DSMB-approved Protocol

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Primary Objective | Overview

Objective: To evaluate the safety of oral daily vitamin D supplementation and its effect on the time to onset of clinical diabetes in participants at risk for diabetes (with pre-diabetes).

Secondary Outcomes

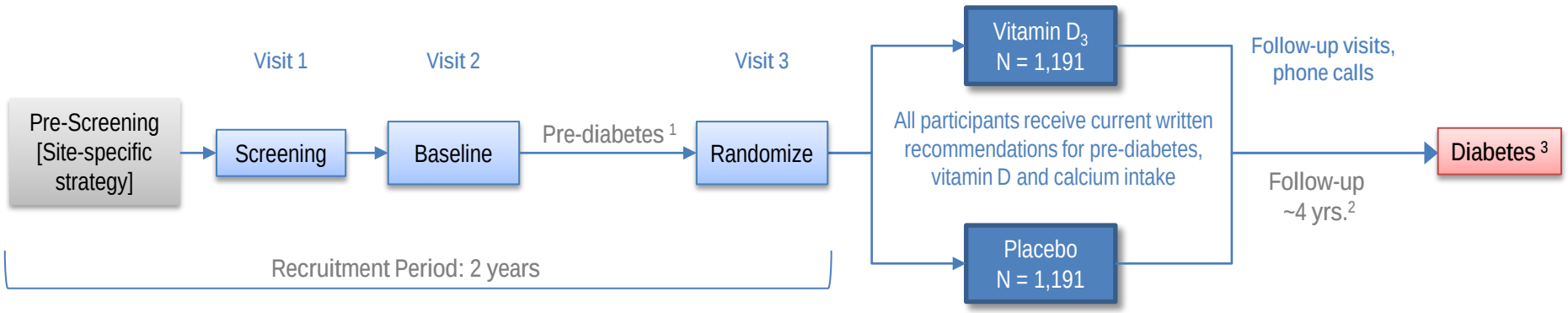
- Variability of response to vitamin D supplementation in subgroups defined by baseline characteristics:
  1. Race and ethnicity (as proxies for skin pigmentation)
  2. BMI
  3. Waist circumference
  4. Age
  5. Geographic location (proxy for sun exposure);
  6. Calcium intake
  7. 25OHD concentration
- Variability of response to vitamin D supplementation by
  1. Adherence based on pills counts
  2. Achieved 25OH concentration
- Glycemia and glucose-insulin dynamics (continuous variables)
  - HbA1c, FPG and 2hPG
  - Insulin resistance, secretion, disposition index (OGTT-based indices)

Secondary Outcomes (cont.)

- Plasma 25OHD concentration and identification of phenotypic characteristics associated with variability on achieved plasma 25OHD concentration
- Cardiovascular risk factors
  - Blood pressure
  - ~~Lipid profile~~
  - ~~CRP~~
- ~~Urine albumin excretion [albumin-creatinine ratio]~~
- Safety and tolerability of vitamin D supplementation
- Major adverse cardiovascular events (as part of AE/SAE)

- **Ancillary studies** will be developed, evaluated, approved and integrated

Overview



1 Pre-diabetes (2 out of 3 glycemic criteria are met: FPG 100-125 mg/dL; HbA1c 5.7-6.4%; 2hrPG 140-199 mg/dL).

2 Participants will be followed up to 4 years, depending upon time of enrollment; mean follow-up is estimated to be ~3 years. Because D2d is an event-driven trial, follow-up periods are estimates and will depend on actual rates of enrollment and retention.

3 Diabetes by laboratory criteria (1 out of 3 glycemic criteria are met: FPG ≥126 mg/dL; Hb A1c ≥6.5%; 2hrPG ≥200mg/dL).

Schedule of Procedures

Point of Contact	Screening[1]	Baseline	Randomization	M03	M06	M09 (Phone)	M12	Interim Phone	Semi-annual	Annual	Confirm	End-of-study	As needed
	Day -49 to -7	Day -21 to -5	Day 0	Day 76 to 104	Day 166 to 194	Day 256 to 284	Day 346 to 374	Midpoint between visits (M15, M21, M27, M33, M39, M45, 6 wks after last visit)	Midpoint between annual visits (M18, M30, M42)	(M24, M36, M48)			
Written informed consent	X												
Medical history	X[2]	[3]		[3]	[3]	[3]	[3]	[3]	[3]	[3]		X[2]	X
Physical examination	X[2]	[4]		[4]	[4]		[4]		[4]	[4]		X[2]	X
Non-study medication review	X	X		X	X	X	X	X	X	X	X	X	X
Vital signs [5]	X	X		X	X		X		X	X		X	X
Waist circumference		X											
Questionnaires													
FFQ		X					X[6]			X[6]			
Physical Activity		X			X		X			X			
Lifestyle counseling [7]		X											
Randomization			X										
Study pill distribution, teaching			X		X		X		X	X			
Study pill adherence					X		X		X	X			
Laboratory specimen collection [8]													
CBC, LFT, Pregnancy [9]	L												L
Serum calcium, creatinine (GFR)	L			L			L			L		L	L
HbA1c, FPG [10]	L	C			C		C		C	C	C[12]	C[15]	C
2hPG (OGTT) [10.11]		C					C			C	C[13]		
Glu_{30} (OGTT) [11]		C					C			C			
25-hydroxyvitamin D		C					C			C			
Insulin [11]		C					C			C			
Urine calcium-creatinine ratio[10]		C		C			C			C		C	
Plasma and serum for storage		C			C		C			C			
Urine for storage		C					C			C			
Whole blood for DNA		C											
Adverse event review		X	X	X	X	X	X	X	X	X	X	X	X
Letter to physician			X[14]		X[14]					X[14]	X[15]		

Inclusion criteria

- Pre-diabetes ("at increased risk for diabetes"), meeting 2-out-of-3 criteria at baseline:
  - Fasting plasma glucose (FPG) 100-125 mg/dL SCR, BAS
  - 2-hour plasma glucose (2hPG) 140-199 mg/dL BAS
  - Hemoglobin A1c (HbA1c) 5.7-6.4% SCR, BAS
- Age ≥ 30 years
- BMI≥ 25 (23 if Asian) and ≤40 kg/m^2
- Written informed consent

Exclusion criteria

- Diabetes
  - Medication use
  - Glycemic criteria (at screening [local] and baseline [central])
- Safety concerns
  - Hyperparathyroidism
  - Nephrolithiasis
  - Hypercalcemia
- Any medical condition (past 3 years) that in the opinion of the site investigator may increase risk for nephrolithiasis or hypercalcemia during the trial (e.g., sarcoidosis).
- Use of tanning beds

Exclusion criteria | Medication and Supplements

- Vitamin D supplement > 1000 IU/d
- Calcium supplement > 600 mg/d
- Use of medications or conditions (e.g. untreated celiac disease) that would interfere with absorption or metabolism of vitamin D
- Weight management medication
- Use of thiazide greater than 37.5 mg/day
- Use of anticonvulsant (=valproate) started within 6m of screening
- Intolerance to vitamin D

Exclusion criteria | Other Medical History

- Symptomatic cardiovascular disease based on history and physical examination
- History (1 yr.) of myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft.
- History (1 yr.) of cerebrovascular disease
- Any type of cancer (5 yrs.) except for basal cell skin cancer.
  - Prostate cancer (for men over age 55) or well-differentiated thyroid cancer not expected to require treatment (except for suppression with thyroid hormone) over the next 4 years, are not exclusions.
- History (past 6 m) of treatment with oral (for > 7 days) or intravenous glucocorticoids or disease likely to require oral or intravenous glucocorticoid therapy during the study
  - Inhaled glucocorticoids are *not* excluded.

