
Outcomes/Events:

Incident diabetes

Outcomes (Events)

- Primary Outcome: Time to incident diabetes
- Definition
 1. Laboratory results by the D2d central lab
 2. Outside of D2d adjudicated by a panel of expert diabetes clinicians
 - ✓ Laboratory-based by D2d is more rigorous but adjudication is consistent with the protocol.

Results after Laboratory Testing at Annual Visits

- Straightforward:
 - No result meets criteria for diabetes
 - 2-out-of-3 results (FPG, 2hPG or HbA1c) are positive for diabetes
- What if only one of three is positive?

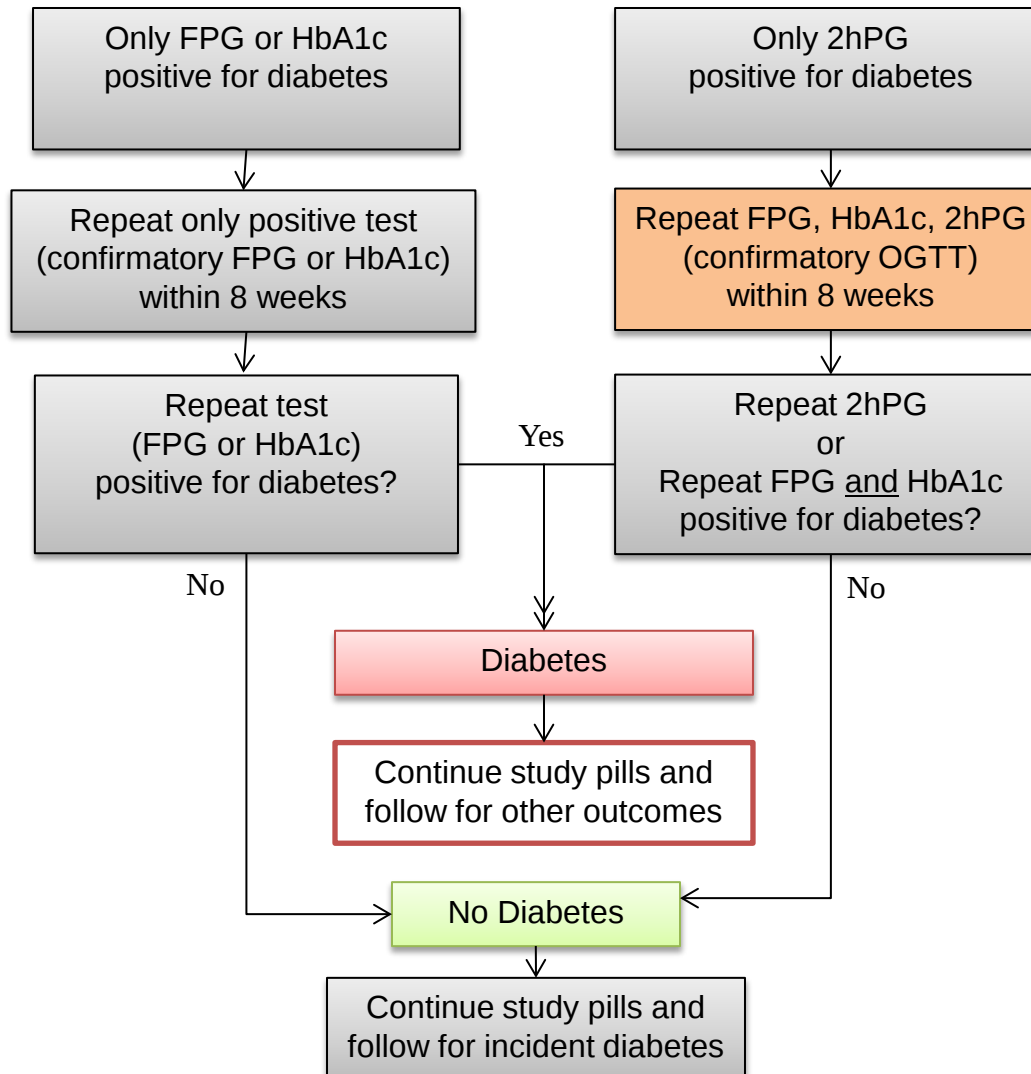
Correct!

Repeat testing to confirm is needed!

An OGTT may need to be repeated!

