# Manual of Procedures (MOP)
# Section 6. Screening

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## 6.1 OVERVIEW

At most sites, the screening and informed consent process are staged into two parts, a *Pre-screening* phase followed by a formal *Screening* visit. Each site, based on its prior experience, has developed a detailed site-specific recruitment plan (based on MOP section 5) that includes a pre-screening recruitment strategy to identify individuals at increased risk for type 2 diabetes who will be invited to the in-person screening visit. Active recruitment will take place year round at regular rates of enrollment to ensure equal exposure of randomized participants to UV-B.

The target for the screening process is to have a screened-to-randomization ratio close to 3:1 or better.

## 6.2 PRE-SCREENING

The goals of the pre-screening phase are to: 1) identify potentially eligible participants; 2) initiate the informed consent process; 3) conduct a preliminary verification of eligibility; 4) promote efficiency by pre-selecting candidates with high likelihood of eligibility after screening; 5) allow sites flexibility in their approach of recruiting participants, while maintaining a study-specific set of inclusion/exclusion criteria.

The pre-screening phase is site-specific and is based on what has worked well previously at the site. Pre-screening takes place in one, two, or more stages that may include an additional visit (e.g. identification of potential participants through databases [pre-screening stage 1], followed by over-the-phone pre-screening [pre-screening stage 2], followed by a visit just for glycemia laboratory measures [pre-screening stage 3]).

Sites will employ a variety of sources including electronic databases (e.g. electronic medical records and research volunteer databases), community-based advertising (e.g. hospital newsletters and specific local newspapers), targeted outpatient hospital clinics (e.g. primary care, cardiology), mailings to primary care physicians in the metropolitan area, social media (e.g. Craigslist), and study press releases to local news media to recruit potential participants (see MOP section 5).

### 6.2.1 Pre-Screening Procedures

The following are examples of pre-screening approaches that sites may follow. Identifying people who are more likely to meet the pre-diabetes criteria at the screening and baseline visits is the most important aspect of the pre-screening process.

#### 6.2.1.1 Over the Phone

When a person calls to inquire about D2d, first impressions are important. Introduce yourself and explain your role in the study (Research Coordinator, Recruitment Coordinator, etc.) to the caller. Phone inquiries about the study are a great way to assess the effectiveness of the site-specific recruitment strategies, so it is important to ask interested volunteers where and how they heard about the study or what prompted them to call.

The research staff reads a simple script (see Appendix) to callers, providing a brief overview of the study, informing them that they will be asked questions to determine preliminary eligibility, and that, if eligible, they will be invited to the research site for an in-person screening visit. The caller will then be asked if she would like to continue with the call and, if she agrees, the research staff will continue with the Pre-screening Questionnaire to evaluate the key inclusion/exclusion criteria (see Appendix).

⇒ During pre-screening, if laboratory information to define the volunteer's diabetes risk (e.g. A1c) is not available, a **diabetes risk score assessment** should be administered. This assessment should be done very early in the pre-screening process, so that if participant is at low risk for diabetes, the remaining pre-screening questions do not need to be completed. The American Diabetes Association Diabetes Risk Test is recommended, which has been adapted for D2d (see Appendix). In general, people who score higher than 5 should be scheduled for a screening visit.

Sites may also use a pre-screening questionnaire on its page on d2dstudy.org for interested volunteers to complete (e.g., see d2dstudy.org, d2dstudy.org/tufts, and d2dstudy.org/Stanford).

#### 6.2.1.2 In Person

Pre-screening may also be conducted in person in a number of settings or events, as described below. In these settings or events, people will be provided information about the study (e.g. study brochures) and pre-screening activities may be completed. Regardless of where the in-person pre-screening takes place, ensuring privacy is essential.

Examples of settings for in-person screening include:

- Waiting rooms in outpatient clinics while patients wait for their appointments.
- Public events where a table can be set-up
    - Recreational events [farmers markets, sports, racing, festivals]
    - Health fairs
    - Community gathering places [bingo, flea markets]
    - Advocacy association events [ADA Step Out]
- Medical center cafeterias

Sites may consider conducting a simple pre-screening visit (e.g. vital signs, point-of-care glucose testing, diabetes risk score assessment) to identify people at risk. These are also opportunities to gather information from people who are interested in participating in research to enter in a participant research database.