Exclusion criteria | Other Medical History (cont.)

- History (past 1 year) of substance abuse or unstable psychiatric disorder that in the opinion of the site investigator would impede competence or adherence with study procedures or hinder completion of the study or increase risk.
- History of bariatric surgery (e.g. Roux-en-Y Gastric Bypass) or planned bariatric surgery in the next 4 years.
- A life-threatening event within 30 days of screening or currently planned major surgery.
- Any other unstable active medical condition that in the opinion of the site investigators would impede competence or adherence with study procedures or increase risk.
- Uncontrolled hypertension (SBP>160 or DBP>100 mmHg).
- Poor venous access.

Exclusion criteria | Laboratory Evaluation

- Serum liver transaminase higher than 3 times ULN
- Anemia, transfusion (within 6m of screening or chronic requirement), blood donation (within 3m of screening) or other condition (hemolysis, hemoglobinopathy) rendering HbA1c results unreliable as indicator of chronic glycemia.
  - Transfusion or blood donation does *not* exclude participant
- Low platelet count (< 50,000).
- Chronic kidney disease, [GFR] < 50 mL/min per 1.73m^2
- Hypercalcemia, defined as serum calcium concentration greater than or equal to the upper limit of normal, measured at the clinical site's laboratory.
  - Hypercalciuria, defined as spot urine (morning void) calcium-creatinine ratio > 0.275 SCR, BAS

Exclusion criteria | Other

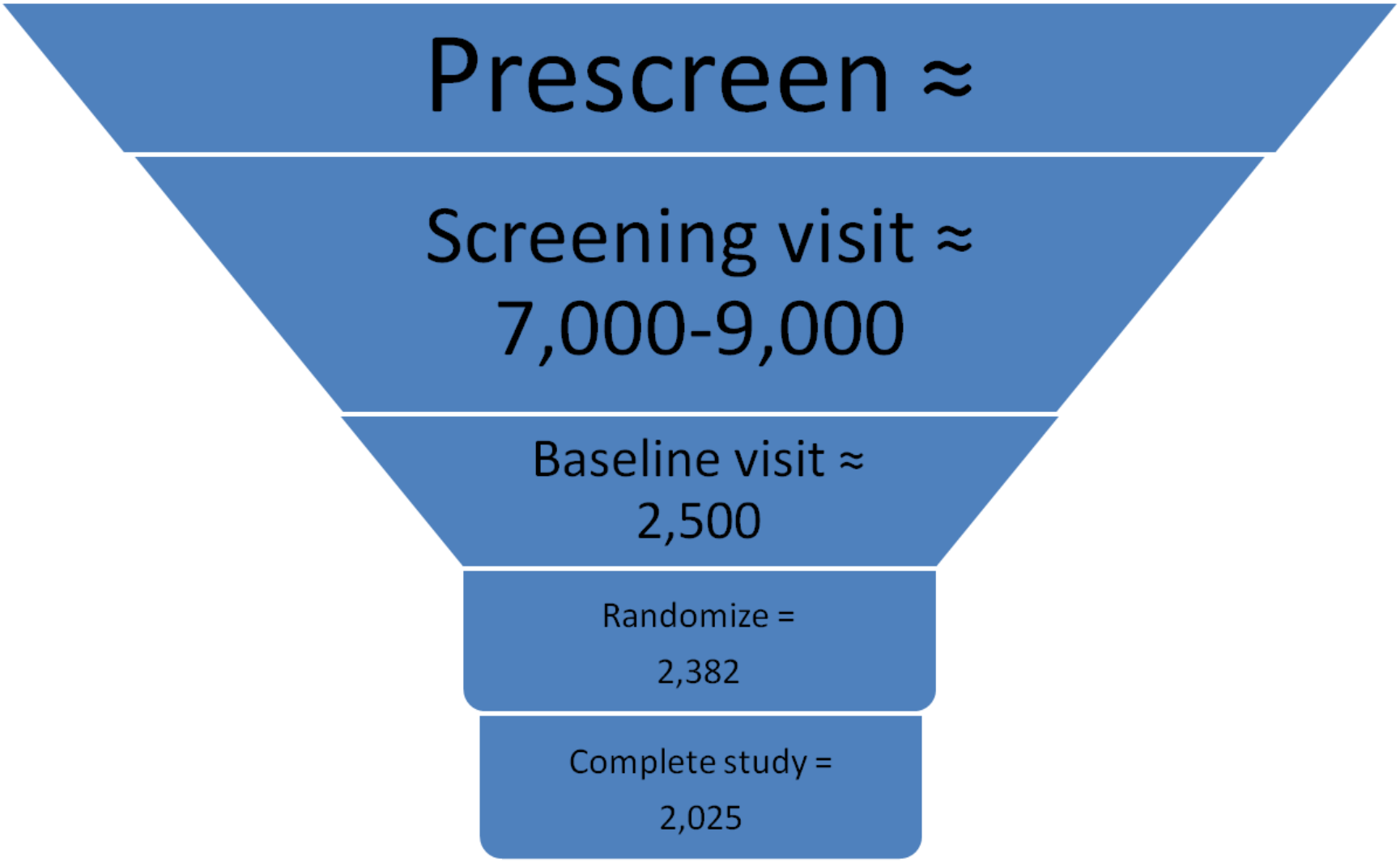
- Participation (within 30 days of screening) in another interventional research study.
- Previous randomization in D2d.
  - Participants who did not qualify after screening may be screened again if the prior reason for exclusion has been addressed (e.g. high blood pressure is treated).
- Any other reason that in the opinion of the site investigator would impede adherence with study procedures or hinder completion of the study or increase risk.