Laboratory testing

At annual visits (with OGTT)



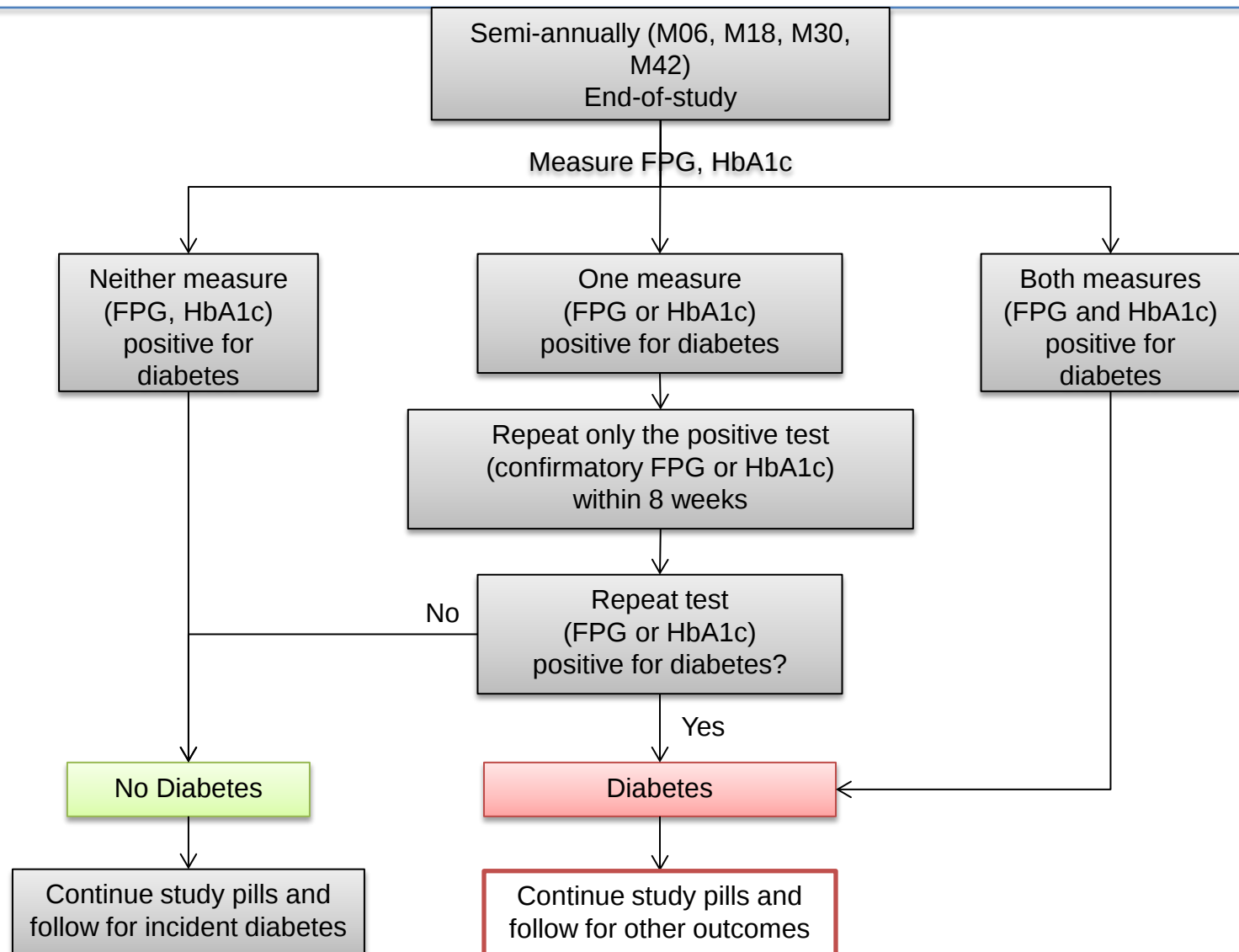
Results after Laboratory testing at Semi-Annual Visits

- Straightforward:
 - No result meets criteria for diabetes
 - Both results (FPG and HbA1c) are positive for diabetes
- What if only one is positive?

Correct!

Repeat testing to confirm is needed!

Diabetes diagnosis – semi-annual visit



Outside of D2d diagnosis of Diabetes

Outside D2d physician

- Makes diagnosis of diabetes and/or
- Prescribes diabetes medication for any reason, whether or not the medication is started by participant

What is the next step?

Outside of D2d diagnosis of Diabetes

Next step:

Determine if participant started the medication and, if so, for how long.

1. Participant has not started it *or* started but has not taken for more than 31 days.
2. Participant has been on medication for more than 31 days.