#### 6.2.1.3 Database Review

Querying databases to identify potentially eligible volunteers is arguably the most efficient and potentially cost-effective recruitment strategy. Below are examples of databases that may be available at the sites. Please refer to MOP section 5 for additional details.

- Electronic Medical Record systems
- Research Participant Databases/Registries
- Medical Center Employee Database

### 6.2.2 Vitamin D and Calcium Supplementation

During prescreening, potential volunteers may report taking vitamin D or calcium supplementation in doses greater than what D2d allows (see below). People who are taking such doses on their own must be willing to reduce their dose to what the study allows to be eligible. The document titled "Talking Points about Vitamin D and Calcium supplementation" (see Appendix) provides an overview of current recommendations for vitamin D and calcium along with "talking points" that sites may consult when discussing use of supplements with potential participants.

#### 6.2.2.1 Vitamin D

People who report taking >1000 units/day of supplemental Vitamin D (from all supplements combined) at pre-screening must agree to reduce their dose to ≤ 1000 units/day for the duration of the study.

- For potential volunteers who are taking > 1000 units/day and ≤ 2000 units/day and are willing to reduce the dose to no greater than 1000 units/day for the duration of the study, the screening and baseline visits should be scheduled such that *at the baseline visit*, the person has been *taking ≤1000 IU/day for at least **8** weeks.*
- For potential volunteers who are taking > 2000 IU per day and are willing to reduce the dose to no greater than 1000 IU for the duration of the study, the screening and baseline visits should be scheduled such that *at the baseline visit, the person has been taking ≤1000 IU/day for at least **12** weeks.*

#### 6.2.2.2 Calcium

Participants who report taking > 600 mg/day of supplemental calcium (from all supplements) at pre-screening must agree to reduce their dose ≤ 600 mg/day for the duration of the study and the screening and baseline visits should be scheduled such that at the baseline visit, the person has been taking ≤ 600 mg/day for at least 1 week.

## 6.3 SCREENING VISIT

If the interested volunteer has met all inclusion and no exclusion criteria during pre-screening (preferably, also including meeting some indication of being at increased risk for diabetes), he will be invited in for a screening visit.

If the potential participant wants to read (or if it would be helpful for him to read) the informed consent forms (ICFs) prior to the screening visit, the forms can be sent to him (by mail or e-mail). A site may also make consent forms available on its page on the study's website for interested volunteers to review.

⇒ ***It is important to inform the potential participant that he should come to the screening visit after fasting for 8 hours, to bring all medications and supplements with him, and to not participate in vigorous physical activity for 24 hours before the visit.***

⇒ If a participant ate the morning of the visit, the entire visit should be rescheduled.

⇒ 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.*

### 6.3.1 Informed Consent Process

At first contact with participants, prior to any study specific procedures, the informed consent process will be started. If the first contact is over the phone (see pre-screening above), a sample script (see Appendix) will be read to the potential participant providing a brief overview of the study, informing her that she will be asked questions to determine if she is potentially eligible, and, if she is potentially eligible, she will be invited to the research site for a screening visit.

At the first (screening) visit, written informed consent for the main study will be obtained prior to any study procedures.

Then, the informed consent process for the D2d Research Repository should be initiated. The informed consent process for the Specimen Repository should be conducted following the same guidelines as the consent for the study.

- ✓ *It is highly recommended that the Repository consent be obtained at the same time as consent for the main study. Obtaining consent for the Repository is part of the study and very important to maximize the value of D2d.*
- ✓ Success rate for obtaining Repository consent is expected to be over 95%.
- ✓ Please see Appendix for tips on maximizing the success rate for Repository consent.

The informed consent process is ongoing and interactive. Participants will be given the opportunity to ask questions throughout their participation in the study.

#### 6.3.1.1 Setting

The consent process should be conducted in a comfortable relaxed setting by the site PI or other qualified member of the site research team (e.g. co-investigator, research coordinator, research assistant or clinical research nurse) with in-depth knowledge of D2d, as delegated by the site PI.

#### 6.3.1.2 Content

The full nature of the study (purpose, procedures, risks, potential benefits, etc.) is reviewed in detail.