Exclusion criteria | Women only

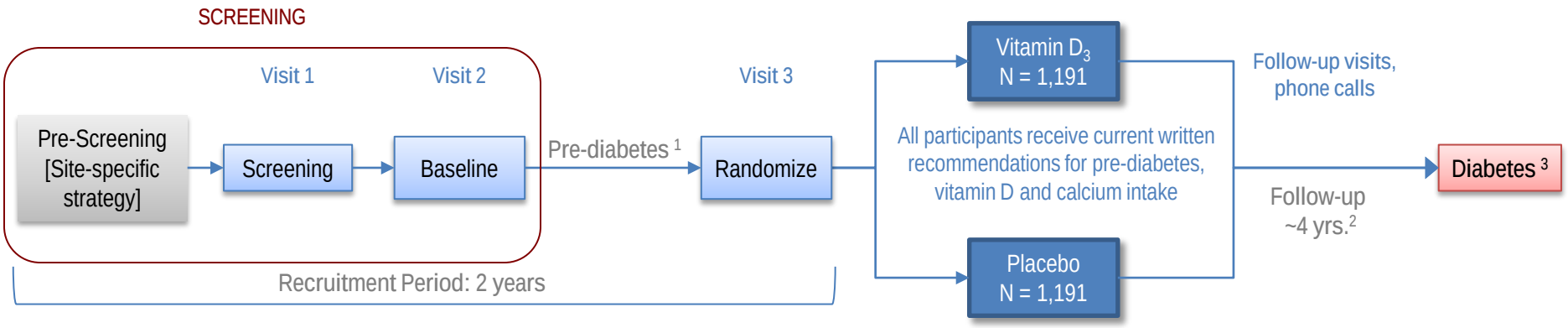
- Pregnancy (past 1 year by report or positive pregnancy test at screening), intent to become pregnant in the next 4 years or unprotected intercourse.
  - History of gestational diabetes is *not* an exclusion criterion.
- Currently breastfeeding.
- Use of oral contraceptives started within 3 months of baseline.
  - Stable regimen of oral contraceptives or any other hormonal method of contraception (e.g. implantable) is allowed.

Questions on Inclusion-Exclusion Criteria?

Recruitment and Enrollment Goals



Screening



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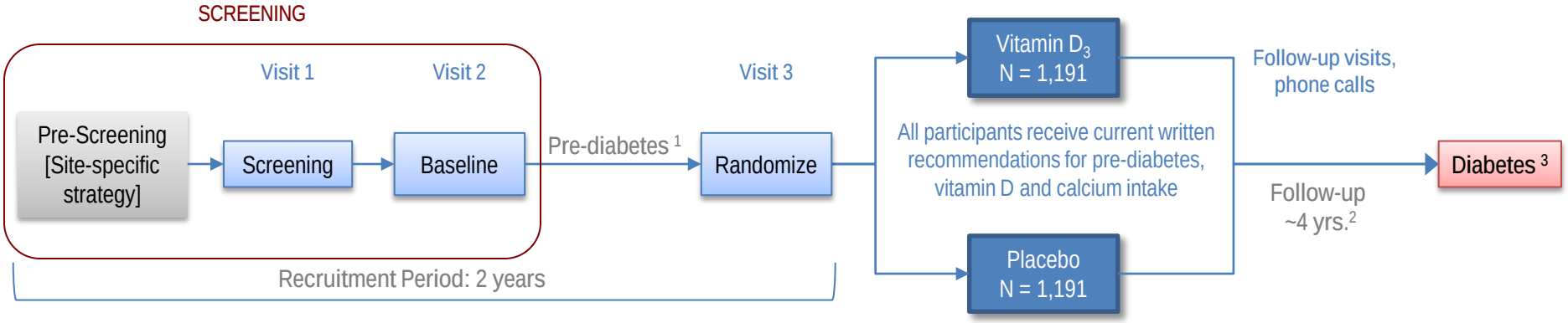
Pre-screening Objectives

1. Promote efficiency in identifying candidates with high likelihood of eligibility after formal screening
2. Initiate the informed consent process
3. Identify *potentially eligible* participants
   - Conduct a preliminary verification of eligibility (e.g. ADA risk score)
4. Site-specific: Allow sites flexibility in their approach of recruiting participants, while maintaining a study-specific set of inclusion/exclusion criteria.
   - Database queries
   - Over the phone
   - Over the web
   - In-person

Screening Visit

- Demographics
- Medical history and physical measurements
- Review concomitant medications and supplements
  - Daily total intake of non-dietary vitamin D and calcium
- Physical examination
- Screening labs (Screening and Baseline visits)



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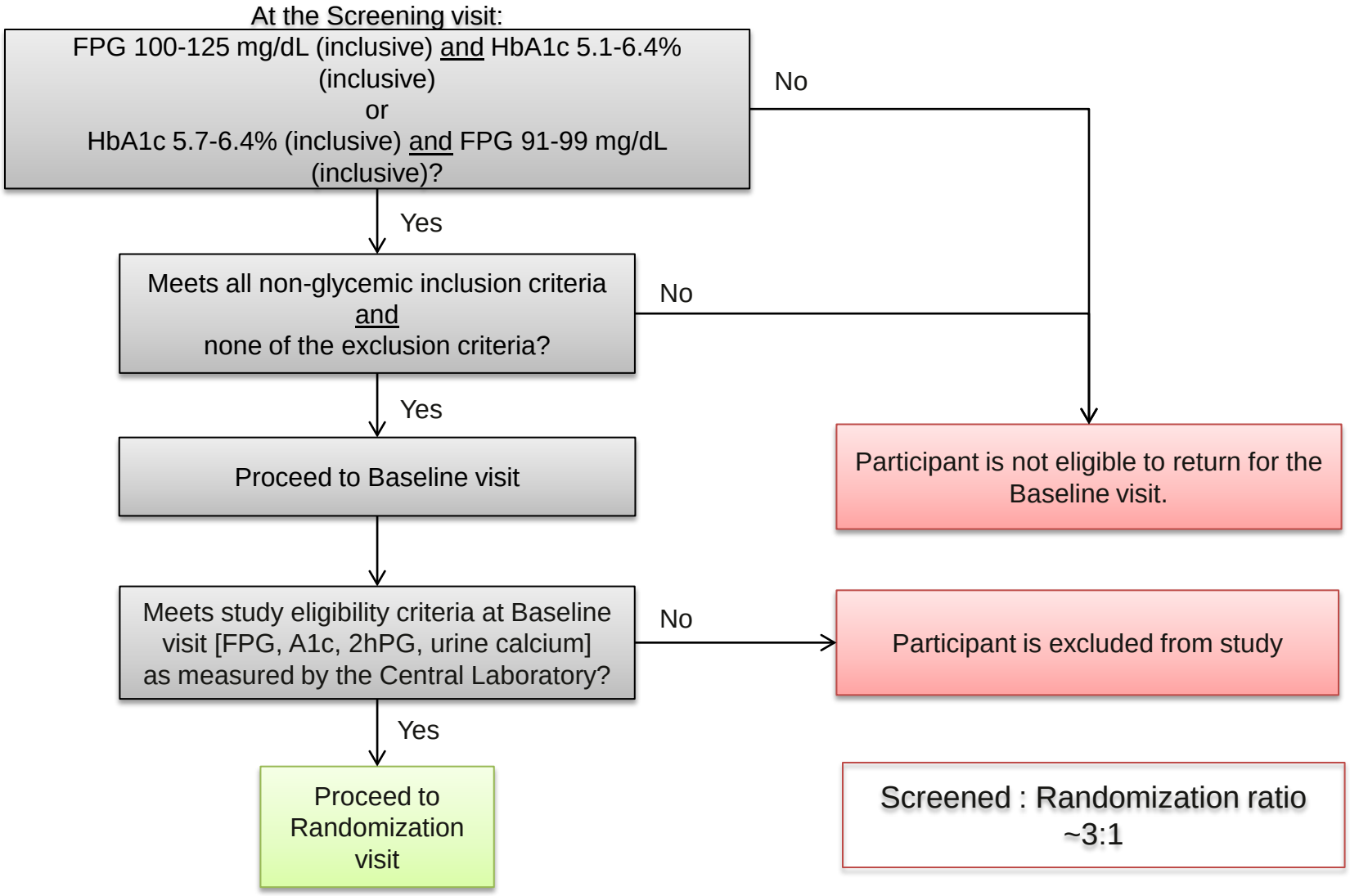
Screening Laboratory Tests