Scenario 1: medication for no more than 31 days or not started

Next steps:

- Site physician talks with **participant** and **participant's physician** (or prescribing physician) to assess:
 - if there is a willingness to withhold treatment and allow diabetes to be diagnosed in the D2d study
or
 - if the intent is to initiate or continue diabetes treatment regardless of D2d results

Scenario 1A: Allow diabetes diagnosis in D2d

- If no medications have been started, bring participant in for unscheduled visit for glycemic testing
- What testing is done at an unscheduled visit?

Correct, only FPG and HbA1c

No OGTT!

Communicate results to PCP

Scenario 1A: Allow diabetes diagnosis in D2d

- If medication has been used for **no more** than 31 days, do appropriate washout of 2-4 weeks depending on medication.

Which medications require 4 weeks?

GLP-1 receptor analogues, thiazolidinediones,
amylin mimetics

- After washout, bring in for unscheduled visit for glycemic testing

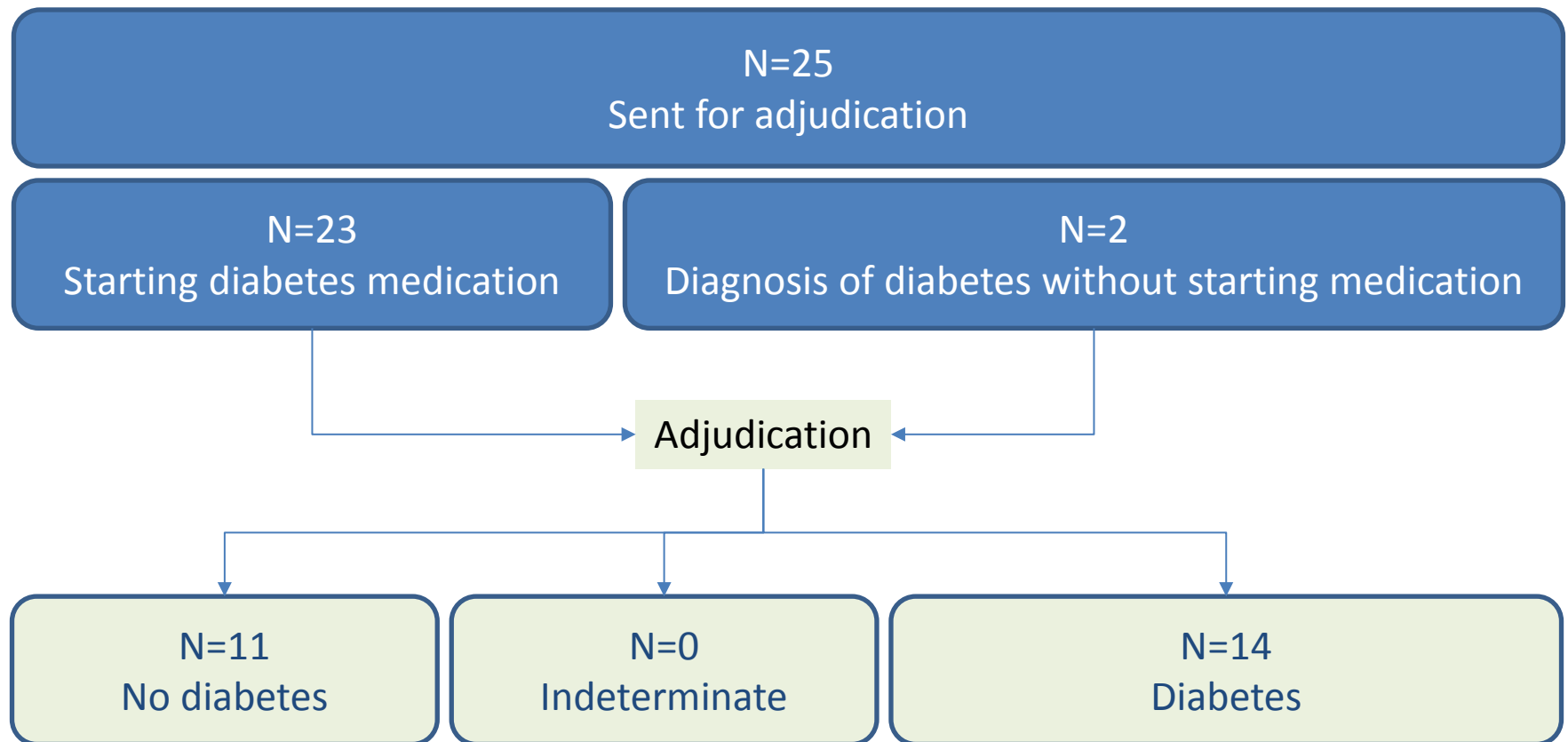
Scenario 2: Determined to start diabetes medication prior to D2d diagnosis or has taken >31 days of medication