⇒ *The importance of the study and the need to return for all scheduled visits and follow all study procedures (even if the study pills have been stopped for any reason) will be emphasized.*

⇒ The importance of not starting any diabetes medications to prevent or treat diabetes without first discussing it with the study physician or research coordinator will be emphasized. Potential participants should be told that because new onset diabetes is the main outcome of D2d, the diagnosis of diabetes should be made using study lab tests and that starting a medication for pre-diabetes should not be done prior to the study physician and the participant's PCP discussing it. Sites staff should also emphasize the importance of obtaining permission from the participant to

communicate with her PCP and access her medical records. See Appendix 12 for additional information and talking points.

Volunteers will be informed that they can cease participating in the study at any time for any reason.

#### 6.3.1.3 Discussion

The person responsible for obtaining consent should encourage questions and a discussion. The process must not be rushed. Volunteers must be given ample time to review the ICFs.

#### 6.3.1.4 Assessment of Comprehension

The volunteer should demonstrate an understanding of the study prior to being asked to sign the ICFs. For example, staff may ask the volunteer questions or the volunteer may verbalize what will happen or ask relevant detailed questions.

#### 6.3.1.5 Documentation of Informed Consent

Once all questions have been answered and concerns addressed, the volunteer participant will be asked to sign the written informed consent form for the main study. The ICF must be signed in the presence of the site PI (or designee). The original must be saved in the participant's folder and a copy of the signed form will be provided to the participant.

As documentation of the informed consent process, the following should be included in the source document: who led the discussion, who was present during the discussion, any issues (including any notable concerns or questions raised by the participant), and the date and time when written informed consent was obtained.

Documentation of informed consent is also recorded in the EDC system.

## 6.4 SCREENING ACTIVITIES

After written informed consent has been obtained, screening should proceed as follows:

Note: If at any point during the screening visit, it is determined that the participant meets an exclusion criterion, the remaining activities do not need to be completed.

### 6.4.1 Basic demographic information (if not done previously)

- ✓ Sex, date of birth, race and ethnicity, education level, and family history of diabetes

### 6.4.2 Physical Measurements (vital signs)

- ✓ Measure blood pressure and heart rate, following procedures in MOP section 11. Blood pressure and heart rate are done first, as other measures (e.g. weight) can be stressful and impact blood pressure and heart rate.
- ✓ Measure height and weight following procedures in MOP section 11.
- ✓ Calculate BMI.

- The calculation may be done by entering the height and weight in the vital signs e-CRF. After saving the form, the BMI is calculated (see MOP section 15)
- An online BMI calculator, such as the one provided by the NIH, can be used to calculate BMI (http://www.nhlbi.nih.gov/guidelines/obesity/BMI/bmicalc.htm). Choose the metric tab, and enter in the height and weight measured.

### 6.4.3 Medical history

✓ Obtain complete medical history. This task must be completed by staff trained to take medical history (e.g. physician investigator, nurse practitioner).

✓ The participant should be asked if she has or had any medical problems related to each system, with emphasis on conditions relevant to the inclusion/exclusion criteria (e.g. have you ever had a kidney stone?).

### 6.4.4 Review of concomitant medications and supplements

✓ If the participant came to the visit with her medications and supplements, go over all prescribed medications, over-the-counter medications, and supplements, recording the dosage, frequency, the reason for taking the medication, and start date (approximate is okay). If the participant did not bring the actual medications but came with a list, review the list with the participant and collect as much detail as possible.

✓ If the participant reports taking a medication that is not for the treatment of any condition reported during the medical history, seek clarification from the participant.

✓ Staff, in consultation with the site PI, should review the participant's concomitant medication and supplement list to ensure that the participant is not taking any excluded medications (see MOP section 8).

✓ The research coordinator must add up the total dosage of non-dietary vitamin D a participant is taking, from all supplements combined, to make sure the total daily supplemental dose does not exceed 1000 units/day. For example, 800 units/day in a multivitamin and 2800 units/week [= 400 units/day] from Fosamax Plus D = 1200 units/day, excludes a volunteer.

✓ The research coordinator must add up the total dosage of non-dietary calcium a participant is taking, from all supplements combined, to make sure the total daily supplemental dose does not exceed 600 mg/day.

⇒ ***Special attention should be made to ensure that the participant understands the calcium and vitamin D supplements restrictions and the rationale behind the restrictions*.**

✓ Remind the participant to call the Research Coordinator or designee to discuss any changes in medications between study visits.

✓ Please note that although all medications and supplement use will be recorded in source documents, only certain medications and supplements will be entered in the EDC (see MOP section 8.5.2).