- Analyzed *at the site's clinical laboratory during the screening visit.*
- Results provided to participants and their health care provider(s).
  - Complete blood count
  - Liver transaminases (AST, ALT)
  - Serum calcium
  - Serum creatinine and estimated creatinine clearance (GFR, calculated centrally)
  - Pregnancy test for women of reproductive potential.
  - FPG (preliminary eligibility)
  - HbA1c (preliminary eligibility)
- Analyzed *at the Central Laboratory during the baseline visit.*
- Results provided to participants and their health care provider(s).
  - Urine calcium-creatinine ratio (early morning spot urine specimen)
  - FPG
  - HbA1c
  - 2hPG (OGTT)

Screening = Screening visit and Baseline visit



Questions on Screening?

Intervention and Randomization Scheme

- Cholecalciferol (D_3) 4,000 IU soft-gel pill or identical placebo taken daily with breakfast (double-masked).

- Randomization (1:1)
  - Stratified:
    - Site
    - BMI (<30 or ≥30 kg/m^2)
    - Race (White vs. non-White)
  - Blocked: 4 or 8 in random order
  - Conducted via web-based system (SPIRS managed by DDC)
- Study pills provided to participants every 6 months

Intervention – Rationale for Dose and Frequency cholecalciferol 4,000 IU/day

- Efficacy
  - Achieve adequate difference in 25OHD between active and placebo arms
  - 4,000 IU/day expected to increase 25OHD ~40-45 ng/mL [Vieth, 2004; Aloia, 2008; Mitri, 2011; Gallagher, 2012]
- Safety
  - 4,000 IU/day is the IOM-Tolerable Upper Intake Level
  - Large infrequent doses may not be physiologic and may be associated with adverse skeletal outcomes.

Intervention – rationale for choice of placebo

- Participants should receive standard of care.
  - IOM age-specific dietary reference intakes (600, 800 IU/day).
- Supply IOM-recommended amount in placebo would complicate study design and cost.

✓ True placebo with recommendations for all to meet IOM recommended amounts for vitamin D.

- ✓ Participants will be allowed up to 1,000 IU/day of vitamin D.

✓ Participants will be allowed up to 600 mg/day of calcium supplements.

Rationale for lack of "low vitamin D status" as an inclusion criterion

- In CaDDM study, vitamin D had effect regardless of baseline 25OHD concentration.
- Controversy about "optimal" 25OHD concentration.
- Difficult to interpret single 25OHD concentration (e.g. seasonal variability).
  - Screening would be cumbersome and expensive
- D2d population will have 25OHD ~20-25 ng/mL
- Widen generalizability of results.
- Use of baseline 25OHD will be used in Heterogeneity of Treatment Effect (HTE) analyses.

Intervention – rationale for lack of 25OHD target

- 25OHD is not a validated health outcome surrogate.
- Specific cut-points for type 2 diabetes are not established.
  - HTE analyses will examine such cutoffs.
- Aiming, achieving and maintaining a target 25OHD is complicated.
- Such an approach:
  - minimizes expense and burden.
  - maximizes clinical applicability.

Questions on study pill choice?

Breaking of Randomization Code (unmasking) = rare

- Unmasking will occur only if
  - Serious adverse event (SAE) or any other adverse event (AE) that is "severe" and "probably/definitely related" to the study pill, *and*
  - The site PI (and site study physician) determines it is necessary for the care of the participant to be unmasked
- It is expected that almost all AE and SAEs will be handled without unmasking.
- Participants who are unmasked will not go "off study"

Modification of Study Intervention

- Study pills will be held or discontinued for safety
  - Permanently discontinued
    - Hypercalcemia, nephrolithiasis, hypercalciuria, kidney dysfunction
  - Held or discontinued
    - Other safety concern
    - Participant's request
  - Held
    - Pregnancy and lactation

Quiz

Participants who discontinue study pills will go “off study.”

- A. True
- B. False

Terms that are easily confused
Non-retention | Non-adherence | Inactive | Lost-to-follow-up

- "Non-retention" (i.e., off study) ≠ "non-adherence" (i.e., off study medication)
- 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.

- Participants, for safety reasons, personal choice or any other reason, may need to go "off study medication." However, they will continue with outcomes assessment as planned.
- Participants who are lost to follow-up but have not gone formally "off study" (i.e. have not provided a verbal or written *withdrawal of consent*) will be termed "inactive" to reflect the possibility that they will resume adherence with study medication and will return for outcomes measurements.

Quiz

The term “lost-to-follow-up” can

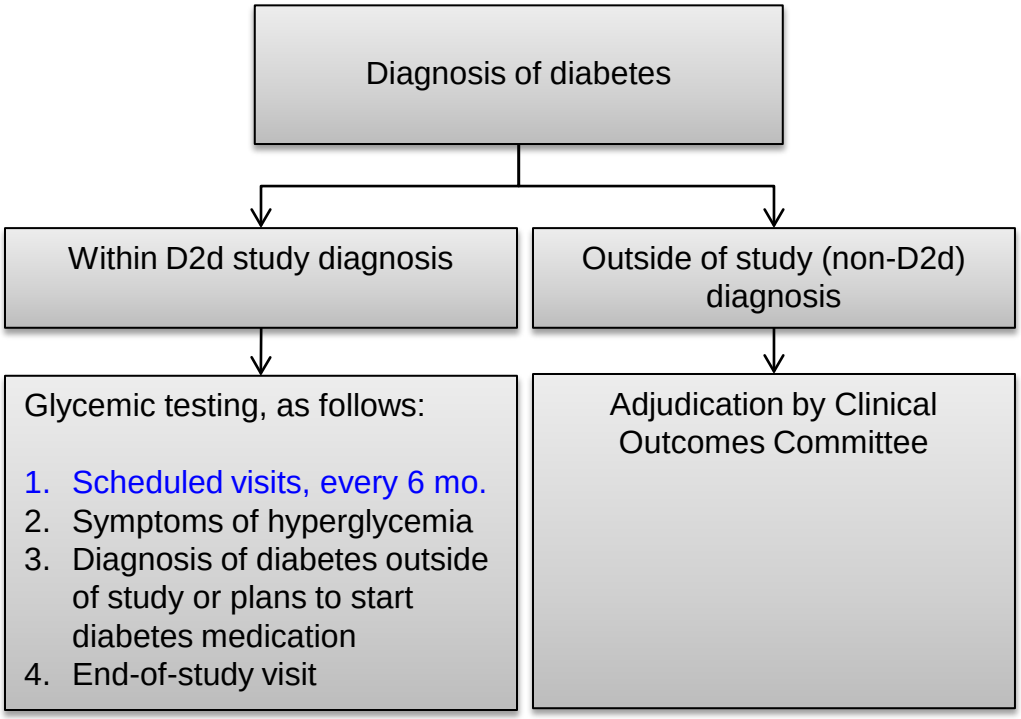
- A. ...be used at any time during the study
- B. …never be used
- C. …only be used after the study ends

