d-specific glycemic testing, then the diagnosis of diabetes or indication for starting a medication is adjudicated by the COC (see section 18.6). Rationale: To prevent occurrences where the medication is temporarily held, D2d-glycemic testing is negative, then participant is placed on diabetes medication likely due to an outside of study diabetes diagnosis that cannot be adjudicated.

Following D2d glycemic testing at UNCO (see Figure 18.4.2) or scheduled D2d visit.

- If D2d testing does *not* confirm the diagnosis of diabetes, the participant is not counted as an incident case of diabetes.
    - The site investigator will communicate to the participant's health care provider that the results of the protocol-specific testing did not meet criteria for diabetes (see template letter in MOP section 17 and phone call discussion points) and will reinforce the principles of the study.
    - If diabetes-specific pharmacotherapy is not initiated based on within-study laboratory glycemic results, participant continues on the assigned D2d treatment and continues to be tested for incident diabetes per protocol.
    - If, *despite the pre-testing discussion between the site PI and PCP*, the participant does start diabetes-specific pharmacotherapy, then participant continues on the assigned D2d treatment and continues to be tested for incident diabetes per protocol, in accordance with the intention-to-treat (ITT) principle. Use of a diabetes medication is noted in EDC because such medications influence the development of diabetes and the information will be considered in the analyses for incident diabetes.
- If testing confirms the diagnosis of diabetes, the participant is referred to her PCP for further care. Study pills will be *continued* and participant remains in the study and completes all subsequent planned measurements and visits for other outcomes beyond incident diabetes (see 18.8).

18.3.4 Glycemic testing after short-term use of diabetes medication

If a participant has started diabetes-specific pharmacotherapy but has been exposed to the medication for no more than 31 days (cumulative, since the last D2d scheduled visit e.g., M06, M24), she will return for a visit to undergo D2d-specific glycemic testing, following an appropriate washout period (see below), *provided the prescribing clinician and participant agree to stop the medication and allow follow-up for diabetes progression within D2d, as per protocol (i.e., by glycemic testing analyzed by the Central Lab).*

- ✓ The period of 31 days is cumulative since the last D2d scheduled visit (e.g., M06, M24).
- ✓ The rationale for limiting short-term exposure to no more than 31 days is as follows: [1] Short-term use of a diabetes medication is not expected to have an impact on long-term glycemic trajectory. [2] A request to hold a medication after a few months of use may confuse the participant and may place the investigators in conflict with the prescribing clinician.

As soon as the site becomes aware of the actual use of a diabetes medication, the site PI (or study physician) should promptly initiate contact with <u>the prescribing clinician</u> *and participant to review the D2d protocol and the need for protocol-specific glycemic testing**.***

The discussion should emphasize that the primary outcome of D2d is the development of diabetes, and thus it is critical that any diagnosis of diabetes be *in adherence with the study protocol* (i.e., by glycemic testing analyzed by the Central Lab). *The discussion should focus on the need for treatment with the diabetes medication and whether the clinician* is willing to stop the diabetes medication, <u>and</u> also not initiate pharmacotherapy for pre-diabetes or other diagnoses (e.g., metabolic syndrome), *and*

allow follow-up for diabetes progression within D2d, as per protocol. In the discussion, the value of glycemic testing within D2d in assessing diabetes progression should be emphasized.

1. If the prescribing clinician and participant agree to stop the diabetes medication to allow follow-up of glycemic status per D2d protocol, then the medication will be stopped and D2d-specific glycemic testing will be done (see Figure 18.4.1), following an appropriate washout period, as follows:

- *2 weeks*: biguanides (e.g. metformin), SGLT2 inhibitors, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, DPP4 inhibitors, bile acid sequestrants, dopamine-2 agonists, insulin.
- *4 weeks*: GLP-1 receptor analogues (e.g. liraglutdie), thiazolidenediones, amylin mimetics

2. If the prescribing clinician and participant do not agree to stop the diabetes medication, then the medication will not be stopped and the diagnosis of diabetes or indication for the medication is adjudicated by the COC (see section 18.6).

18.3.5 Glycemic testing at end-of-study visit

At the end-of-study visit, which will take place within 3 months after study close-out begins, FPG and HbA1c will be measured and the algorithm for the semi-annual visit (Figure 18.3) will be followed to assess for incident diabetes.