### 6.4.5 Laboratory Specimen Collection

- ✓ Blood will be collected, while participant is fasting. 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 9 for detailed collection instructions.

- ✓ Urine for pregnancy testing will be collected for all women who are premenopausal and not surgically sterile.

- ✓ Provide the participant with food and drink.

- ✓ Review assessment of eligibility based on safety laboratory criteria.

- ✓ Assessment of further eligibility based on glycemic criteria is shown in Figure 6.1 (same as Protocol Figure 6.1)

#### 6.4.5.1 Use of Laboratory Tests done outside of D2d or by finger-stick

If a potential participant had the D2d screening laboratory tests done outside of D2d, the results may *be used in lieu of these labs done at the D2d screening visit, only if all the following criteria are met:*

- Blood samples were obtained via phlebotomy (i.e., not a finger-stick).
- The glucose (plasma or serum) drawn in clinical practice was done while fasting >8 hours overnight.
- The laboratory tests were run at the same local laboratory used by D2d.
- The laboratory tests were done within the time window allowed between screening and baseline visit (see MOP Table 4.2).

⇒ Sites may use a glucose and/or HbA1c result from a finger-stick as a pre-screening approach to see if the participant should proceed to a full screening visit. However, *before qualifying for the baseline visit, results of fasting glucose (from a sodium fluoride tube) and HbA1c (from an EDTA tube*) by the local laboratory must be available.*

**In lieu of an A1c measured by the local laboratory, a site may use a Point-of-Care device for A1c, as long as the device is NGSP-certified.*

### 6.4.6 Eligibility to proceed to Baseline visit

Volunteers will be invited to the baseline visit if they meet the following criteria at the screening visit: (see Figure 6.1):

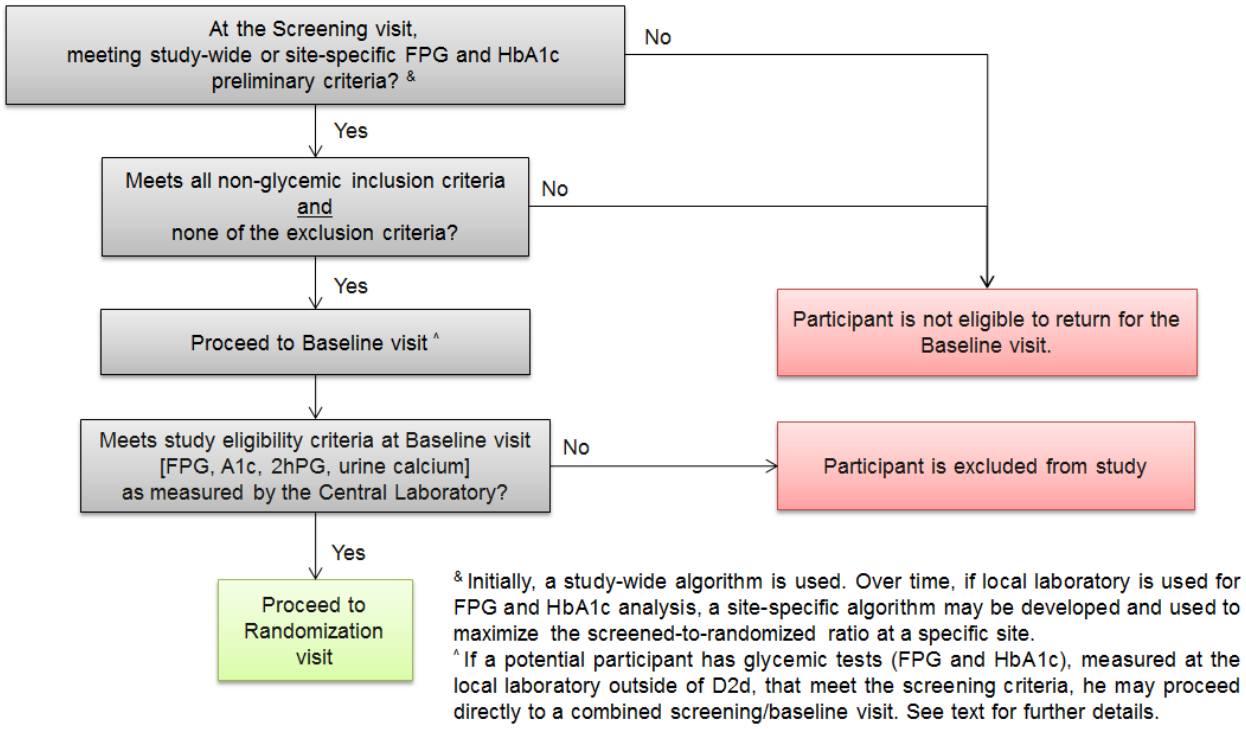
1. FPG and HbA1c results are within range to proceed to the baseline visit, as defined by the study-wide or site-specific glycemic algorithm.

