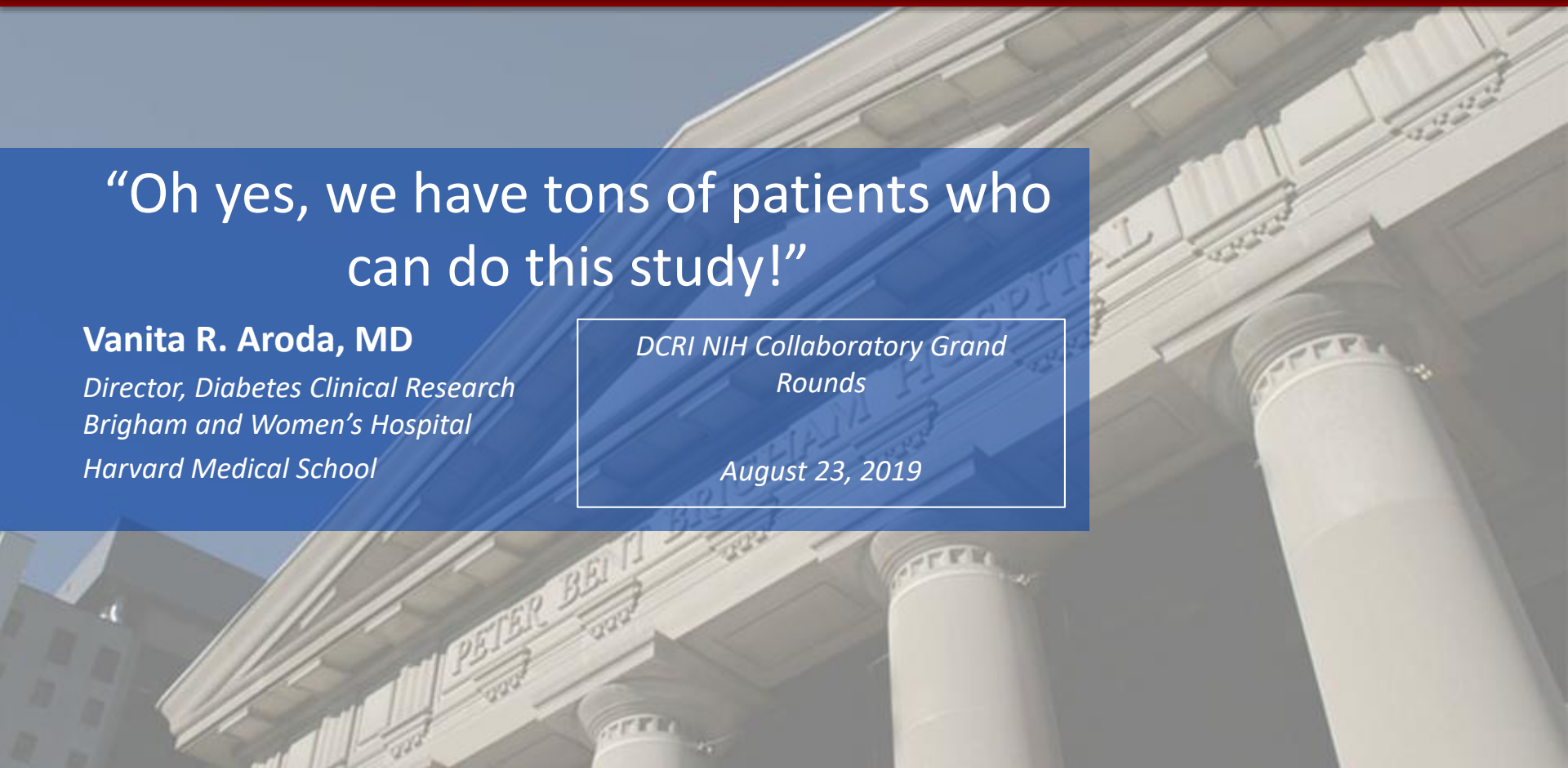
BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL



"Oh yes, we have tons of patients who can do this study!"

Vanita R. Aroda, MD

Director, Diabetes Clinical Research
Brigham and Women's Hospital
Harvard Medical School

DCRI NIH Collaboratory Grand Rounds

August 23, 2019

Presenter Disclosures
Vanita R. Aroda, MD

Board Member: none
Consultant: Adocia, Astra Zeneca, BD, Novo Nordisk, Sanofi, Zafgen, IMNE
Employee: Brigham and Women's Hospital, Boston, MA; Merck Research Laboratories (Spouse)
Research Support: Astra Zeneca/BMS, Calibra, Eisai, Fractyl, Janssen, Novo Nordisk, Sanofi, Theracos
Speaker's Bureau: none
Stock/Shareholder: none
Other: none

“Map” – Practical!