18.3.6 Procedures to optimize fidelity of D2d glycemic testing and minimize use of diabetes-specific pharmacotherapy prior to in-study diabetes diagnosis.

1. At baseline and every visit, site staff will educate participants to *contact the Research Coordinator as soon as possible* after a clinician outside of the D2d study makes the diagnosis of diabetes or if the clinician plans to initiate diabetes-specific pharmacotherapy (for any reason).

2. Participants are told to not start diabetes-specific pharmacotherapy until they communicate with D2d study staff and the study PI (or study physician) speaks with the prescribing clinician.

⇒ ***This reminder is critically important so that very few participants actually start on a diabetes medication prior to the discussion between the study PI (or study physician) and prescribing clinician.***

3. At each visit, provide participants with the Participant Pamphlet, which includes a list of diabetes medications that are restricted during the study (see also Appendix). The list should be reviewed at every visit.

4. At each visit, provide participants with the D2d-specific appointment card, which includes key information about the study.

5. Engage the participant's primary care and other health care providers with frequent status updates (see MOP section 17 for template letters). Keeping providers informed after each scheduled visit about D2d and the need to evaluate diabetes status based on test results by the

D2d Central Laboratory reduces the likelihood that the participant will start diabetes-specific pharmacotherapy before study-specific glycemic testing.

6. When a participant reports that he was diagnosed with diabetes or if his health care provider plans to initiate (or has started) diabetes-specific pharmacotherapy (for any reason), the Non-D2d Diabetes Diagnosis/Medication worksheet (see MOP section 18.5.1 and Appendix) will be used to collect relevant data. Participants must be able to easily get in contact with the site Research Coordinator, either by phone or email or any other method that is preferred by participants.

7. At the initial contact over the phone (or email), participants will be asked questions related to their non-study visit and responses are entered in the Non-D2d Diabetes Diagnosis/Medication worksheet.

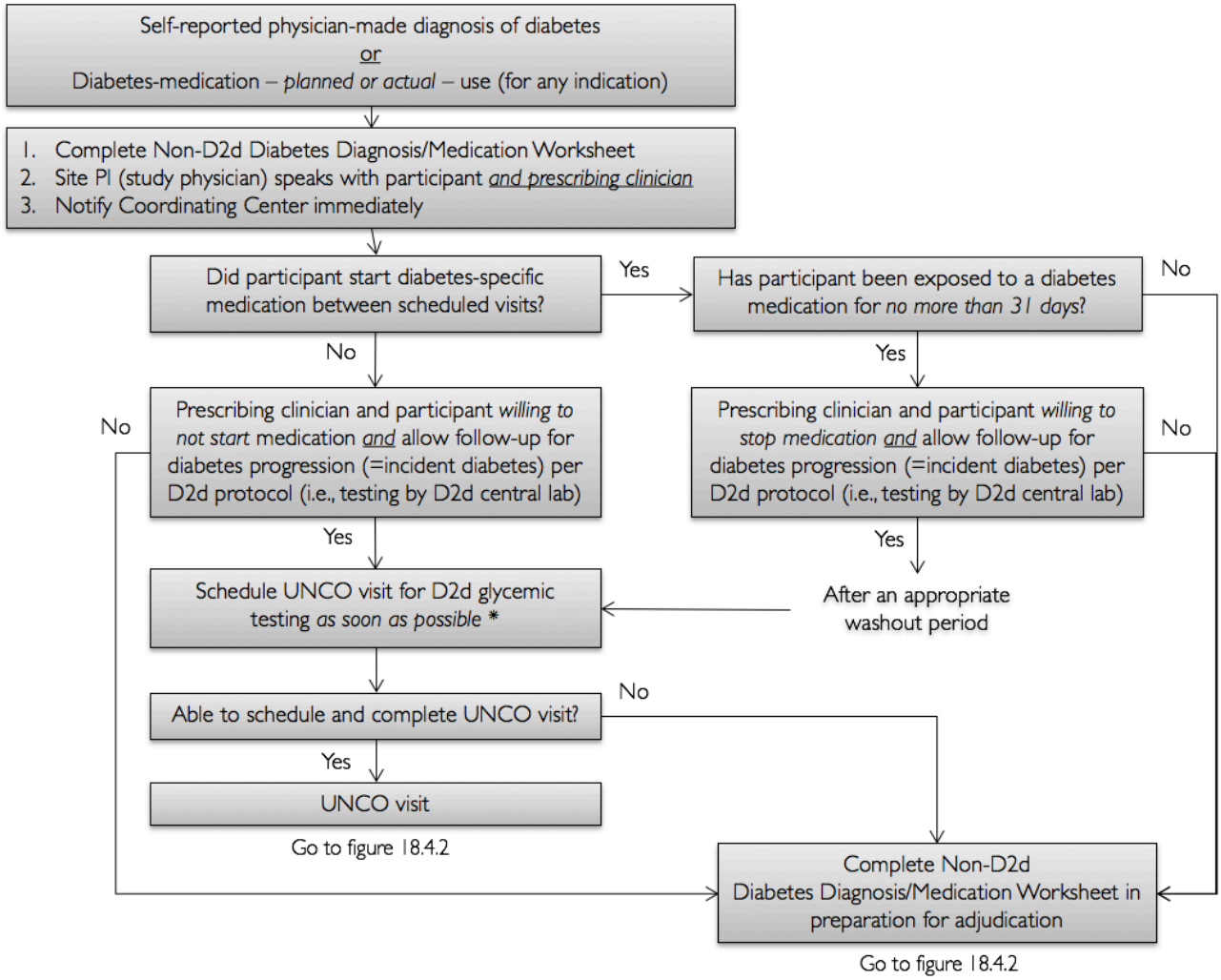
8. ***As soon as the site becomes aware of the potential (or actual) use of a diabetes medication, the site PI (or study physician) should promptly initiate contact <u>with the prescribing clinician</u> and participant*** *to discuss the need for protocol-specific glycemic testing.*