    a. Sites using the Central Laboratory to analyze FPG and HbA1c will use the study-wide default algorithm (see 6.4.6.1 and Appendix).
    b. Sites using a local laboratory to analyze FPG and HbA1c will use the study-wide default

algorithm initially. The success of the default algorithm for a specific site is reviewed by the CC periodically and, if appropriate, a site-specific algorithm can be developed to maximize the screened-to-randomized ratio (see 6.4.6.2).

2. All other non-glycemic inclusion criteria and none of the exclusion criteria

Figure 6.1: Flow diagram of assessment of eligibility at screening and baseline visits

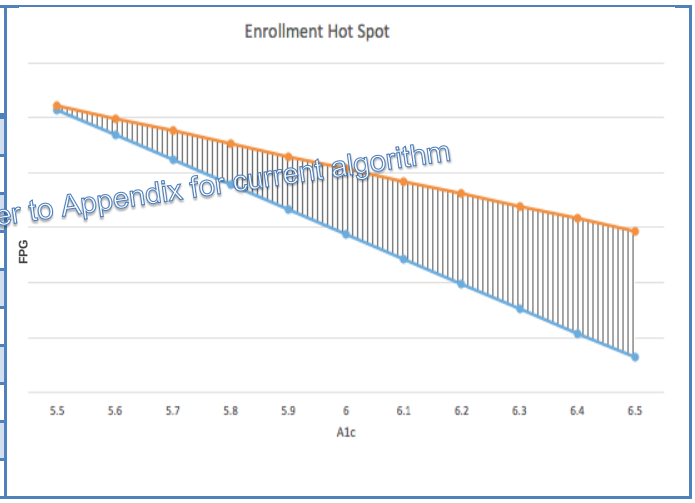



### 6.4.6.1 Default (study-wide) Screening-to-Baseline glycemic algorithm

The study-wide Screening-to-Baseline glycemic algorithm will be used by sites that are (1) using the Central Laboratory for the screening FPG and HbA1c, or (2) using a local laboratory and do not have a site-specific algorithm developed yet. The default algorithm is developed by analyzing available glycemic results to determine glycemia values at screening that will most likely result in eligibility at baseline. The CC will periodically re-evaluate the algorithm and modify, as needed. Please see Appendix for the current algorithm.

Table 6.4.6.1. **Example** Screening to baseline default algorithm

| If HbA1 (%) is: | FPG (mg/dL) must be within this range |
|---|---|
| 5.6 | # - # |
| 5.7 | # - # |
| 5.8 | # - # |
| 5.9 | # - # |
| 6.0 | # - # |
| 6.1 | # - # |
| 6.2 | # - # |
| 6.3 | # - # |
| 6.4 | # - # |
| 6.5 | # - # |




### 6.4.6.2 Site-Specific Screening-to-Baseline glycemic algorithm

The success of the default Screening-to-Baseline algorithm for a specific site is reviewed periodically by the site and Coordinating Center, and, if appropriate, a site-specific algorithm is developed to maximize the screened-to-randomized ratio for that site, as follows:

- The CC provides to the sites a table with the glycemic data obtained at the Screening visit (by the local laboratory) and Baseline visit (by the Central Laboratory)
- The site reviews and compares the results of the FPG and HbA1c obtained at the Screening visit to the results obtained at the Baseline visit.
- The site proposes to the CC a Site Specific Screening-to-Baseline glycemic algorithm in writing, using the Site Specific Screening-to-Baseline Glycemic Algorithm Proposal form (see appendix). The proposal must include the specific algorithm to be followed and the rationale for it.
- The CC reviews and approves the algorithm prior to site's adopting the site-specific algorithm.
- Alternatively, the CC may propose an algorithm that the site must review and approve.