- Do not do D2d lab testing!
- Collect medical records especially outside laboratory glycemic test results
- Adjudication of results to determine status:
 - Diabetes
 - No diabetes
 - Indeterminate

Clinical Outcomes Committee (COC)

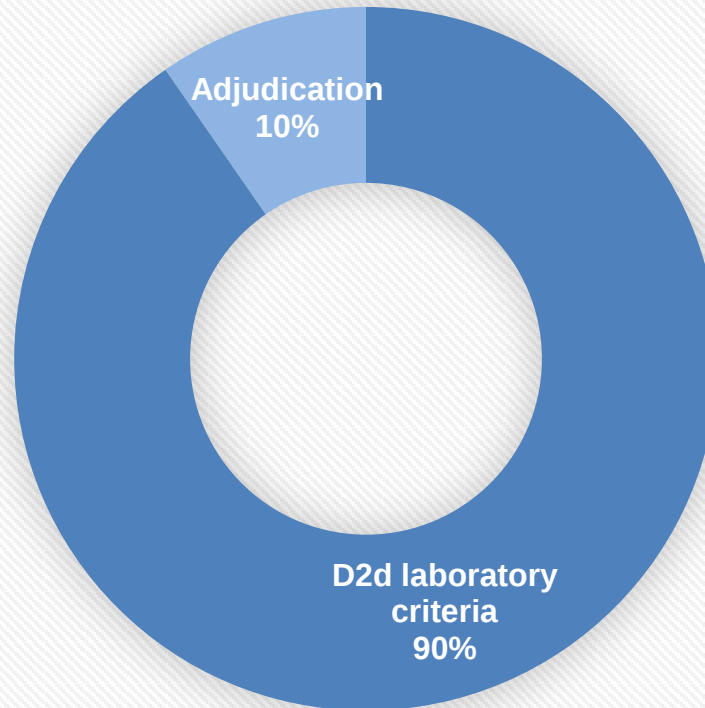
- Mission: to adjudicate primary outcome
- Membership:
 - Joshua Barzilay, MD. Kaiser Permanente, Atlanta, GA
 - Alexander Turchin, MD. Brigham and Womens Hospital, Boston, MA
 - Enrico Cagliero, MD. Massachusetts General Hospital, Boston, MA
 - Sara Alexanian, MD. Boston Medical Center, Boston, MA

Adjudication Results 9/16/2016



Incident diabetes, n=144 (9/16/2016)