9. If it is determined that D2d-specific glycemic testing is appropriate and feasible, a visit is scheduled as soon as possible, either outside of the study schedule (UNCO) or at the next scheduled D2d visit (e.g. M06, M12), if the next visit scheduled visit is approaching (see Figure 18.4.1 and 18.4.2). Site staff – in consultation with the Coordinating Center – will determine whether the participant undergoes an UNCO or waits for the next scheduled D2d visit

10. Instruct the participant to bring all medications and supplements he is taking to the visit with him, including the prescribed diabetes medication(s) and study pills, whether or not any of it was taken.

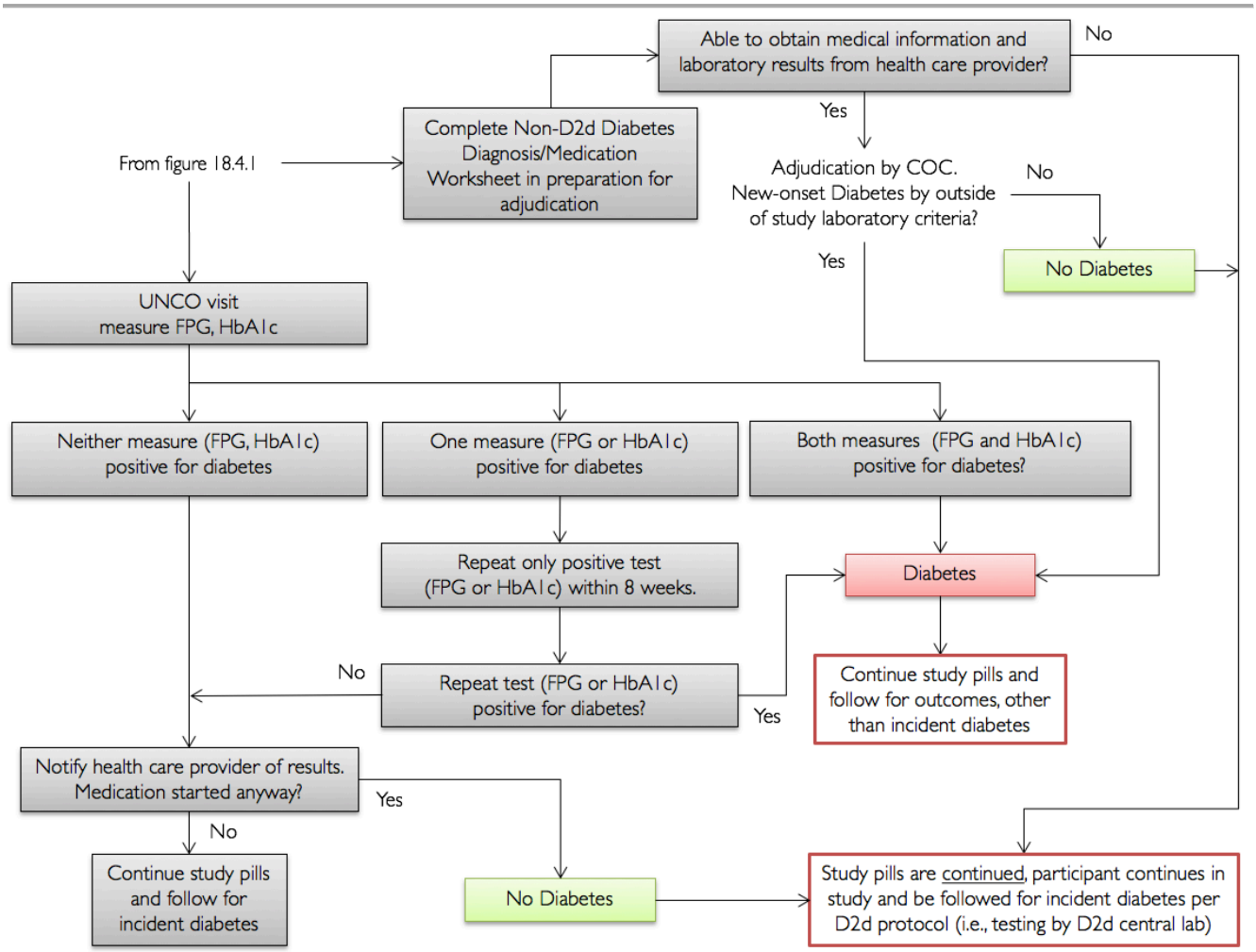
11. If based on the responses on the Non-D2d Diabetes Diagnosis/Medication worksheet, it is determined that D2d-specific glycemic testing cannot be done (e.g., participant is already on a diabetes-specific medication and does not meet the criteria to stop it, unable to schedule visit), medical records pertaining to the start of the medication and any glycemia testing will be collected for use by the COC to adjudicate the diagnosis of diabetes.