### 6.4.6.3 Repeating Screening Glycemic Labs

If a participant misses a screening glycemic criterion, by a small margin (defined as margin of error for FPG ± 3 mg/dL or HbA1c ± 0.1%), the glycemic criterion that missed the margin (FPG or HbA1c) can be repeated once. The repeat test should be done within a short period to ensure that the time elapsed between the original screening date and the baseline visit remains within the allotted window (see schedule in see MOP Table 4.2).

If a participant misses a screening glycemic criterion, and it is determined, after the visit, that there is a clear explanation for a larger margin than the one indicated above (e.g. participant donated whole blood or had an infection a few weeks before the visit), the glycemic criterion that missed the margin (FPG or HbA1c) may be repeated; however, *such exceptions should be uncommon* and supported by an explanation that needs to be documented in the source documents.

The result of the repeat measure will be entered into the EDC screening local laboratory e-CRF and the new value will be used to determine if the participant meets the criteria to proceed to the baseline visit.

- ✓ Site staff should enter the result of the repeat measure by replacing the original value.
- ✓ The date of the repeat measure cannot be entered in the e-CRF

### 6.4.7 Screening Visit Administrative Activities

If it appears from the history and physical measures that the participant may be eligible to return for the baseline visit, obtain the following information, if it was not obtained previously.

#### 6.4.7.1 Contact Information

Participants will state their preferred method of communication (email, phone, text, etc.) with the research staff. If e-mail is agreed upon as the preferred method of communication, participants should be instructed to respond to emails, thereby letting the research staff sender know the message was received. It is best to obtain a few different ways to reach the participant. Please see source document titled Participant Contact Information in MOP section 13.

#### 6.4.7.2 Medical Release

- ✓ Offer to share the participant's laboratory results with her primary care provider (PCP).
    - o However, explain that actual results will be provided only at the BAS visit and after diabetes has been diagnosed. Until that point, only the outcome of the results (e.g. diabetes has not yet developed) will be available.
- ✓ Explain that D2d procedures require that the PCP provides results of laboratory tests done in the PCP's office to D2d site staff.
- ✓ Have the participant sign a medical release authorizing you to share information with the PCP and authorizing the PCP to share information with the research staff.
- ✓ There is no template form provided by D2d. Please use a site-specific medical release form.

### 6.4.8 Establish a follow-up plan with the participant

A site can either:

a. Make a tentative baseline appointment for the participant and confirm the date once the glycemia and safety laboratory results have been reviewed.

b. Set up a time to call the participant and report the results and, if participant qualifies, schedule the baseline appointment.

### 6.4.9 Screening failures

If, during the screening visit, it is determined a participant meets an exclusion criterion, his participation will end and no other screening activities need to be completed. The participant should be provided with a snack and drink and thanked for his time and effort.

If, after reviewing the screening laboratory results, the participant does not qualify to return for the baseline visit, she should be notified by her preferred method of communication (e.g. phone, email).

- ✓ A personal thank you note signed by the staff that met with the participant should be sent a few days after the visit, thanking the person for her willingness to come to a screening visit. Personal thank you notes are often a pleasant surprise and an appreciated gesture, which may lead to future willingness to participate in research, or may lead to referrals from friends or relatives who may also be at risk for diabetes.

#### 6.4.9.1 Repeat screening

A repeat screening is defined as a full screening, i.e., <u>all</u> screening procedures are repeated.

PLEASE NOTE (see also section 6.4.6.3): If a participant misses a screening criterion (e.g. creatinine) by a small margin, he may return to have just that criterion re-measured, *within a short period to ensure that the time elapsed between the original screening date and the baseline visit remains within the allotted window*. If the participant cannot return within a short period to respect the screening-randomization window, the entire screening visit will need to be repeated (see below).

- ✓ A repeat screening is encouraged ONLY if there is a high likelihood that a participant will meet the inclusion/exclusion criteria at the repeat screening because the exclusion criterion is modifiable and may improve (e.g. elevated blood pressure, recent initiation of oral contraceptives) or may evolve (e.g. the participant missed two out of three glycemic criteria by a small margin at the prior screening visit, but it is now a year later and the participant has gained or lost some weight).

If there is a high likelihood that a participant will meet the inclusion/exclusion criteria at a repeat screening, the participant should be informed to contact the site in the future for re-screening. The site should also note the circumstances and plan on re-contacting the participant if appropriate.