Outcomes



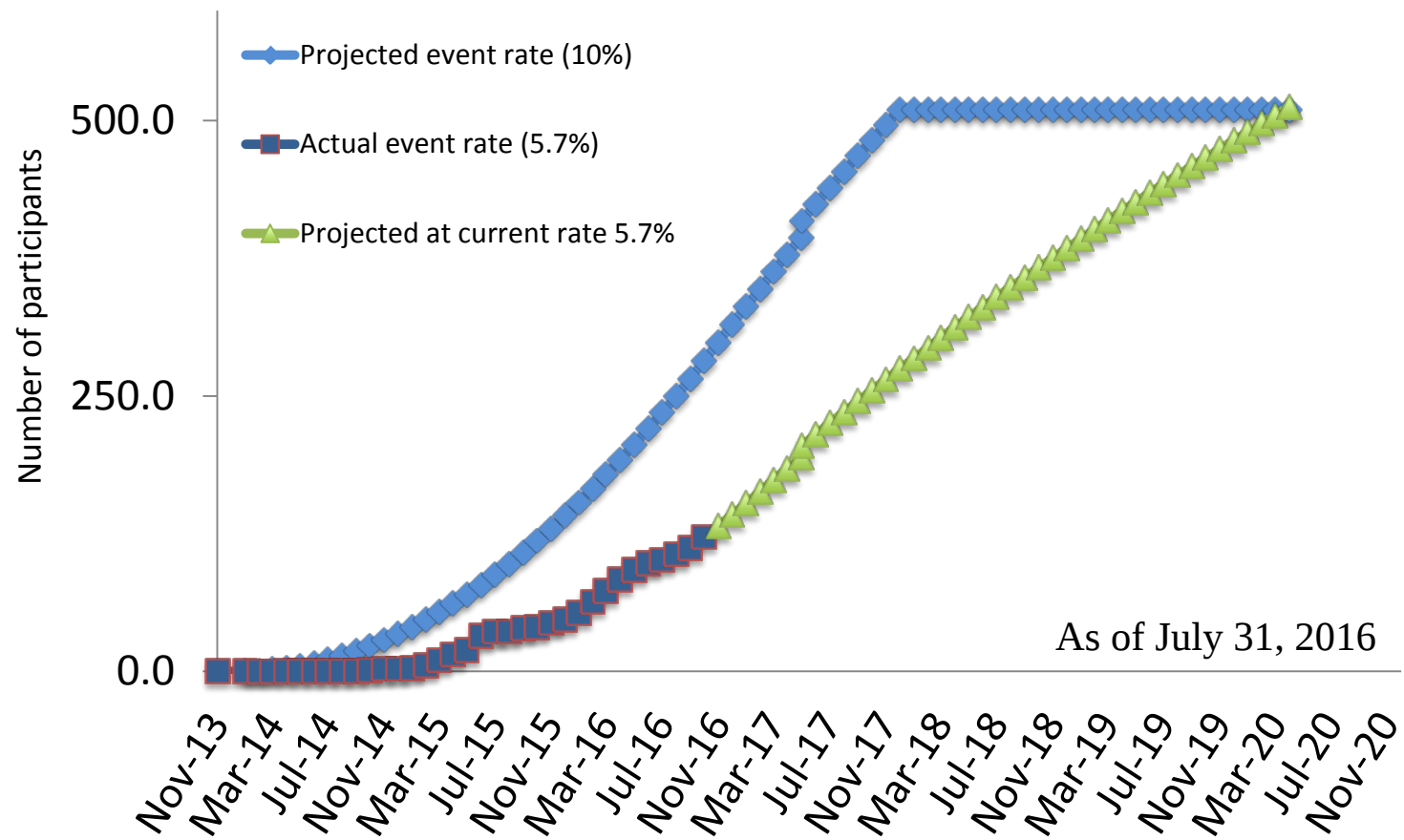
Detail on Diagnosis of Diabetes

	Overall	M06	M12	M18	M24	M30	M36	M42	M48
Semi-annual visits	2616	1712	-	806 ¹	-	98	-	-	-
Diabetes, n (% visits)	62 (2.4)	46 (2.7)	-	16 (2.0)	-	0	-	-	-
Positive A1c and FPG	26	19	-	7	-	0	-	-	-
Positive A1c or FPG, pos. confirmatory	36	27	-	9	-	0	-	-	-
No diabetes, n	2554	1666	-	790	-	98	-	-	-
Negative A1c and FPG	2490	1617	-	777	-	96	-	-	-
Positive A1c or FPG, neg. confirmatory	64	49	-	13	-	2	-	-	-
Weight change (% from baseline)		-0.25%		-0.03%		-0.22%			
Annual visits	1689	-	1240 ¹	-	449	-	-	-	-
Diabetes, n (% visits)	66 (3.9)	-	52 (4.2)	-	14 (3.1)	-	-	-	-
Positive, met 2 criteria	22	-	18	-	4	-	-	-	-
Positive, met 1 criterion, pos. confirmatory	44	-	34	-	10	-	-	-	-
No diabetes, n	1623	-	1188	-	435	-	-	-	-
All 3 criteria negative	1533	-	1118	-	415	-	-	-	-
Met 1 criterion, neg. confirmatory	90	-	70	-	20	-	-	-	-
Weight change (% from baseline)			-0.11%		-0.28%				
Outside of study events by adjudication ²	14	2	6	2	2	2			
Total events	142	48	58	18	16	2			

¹ Number excludes participants who have reached the *diabetes outcome* [by D2d criteria or adjudication].

² If diabetes outcome was adjudicated before stated interval, it is shown under stated interval. For example, adjudicated outcomes between the M06 and M12 visits are shown under M12. Longitudinal analyses (when conducted) will be based on “time-to-event.”