Figure 18.4.1. Flow diagram of evaluating self-reported physician-diagnosis of diabetes or initiation of diabetes-specific pharmacotherapy between scheduled visits.



- **In lieu of an Unscheduled Confirmatory (UNCO) visit, a regular D2d visit may be done provided the visit window is approaching**

Figure 18.4.2. Flow diagram for (planned or actual) use of diabetes-specific pharmacotherapy between scheduled visits.



18.4 POSTPONEMENT OF GLYCEMIA TESTING

Tests for glycemia are performed without interrupting the assigned study treatment. Testing at one of the scheduled follow-up visits or confirmatory visits will be postponed for up to 8 weeks if, in the opinion of the site investigators, a temporary concomitant condition exists that would affect glucose tolerance (e.g. active infection, hospitalization which may also require use of a diabetes medication, short-term use of glucocorticoids), its assessment (e.g. blood transfusion or blood donation) or for any other administrative or social reason.

18.5 NON-D2D DIABETES DIAGNOSIS/MEDICATION WORKSHEET

The following questions will be asked when a participant first reports that he has been diagnosed with diabetes outside of the study or has been prescribed diabetes specific-pharmacotherapy (whether he has started the medication or not). Responses will be first collected at the initial contact (e.g. over the phone). Questions and responses will be reviewed and additional information obtained or clarification provided during subsequent contacts, including visits.

✓ Please utilize the Non-D2d Diabetes Diagnosis/Medication worksheet (see Appendix) for data collection and ensure all required questions are asked during a participant contact. Start with open-ended questions and then ask specific questions to ensure all of the information required is collected. *Site should have the worksheet readily available to use when a participant calls.*

1. **Date participant reported the diagnosis of diabetes to the site or the prescribing of or start of a diabetes-specific pharmacotherapy.** This is the *date of the first communication* (phone, email etc.) when the participant notified the site that he was given the diagnosis of diabetes outside of D2d or was asked to start a diabetes-specific pharmacotherapy or started the medication.

   ⇒ *If the participant was prescribed a diabetes-specific medication for an indication other than diabetes, the Worksheet still needs to be completed, e.g., metformin for PCOS.*

2. **Type of initial contact with the site.** For example, telephone, email, study visit, other.