- ✓ It is strongly recommended than participants do not return for a repeat (full) screening until 6 months have passed since the prior screening. This is recommended to ensure that a condition that previously disqualified a participant has changed sufficiently to increase the odds of the participant meeting the criteria on repeat screening.
- ✓ When a participant returns for a repeat screening visit 6 months or more after the original screening visit, a new ID number is generated as if the participant was a new participant.
- ✓ All data from the repeat screening (and all subsequent visits) are entered into EDC using the new ID number. <u>Data from the prior screening are not replaced.</u>
- ✓ When entering the participant into EDC, the original ID number should be recorded on the Subject Form to provide a link to the initial screening/baseline visits.

⇒ A participant may be re-screened up to an additional two times (i.e., total of three D2d screenings).

#### 6.4.9.2 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 at the screening (either HbA1c or FPG exceeds the site specific algorithm) or baseline (HbA1c ≥ 6.5%, FPG ≥ 126 mg/dL, or 2hPG ≥ 200 mg/dL) visits. These people are ineligible to participate in D2d and they will receive an informational letter (see Appendix) 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:

- ✓ 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.

#### 6.4.9.3 Hemoglobin Variant (S, C, or E) detected at the Baseline visit

As part of the routine HbA1c assay at baseline, the Central Laboratory may identify hemoglobin variants, which are detected as different spikes on HPLC. Hemoglobin variants may have implications for the HbA1c assay, as some variants interfere with the assay. The Central Laboratory uses the ion-exchange HPLC method on Tosoh G8. Hemoglobin E is a common variant hemoglobin that interferes with the assay.

If a hemoglobin **S** or **C** variant is detected, the Central Laboratory will send the site an e-mail notifying the site that a variant trait was detected and that the HbA1c result will be uploaded to EDC. The following is the sample e-mail text:

> *Evidence of Hemoglobin (INSERT S or C) trait was identified in the course of performing HbA1c testing. This testing, while performed in CLIA-certified laboratories, was performed for research purposes. If this condition was previously unknown to the participant, then consideration should be given to confirmatory testing in a clinical setting if clinically indicated. This data will be uploaded shortly. Please confirm you have received and read this email at your earliest convenience.*

If a hemoglobin **E** variant is detected, the Central Laboratory will send the site an e-mail notifying them that the trait was detected and that the HbA1c results will not be uploaded to the EDC. Participants with the hemoglobin E variant are not eligible for participation in the study.

- ✓ The site investigator or research team member will notify study eligible participant's during the randomization visit that a hemoglobin variant was detected and provide the participant with the participant information handout specific (see appendices 7, 8, 9) to the variant detected.

- ✓ Participants who do not meet the eligibility criteria to proceed to randomization will be notified during the follow-up phone call and will be sent the participant information handout specific (see appendices 7, 8, 9) to the variant detected.
- ✓ If the participant signed a release of medical information, the study site will send a letter to the participant's primary care provider including information on the detection of the hemoglobin variant.

Participants will be encouraged to share the information with their primary care provider and have the presence of the variant confirmed in a clinical laboratory.

## 6.5 COMBINED SCREENING/BASELINE VISIT

The combined Screening/Baseline visit can be an efficient way to screen participants who are highly likely to be eligible.

### 6.5.1 Requirements for a combined screening/baseline visit

If a potential participant has glycemic tests (FPG and/or HbA1c), measured outside of D2d, and the results meet the screening criteria, he may proceed directly to a combined screening/baseline visit, as long as all criteria outlined below are met.

- Blood samples were obtained via phlebotomy (i.e., not a finger-stick).
- The glucose (plasma or serum) drawn in clinical practice was done while fasting >8 hours overnight.
- The laboratory tests were done within 12 months of the combined screening/baseline visit.

### 6.5.2 Procedures during a combined screening/baseline visit

- ✓ The informed consent process must be completed before any study procedures are started.
- ✓ Any screening blood tests that have not been done by the local laboratory in the past 6 weeks will be drawn and sent to the local laboratory for analysis.
- ✓ All baseline blood and urine will be collected (fasting and during the 2-hour OGTT) for baseline measurements and processed as described in MOP section 9. However, data relevant to the baseline visit will not be entered in EDC and samples will not be sent to the Central Laboratory until it is determined that the participant meets *all screening criteria, i.e., all screening local laboratory results have been received, reviewed, and entered into EDC. If the participant does not meet the screening eligibility criteria, the baseline specimens will not be sent to the Central Laboratory and will be discarded*.