Support and Education Program

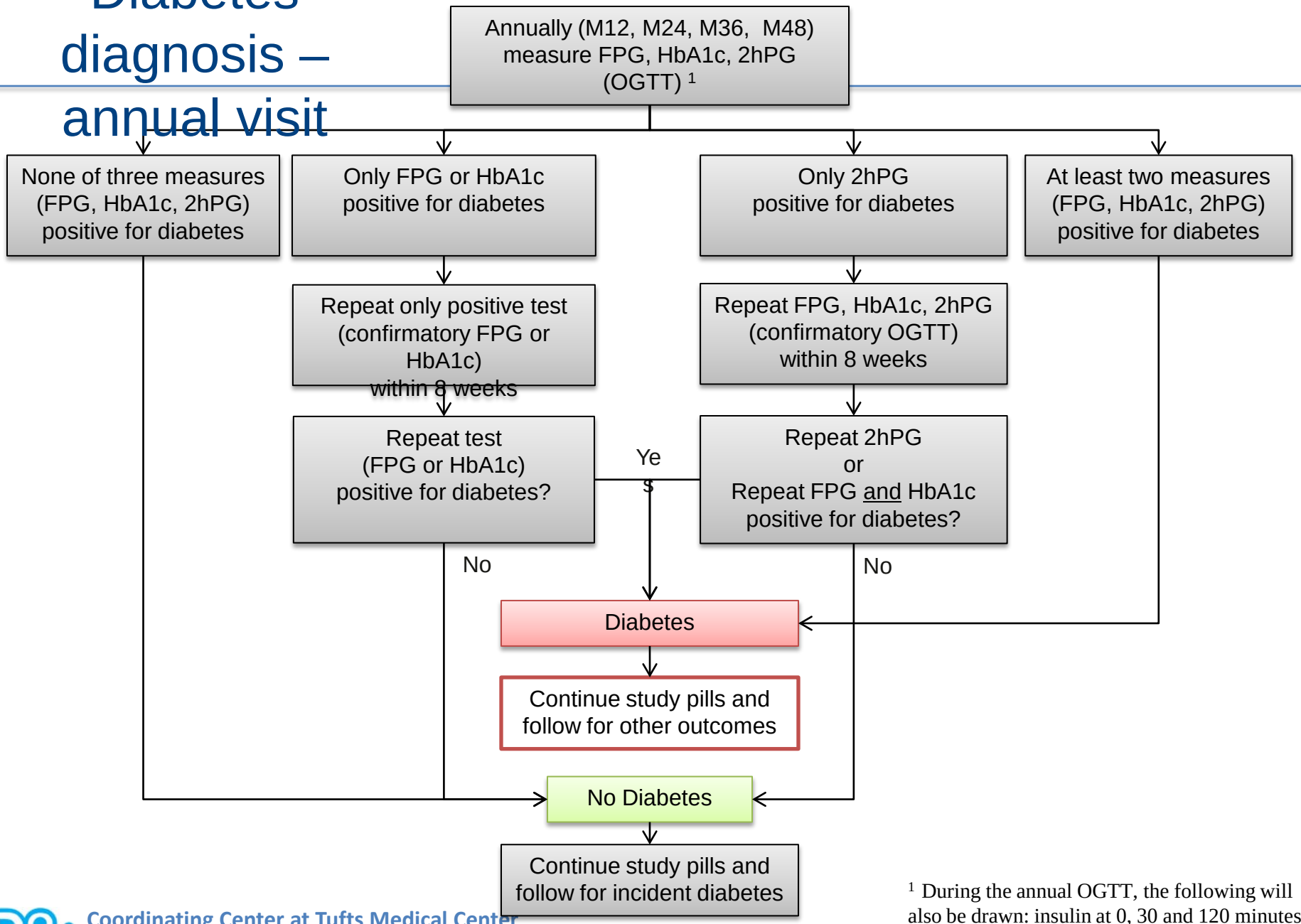
- Baseline
  - Written information
    - National Diabetes Education Program
  - Send letter to participants' physicians
- Intra-study Support and Educational Program
  - Twice yearly group meetings covering a variety of lifestyle-based topics
  - Newsletter that may include lifestyle advice

Questions on Intervention?