3. **Setting of diabetes diagnosis or prescribing of diabetes-specific medication**. Indicate where the diagnosis of diabetes was made or where a diabetes-specific medication was prescribed. For example:
   - Outpatient clinic or office
     - Primary care
     - Medical-surgical specialist
   - Hospital
     - Emergency room
     - Inpatient
     - Day surgery
   - Health Screening
     - Community health fair
     - Employee health

- o Other (e.g. pharmacy). Indicate _____

4. **Professional making the diagnosis of diabetes or prescribing diabetes-specific medication**. Enter information about the professional who evaluated glycemic results and made the diagnosis of diabetes or who prescribed diabetes-specific medication. For example:
    a. Physician
    b. Nurse practitioner, physician assistant, surgical assistant
    c. Nurse
    d. Community health worker (lay person)
    e. Pharmacist
    f. Other. Indicate _____

✓ Be sure to record on the worksheet details related to the setting (name and address of the facility, or medical practice, etc.), who made the diagnosis or prescribed a medication (e.g. name of physician), their contact information and the date of diagnosis or prescription. This will be useful when obtaining medical records and/or sharing follow-up information.

5. **Date of diabetes diagnosis or prescribing of diabetes-specific medication.** Indicate when the participant was tested for diabetes or given a prescription for a diabetes medication or started a medication. If the participant does not remember the date, ask additional questions to help him remember or to limit the date range, e.g. if participant says the end of December, ask if it was before or after Christmas.

6. **Reason for testing or reason for prescribing a diabetes-specific medication.** The diagnosis of diabetes can be made for a variety of reasons, e.g.
    a. Routine (e.g. well visit, pre-operative testing, health screening)
    b. Symptoms of diabetes (provide details)
    c. Other illness or hospitalization, e.g. inpatient or emergency room (provide details)
    d. Other (provide details, especially if reason for prescribing a medication was not diabetes)

✓ Ask open-ended questions, e.g. why were you tested for diabetes? If the participant does not know or the response is unclear, ask a more detailed or probing question, e.g. why did you go to the doctor? Were you having symptoms? What kind of symptoms?
✓ Provide details and/or additional information

7. **Diabetes-specific medication prescribed**. Ask the participant if he has had any medications prescribed and whether it was for diabetes or not. If yes, for each medication collect the following:
    a. Name, dose, route, frequency
    b. Start date / end date
    c. Reason

✓ The goal of this question is to determine if the participant started any diabetes-specific medication (See Appendix for list of medications approved for diabetes).

⇒ If the participant was given prescription(s) but has not started the medication(s), reinforce with the participant the need to not the start the medication until the site PI (or study physician) has had a

conversation with the prescribing physician. ***It is imperative that the communication between the site PI (or study physician) happen as soon as possible.***

8. **Changes in lifestyle.** Ask the participant if he has made any changes to lifestyle (diet or physical activity) since he was told of the diagnosis of diabetes. If yes, ask the participant to provide details regarding the changes he has made, when he made them.

9. **Action taken at site.** Record all action taken by site once diabetes diagnosis or prescription of medication was reported. Retain copies of all communication (including note from phone contact) with participant and PCP in source documents.

The worksheet should be submitted to the Coordinating Center at initial completion and once a conclusion is reached. Prior to sending, the site PI must review and sign.

18.5.1 Retrieval of medical records

- ✓ If a diagnosis of diabetes is made outside the D2d study or a participant has been prescribed (or started) a diabetes medication and there is no D2d-specific glycemic testing available (e.g., a participant has been taking a diabetes-specific medication for 2 months), then medical records need to be retrieved to adjudicate the diagnosis of diabetes.
- ✓ If not already done, ask the participant to sign a medical release form and obtain records from the health care provider(s), with special emphasis on obtaining the most recent laboratory values for FPG, HbA1c and 2hPG and any glucose results from fingersticks, before any diabetes-specific medication was started. Inform the participant that it is essential for the study to obtain any medical records related to the diagnosis of diabetes. Ideally, getting medical records should be done as soon as possible after the initial self-report of the diagnosis of diabetes or use of diabetes-specific medication. The medical release form – which is specific to each clinic/hospital – can be e-mailed, faxed or mailed to the participant and the participant should be instructed to return it the Research Coordinator in the most efficient and reliable way.
- ✓ If the participant has a printout of the laboratory results, ask him to bring them to the visit.
- ✓ The medical records will be reviewed and relevant information will be entered in the Non-D2d Diabetes Diagnosis/Medication worksheet.