Incident Diabetes



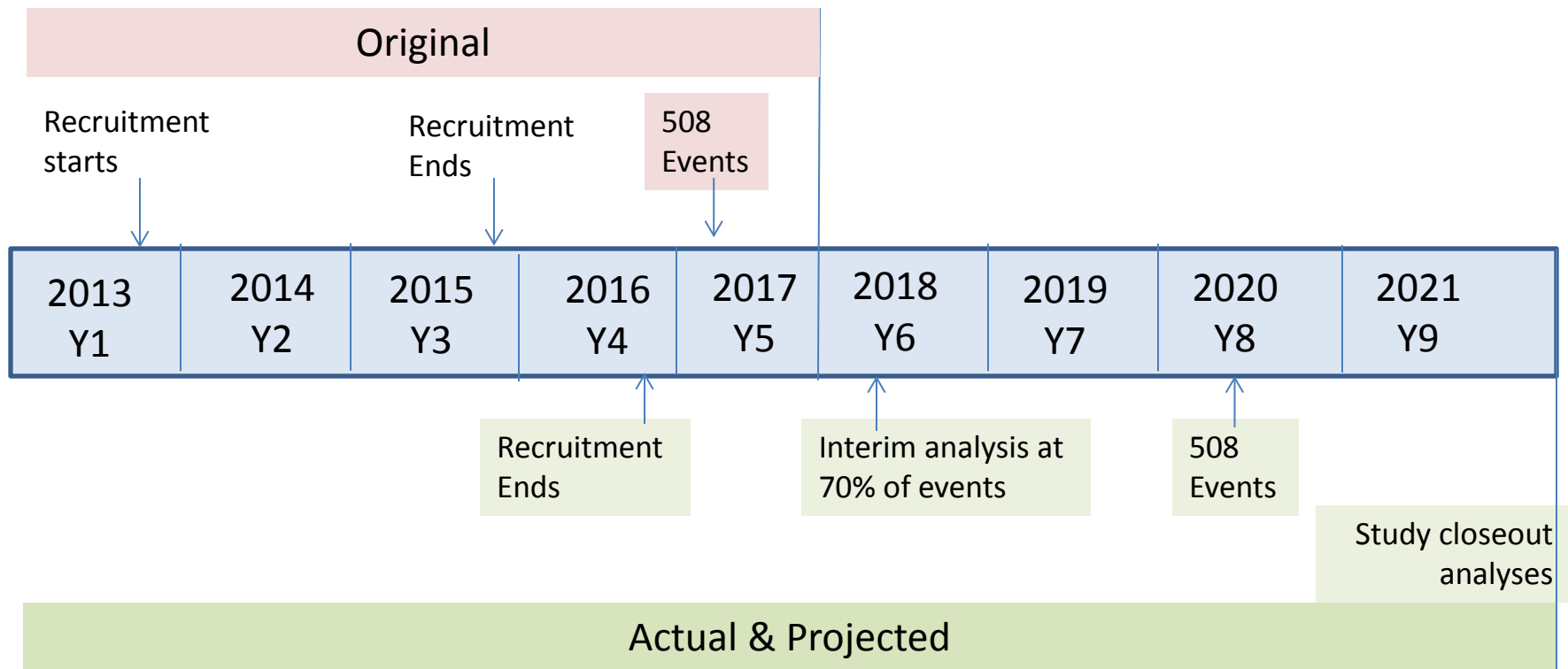
DPP vs D2d

	DPP	D2d
Entry Glycemic criteria	FBG: 95 -125 mg/dl <u>and</u> 2-h glucose 140-199 mg/dl	2-out-of-3 ADA criteria: • FBG 100-125 mg/dl • 2-h glucose 140-199 mg/dl • HbA1c 5.7-6.4%
FBG	106.5 (8.3)	107.7 (7.5)
2-h glucose	164.6 (17)	137.4 (33.6)
HbA1c	5.91 (0.5)	5.91 (0.22)
Age	50.6 (10)	59.0 (10)
BMI	34 (6.7)	32.2 (4.5)
% AA	19.9	27.7
% Hispanic	15.7	10.3

Incident Diabetes

- Estimated date for reaching 508 events
 - Based on current rate: Spring of 2020 (at end of Y08)
- Interim analysis to be done at 70% of events (N=356)
 - Based on current rate: Fall 2018 (mid Y06)

Proposed and Actual Timeline



Dates shown are grant years, e.g., 2013 is June 2013 to May 2014

Thank you for your attention
and all your hard work on
behalf of the D2d study!
Myrlene

Projections

Randomized
2,382

Events needed
508

Accrual (monthly) 66

Withdrawal rate (annual)
5%

Event rate (annual)
6.35%