Primary outcome: incident diabetes | Overview of diagnosis



Diabetes diagnosis – 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

Quiz

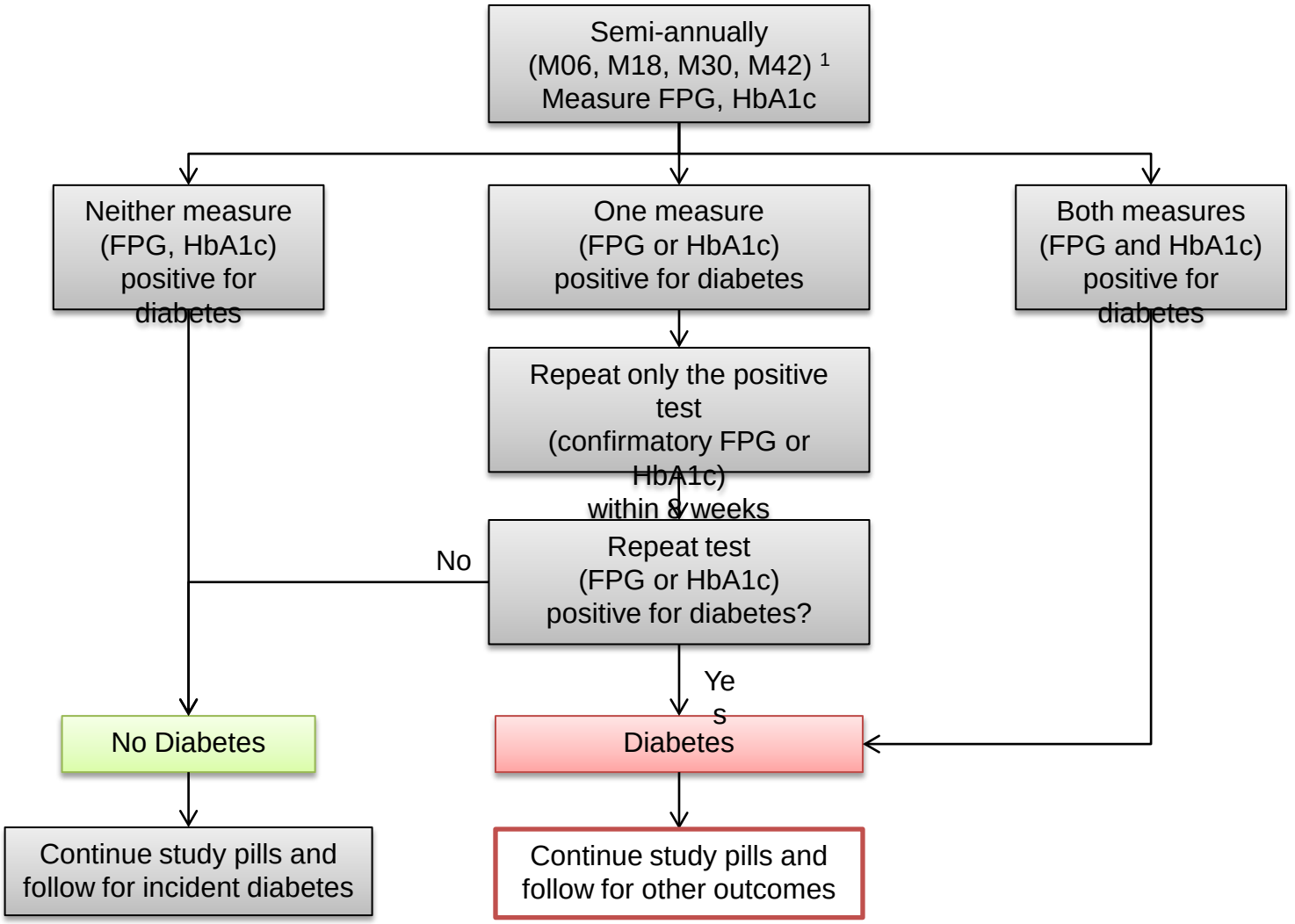
- *HbA1c = 6.5%*, FPG = 119 mg/dL and 2hPG = 178 mg/dL at the scheduled annual follow-up visit. Next step?
- *HbA1c = 6.6%* at the confirmatory visit. Diabetes, Y/N?

✓ Participant is diagnosed with diabetes.

- HbA1c = 6.4%, FPG = 122 mg/dL and *2hPG = 204 mg/dL* at the scheduled annual follow-up visit. Next step?
- *HbA1c = 6.6%, FPG 128 mg/dL* and 2hPG = 189 mg/dL at the confirmatory visit. Diabetes, Y/N?

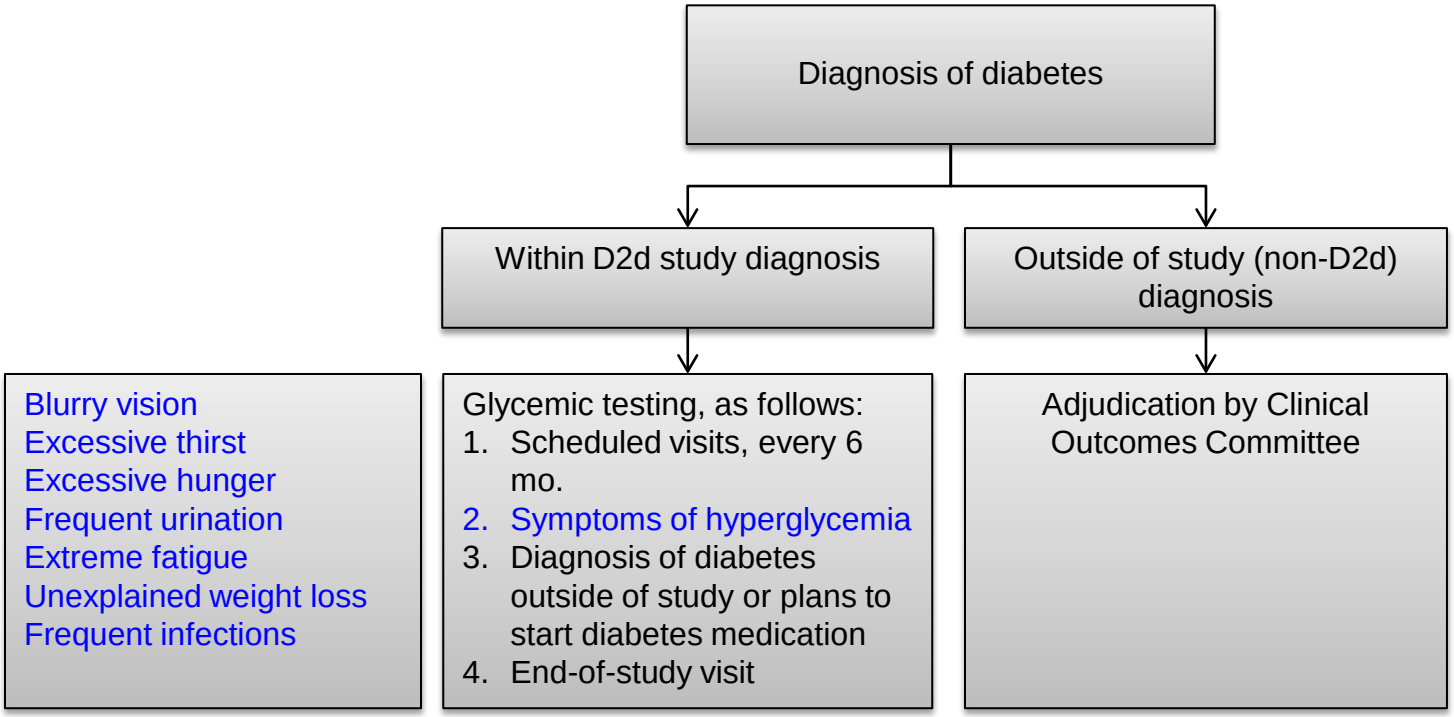
✓ Participant is diagnosed with diabetes.

Diabetes diagnosis – semi-annual visit



[1] FPG and HbA1c will also be measured in between scheduled visits at any time when (1)symptoms consistent with hyperglycemia are reported or (2) when a participant is given a diagnosis of diabetes outside of the D2d study or plans to start diabetes-specific pharmacotherapy (prescribed for any reason).