18.6 ADJUDICATION OF DIAGNOSIS OF DIABETES

For every participant who is diagnosed with diabetes outside of the study or started diabetes-specific pharmacotherapy (for any indication) *and no D2d glycemia data by the Central Laboratory are available*, the diagnosis of diabetes will be adjudicated by the COC.

- The site Research Coordinator will send to the CC (d2d@tuftsmedicalcenter.org) copies of the completed Non-D2d Diabetes Diagnosis/Medication worksheet and all relevant medical records with all identifying information concealed or obliterated. See MOP section 18.8 for information on submitting records to the CC and concealing identifying information from the medical records. The site PI will ensure the completeness and accuracy of the submitted data.
- The CC will review the submitted worksheet and medical records for completeness, to ensure identifying or potentially unmasking information is not showing.

- The CC will compile a Non-D2d Diabetes/Medication Adjudication file consisting of the following documents:
    - Diabetes Adjudication eCRF. The site enters information in the form and the CC verifies the information entered. If needed, sites will be asked to make corrections in the information that was entered in the Diabetes Adjudication eCRF and/or obtain additional records.
    - Relevant medical records with identifying information concealed (refer to MOP section 18.9).
    - Non-D2d Diabetes/Medication Adjudication Review Form (see Appendix).
- As soon as the Non-D2d Diabetes/Medication Adjudication file is complete, it will be sent for review to two members of the COC.
- The COC reviewers will review the material to determine whether the outside laboratory results and relevant medical history are sufficient to make the diagnosis of diabetes. During the adjudication process, the reviewers are encouraged to follow, as closely as possible, the D2d glycemic algorithms (Figure 18.2 and 18.3). However, because it is highly unlikely that routine clinical practice will follow the strict D2d algorithms *(e.g., repeating testing is not commonly done in clinical practice and may be limited by insurance reimbursement rules),* the COC should follow the ADA threshold glycemic criteria and use clinical judgment when adjudicating cases of diabetes.
    - Example 1: a single HbA1c measured in clinical practice that meets the ADA threshold (e.g., 6.5%) suffices for the COC to make the diagnosis of diabetes.
    - Example 2: fingersticks that show results in the diabetes range (e.g. a few fasting glucose results above 125 mg/dL) may also suffice to make the diagnosis of diabetes in the setting of other supportive medical history.
- The reviewers will adjudicate the event by selecting one of the following three options:
    - *Participant experienced new-onset diabetes*. Date of diagnosis will be indicated.
    - *Participant did not experience new-onset diabetes*. If applicable, start date of diabetes-specific pharmacotherapy will be indicated.
    - *Insufficient information for adjudication*. If applicable, start date of diabetes-specific pharmacotherapy will be indicated.
- The reviewers will complete the Non-D2d Diabetes Adjudication Review Form and return it to the CC (d2d@tuftsmedicalcenter.org).
- Upon receipt of the Non-D2d Diabetes/Medication Adjudication Review Form from both committee members, the D2d Project Manager (or designee) will review the forms.
- If the two reviewers agree (e.g. both concluded there was insufficient information for adjudication), their assessment will be accepted as the adjudicated outcome and entered into the Diabetes Adjudication eCRF by the CC Project Manager (or designee).
- If the reviewers agree that participant developed new-onset diabetes, but there is discordance in the date of onset, the earliest date provided will be the date of diabetes onset.
- If there is discordance on the diagnosis of diabetes between the two reviewers that cannot be resolved between them, the Non-D2d Diabetes/Medication Adjudication file will be sent to another COC member who will act as the third reviewer. A majority decision will prevail. If there is discordance among all three reviewers (i.e., presence of new-onset diabetes vs. absence of new-onset diabetes vs. insufficient information), a conference call will be arranged by the CC with the goal of reaching consensus among the three reviewers. Discussion will continue until there is a consensus or a majority (i.e., 2 out of 3 reviewers) agrees on the presence of new-onset diabetes,

absence of new-onset diabetes or the insufficiency of the information for adjudication. The majority judgment will be accepted as final and entered into the Diabetes Adjudication e-CRF by the CC Project Manager (or designee).