  **Note:** if a combined screening/baseline visit is being conducted, the Central Laboratory cannot be used for the analysis of the screening FPG and HbA1c.

⇒ The combined screening/baseline visit is a very efficient method for screening but should be done *only if there is a very high likelihood that the volunteer will qualify for the study*. For example, if a volunteer had an A1c of 6% and normal GFR five months ago and no other data, a combined visit would be appropriate. However, if a volunteer had a glucose concentration of 120 mg/dL at 10 am and no other data, a combined visit would not be appropriate. Also, the combined visit should only

be done if the site has a quick turnaround of local laboratory results to ensure that the schedule for sending blood/urine to the Central Laboratory is not compromised.

EXAMPLE: Four weeks ago, a potential volunteer had HbA1c (6%) ALT, AST, and creatinine (normal) measured at the local laboratory as part of routine care (outside of D2d), within the time frame described above. If these tests meet the D2d criteria, the volunteer can come in for a combined screening/baseline visit to complete the remaining screening procedures (e.g. signing of informed consent form, BMI, blood pressure, FPG, CBC, serum calcium) and the OGTT. Blood and urine collected for baseline measurements are processed locally and saved. All screening data are entered into EDC and if the participant meets all screening criteria (including the missing laboratory tests done at the visit), data relevant to the BAS visit are entered in EDC, and the blood and urine are sent to the central laboratory.

#### 6.5.2.1 Screening/Baseline Visit Activities

- ☐ Written informed consent
- ☐ Vital signs, including waist circumference: *Confirm that participant meets BMI and blood pressure eligibility criteria before proceeding*
- ☐ Medical history: *Confirm that participant meets eligibility criteria before proceeding*
- ☐ Medication and supplement review: *Confirm that participant is not taking any excluded medications (see MOP 8, section 8.4)*
- ☐ Physical Exam (may be done at the randomization visit, prior to randomization in SPIRS).
- ☐ OGTT procedure
- ☐ Fasting laboratory specimen collection (MOP 9, section 9.7.3 and appendix 7)
    - o FPG*
    - o HbA1c*
    - o Urine pregnancy test (if female of reproductive potential)
    - o CBC without differential*
    - o ALT, AST*
    - o Serum calcium*
    - o Serum creatinine*
    - o Baseline fasting tubes for the Central Laboratory
- ☐ *Send specimens for local analysis to local laboratory and begin processing specimens for the Central Laboratory*
- ☐ Begin questionnaires (FFQ, IPAQ)
- ☐ 30 minute laboratory specimen collection (MOP 9, section 9.7.3 and appendix 7)
- ☐ 120 minute laboratory specimen collection (MOP 9, section 9.7.3 and appendix 7)
- ☐ Complete all screening e-CRFs
- ☐ If participant meets screening eligibility criteria complete baseline e-CRFs and send specimens to Central Laboratory. *Do not send specimens to Central laboratory until all Screening e-CRFs and baseline e-CRFs have been completed.*

** Repeat if not available (see 6.5.1)*

## 6.6 APPENDICES

**Appendix 1** **Pre-screening Template Introductory Phone Script**

**Appendix 2** **Pre-screening Template Inclusion Exclusion Criteria Questionnaire (includes BMI Table)**

**Appendix 3** **Diabetes Risk Test**

**Appendix 4** **Talking Points about Vitamin D and Calcium supplementation**

**Appendix 5** **Site-specific Glycemic Algorithm Proposal Form**

**Appendix 6a** **Letter to Provider – Screening/Baseline Diabetes**

**Appendix 6b** **Letter to Participant – Not eligible after Screening**

**Appendix 6c** **Letter to Participant – Not eligible after Baseline**

**Appendix 7** **Participant Information Hemoglobin Variant S**

**Appendix 8** **Participant Information Hemoglobin Variant C**

**Appendix 9** **Participant Information Hemoglobin Variant E**

**Appendix 10** **Study-wide Screening-to-Baseline Glycemic Algorithm**

**Appendix 11** **Tips on the Consenting Process for the D2d Biorepository**

**Appendix 12** **Talking Points about Vitamin D and Calcium supplementation**