Primary outcome: incident diabetes | Overview of diagnosis



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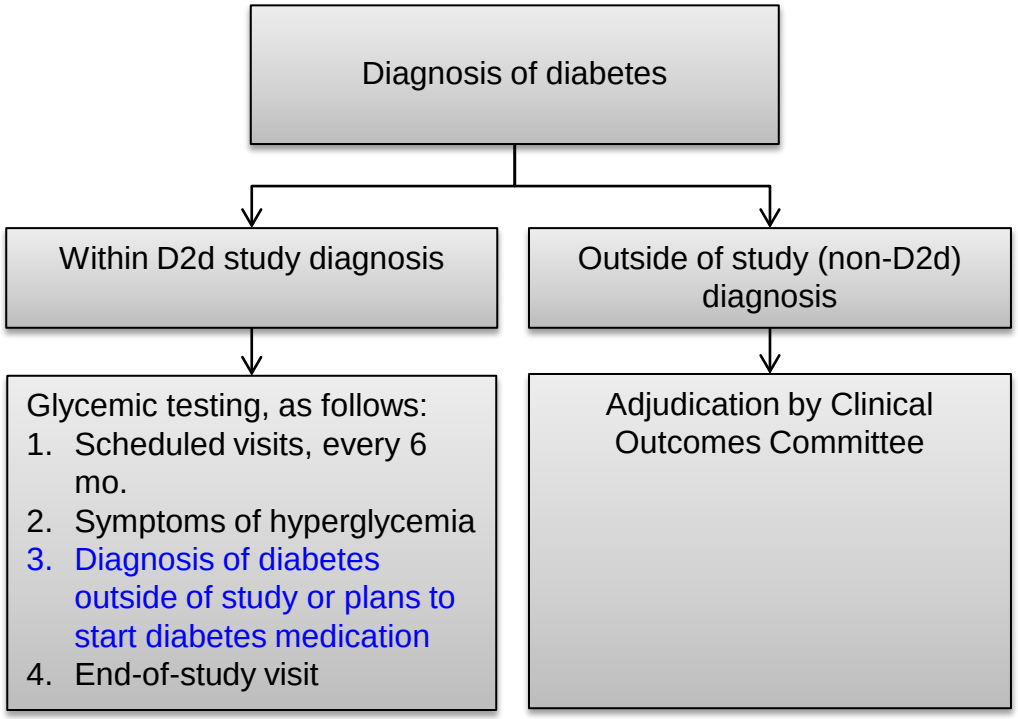
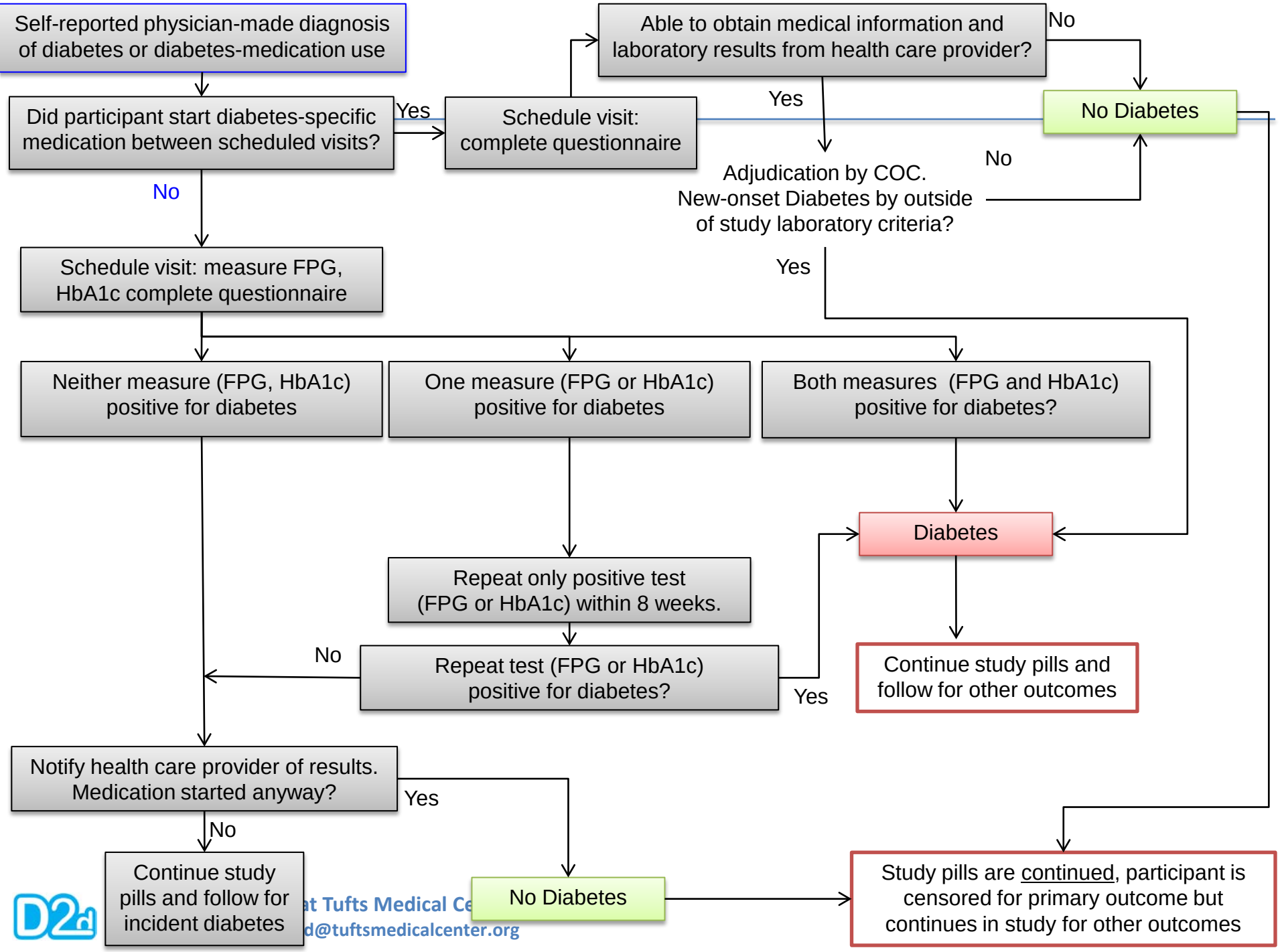


Diabetes dx – self-reported or prior to initiation of diabetes specific pharmacotherapy



at Tufts Medical Ce
d@tuftsmedicalcenter.org

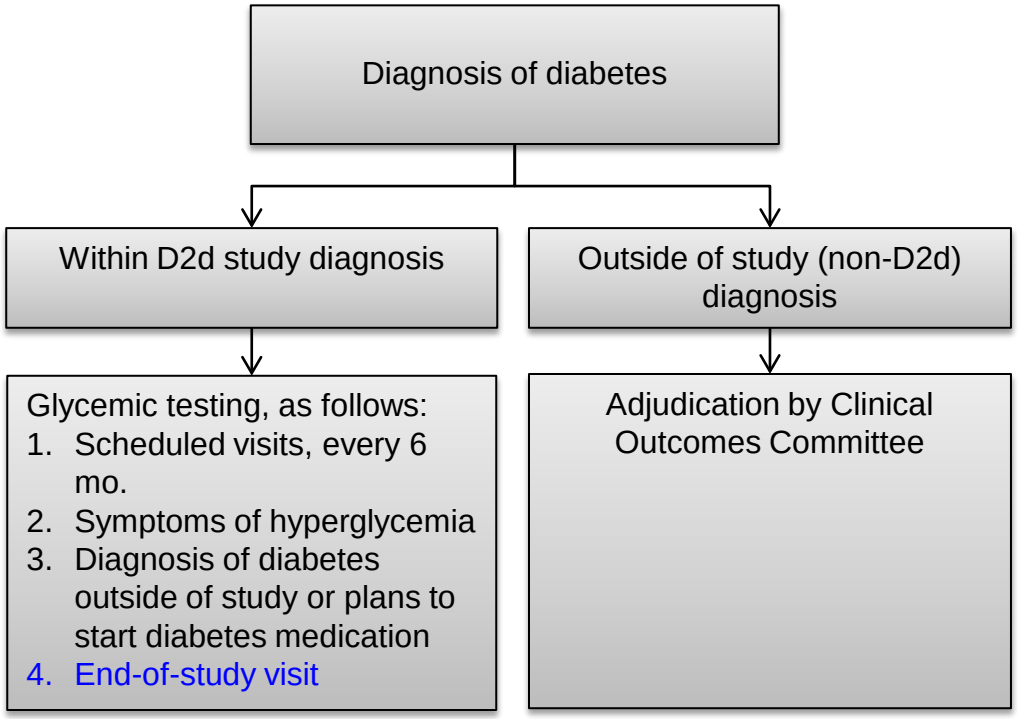
Diabetes diagnosis outside of D2d procedures