- If at any point during the adjudication process, a reviewer determines that further information is needed, the CC will work with the site staff to determine if additional information pertaining to the diagnosis of diabetes is available. If new or additional information is available, it will be obtained and incorporated into the Non-D2d Diabetes/Medication Adjudication file and the reviewers will re-evaluate the diagnosis of diabetes in the setting of the new information provided.

  ⇒ **Note: If laboratory data from the health care provider cannot be obtained, then the participant will be considered as not having reached the diabetes outcome and will be coded as *insufficient information for adjudication.***

- Consistent with the double-masked study design of the D2d study, the COC members will remain masked to study group assignment during the adjudication process.
- At each Safety and Outcomes Subcommittee (SOS) meeting, the CC will report on the number of diabetes cases that have been reviewed and adjudicated by the COC.
- The full SOS will consider improvements in the diabetes adjudication process at its regular meetings.

18.7 DATE OF DIABETES ONSET

✓ If the diagnosis of diabetes is made within the study (i.e., using results by the Central Laboratory), the date of onset of diabetes is defined as the date of the *first diagnostic glycemic value*.

✓ If the diagnosis of diabetes is made outside of study (i.e., adjudicated by the COC), the date of onset of diabetes will be determined during the adjudication process and will be indicated in the Non-D2d Diabetes/Medication Adjudication Review Form.

If the COC determines that participant did not experience new-onset diabetes or there is insufficient information for adjudication and the participant has started diabetes pharmacotherapy, then participant continues on the assigned D2d treatment and continues to be tested for incident diabetes per protocol, in accordance with the intention-to-treat (ITT) principle.

18.8 MANAGEMENT OF PARTICIPANTS AFTER DIAGNOSIS OF DIABETES

After the primary outcome of diabetes has been reached (by D2d glycemic criteria or by adjudication), study pills will be *continued* and participant will be referred to their primary care physician for further care in relation to diabetes. Participant remains in the study and returns for scheduled visits for assessment of other outcomes beyond incident diabetes.

✓ After the diagnosis of diabetes is made, a letter will be sent to the participant's primary care physician or health care provider who will manage the participant's diabetes (see template letter in MOP section 17). The letter will:

- Provide the actual results of the D2d glycemia measures diagnostic for diabetes.
- Reinforce that the participant will continue the study pills and remains in D2d for assessment of other outcomes beyond incident diabetes.

- Inform the health care provider that the participant's diabetes will not be managed by the study investigator / physician.

If the participant has started and intends to continue taking diabetes-specific pharmacotherapy and the diagnosis of diabetes is not established (by D2d criteria or adjudication), then participant continues on the assigned D2d treatment and continues to be tested for incident diabetes per protocol, in accordance with the intention-to-treat (ITT) principle. Use of a diabetes medication is noted in EDC because such medications influence the development of diabetes and the information will be considered in the analyses for incident diabetes.

18.9 SUBMITTING RECORDS TO THE COORDINATING CENTER

Sites will send records related to a non-D2d diagnosis of diabetes to the CC using the Non-D2d Diabetes Adjudication Source Documents Coversheet (see Appendix), as follows:

1. The participant's enrollment ID must be recorded on each page sent.
2. All pages should be numbered in the following format: page #/ # of pages, e.g., if 3 pages are sent, these should be numbered 1/3, 2/3, 3/3.
3. Any information that could identify the participant must be concealed/obliterated.
    a. Identifying information includes:
        i. Name
        ii. Date of birth
        iii. Medical record, or social security number
        iv. Address or place of residence
        v. Identifying information of family members
    b. To conceal identifiers:
        i. Make a copy of the source documents. Keep the original in your files
        Note: the original source documents with the identifying information should not be altered. The identifiers must always be visible on the original source documents.
        ii. With a black Sharpie type marker or a Bic Wite-out correction tape type marker, mark/cover over all identifying information on the copy. Care must be taken to not cover non-identifying information.
        iii. Make a photocopy of the marked up document and review it to ensure the identifiers are not visible prior to sending it to the CC.

⇒ Submitting any participant documents to the CC that include identifying information is a serious violation.

18.10 APPENDICES

Appendix 1. Diabetes Specific Medications

Appendix 2. Non-D2d Diabetes Diagnosis/Medication Worksheet

Appendix 3. Non-D2d Diabetes/Medication Adjudication Review Form

Appendix 4. Adjudication Source Document Coversheet