1. Complete Non-D2d Diabetes Diagnosis worksheet
   - Date of diagnosis, setting, etc.
2. ASAP Schedule D2d “semi-annual” visit
3. If no D2d-specific glycemic measures are available (=started on diabetes medication), diabetes needs to be adjudicated by Clinical Outcomes Committee

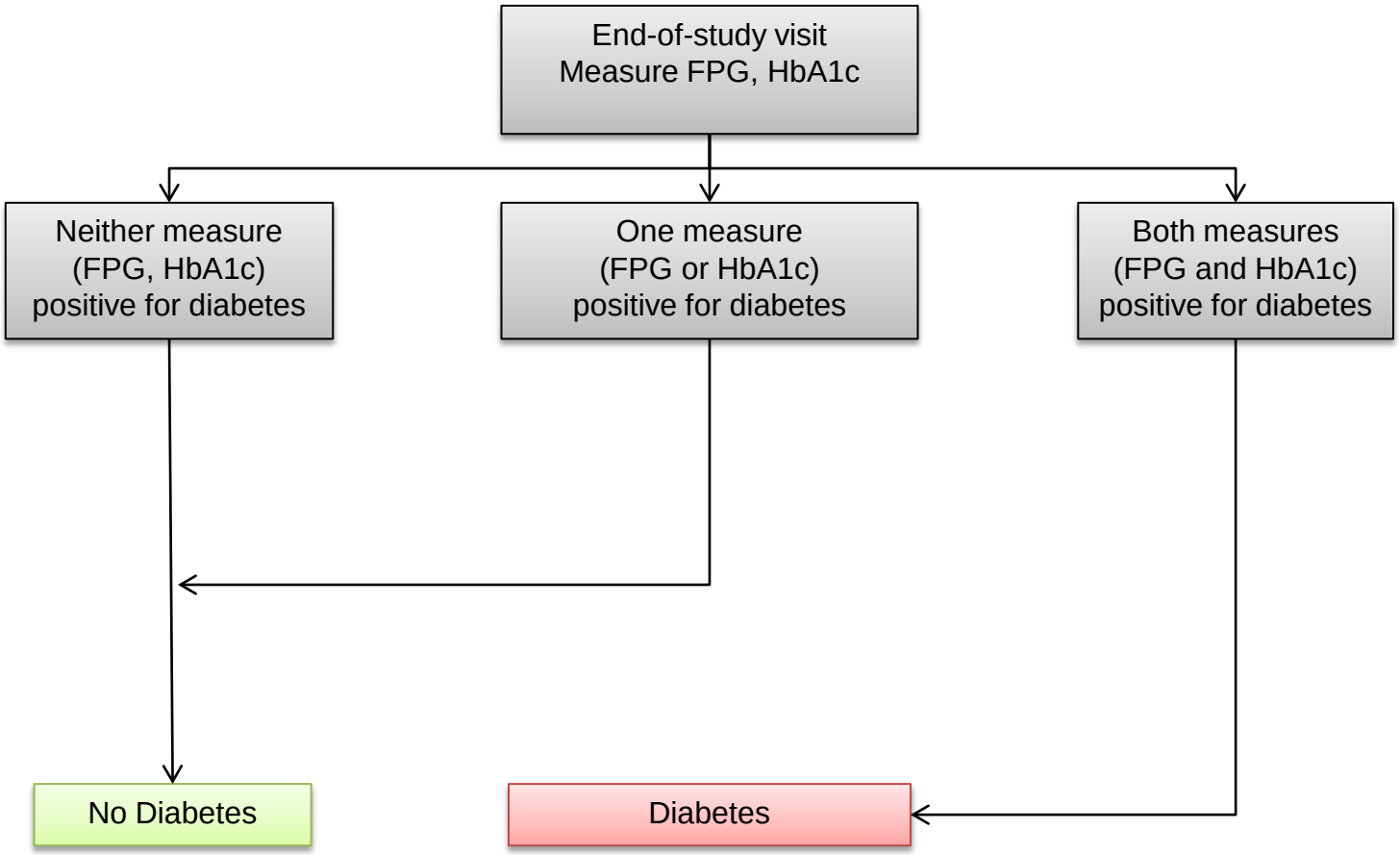
Diabetes Adjudication by Clinical Outcomes Committee

- COC is composed of clinical expert diabetologists independent of the D2d Study Group
- The COC reviews material to determine whether the outside laboratory results meet the study glycemic criteria for diabetes, following, as closely as possible, the D2d glycemic algorithms shown
- Adjudication options:
  - *Participant experienced new-onset diabetes*.
  - *Participant did not experience new-onset diabetes*
  - *Insufficient information for adjudication*.

Primary outcome: incident diabetes | Overview of diagnosis



Diabetes diagnosis – end of study visit (within 3 months of close-out)



Date of diabetes diagnosis

- Date of onset of diabetes = 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 is determined during the adjudication process.

Management of participants after diabetes diagnosis

- Study pills will be *continue*d and participants will be referred to PCP for further care in relation to diabetes.
- Participants will continue in D2d and return for scheduled visits for assessment of other outcomes.
- Letter will be sent to the participant's PCP
  - Provide results of the D2d glycemia measures.
  - Reinforce that the participant will continue study pills and participation in D2d
  - Inform the health care provider that:
    - Glycemic results need to be repeated in the clinical setting before the diagnosis of diabetes is established clinically.
    - The participant's diabetes will not be managed by the study investigator /physician

Questions on Primary Outcome?

Summary of changes since DSMB meeting

- Design change to event-driven trial
- Glycemia results not shared with participants/PCP until diagnosis of diabetes
- Continue study pills after diabetes diagnosis
- Pregnancy = “inactive” status
- End-of-study visit with fasting labs (A1c, FPG, Calcium, creatinine)
- Phone call after end-of-study for AE assessment