- Impact of Clinical Trial Engagement and Recruitment
- More Than Just Steps: The Human Element
- D2d - a Scaled Example
- Concluding Words: The Joy of Clinical Trials

HOMAGE: "All that we know about caring for patients, we know from people like you."

- To the **participants** who have defined our current standards of care → patients
- To the **investigators** with the foresight to ask the right questions → clinicians
- To the **teams** who made it possible to answer these questions → healthcare community

(n=57,534)

Prediabetes

->Can type 2 diabetes be prevented or delayed in persons at high risk?

- **DPP/DPPOS (n=3,234)**

Newly Diagnosed Diabetes

->Can we reduce complications with intensive treatment?

- **UKPDS (n=5,102)**

Initial Glucose-Lowering Therapy

->Does any specific initial therapy confer particular benefit?

- **UKPDS (n=5,102)**
- **ADOPT (n=4,360)**

Adjunctive Therapy

->What is the efficacy of intensive medical therapy alone versus medical therapy plus gastric bypass/sleeve gastrectomy in obese patients with T2DM?

- **STAMPEDE (n=150)**

Effects of Intensive Therapy on CV Outcomes

->Does intensive therapy reduce CV events?

- **LOOK AHEAD (n=5,145)**
- **ACCORD (n=10,251)**
- **VADT (n=1,791)**
- **ADVANCE (n=11,140)**

Effects of Specific Drugs on CV Outcomes

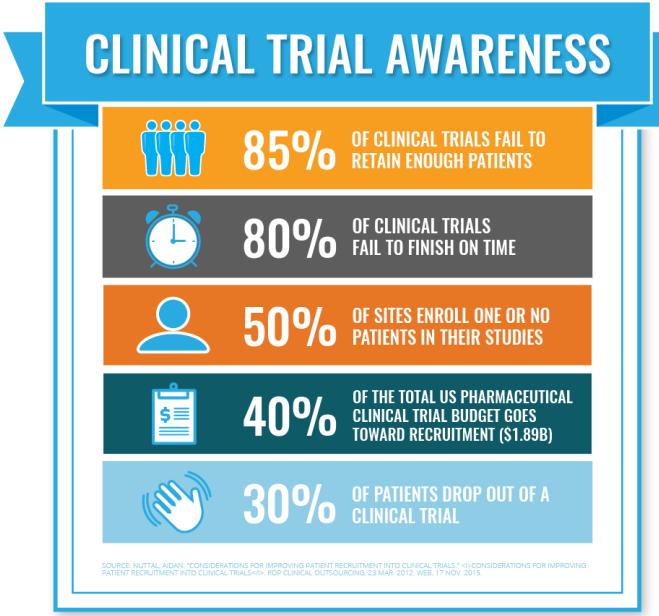
->What are effects of specific medications compared to standard of care on CV morbidity and mortality in T2DM?

- **EMPA-REG (n=7,020)**
- **LEADER (n=9,341)**

CDC National Diabetes Statistics Report, 2017: More than **100 million** Americans have diabetes or prediabetes.

Implications of Ineffective Clinical Trial Engagement and Recruitment

- Extent of the problem:
  - Cross-sectional study of terminated clinical trials ClinicalTrials.gov as of Feb 2013:
    - 12% terminated; insufficient rate of accrual being the lead reason for termination (57%)
- Consequences:
  - **Scientific**:
    - Underpowered study
      - Unable to answer primary question meaningfully
      - Fail to establish true value of intervention
    - Outdated – Science has moved on
  - **Economic**: extended length of trial, cost, feasibility
  - **Ethical**: undermines contribution of those who do participate (2011: >48,000 patients enrolled in trials that failed to answer primary question meaningfully)



Treweek S *et al; BMJ Open* 2013; 3:e002360
Carlisle B et al; *Clin Trials* 2015; 12(1):77-83
Fogel DB *Contemp Clin Trials Commun* 2018; 11:156-164
Williams RJ *et al*; PLoS One 2015; 10(5):e0127242
Image from http://garthright.blogspot.com/2014/04/a-rising-tide-lifts-all-boats.html, accessed 19 Aug, 2019 for educational purposes
Image from https://medrio.com/blog/overcoming-patient-recruitment-and-retention-hurdles/ accessed 19 Aug, 2019 for educational purposes

“Oh yes, I have tons of patients who can do this study!”

Clinical Study Feasibility Exercise

patients in panel: 2000
patients with type 2 diabetes: 400
patients on metformin only: 200
patients on at least 1500 mg metformin a day: 100
patients on stable dose for at least 3 months: 67
patients on stable antihypertensive and lipid-lowering therapy for at least 1 month : 60
patients without significant cardiovascular disease, renal disease, hepatic disease, infectious disease, or history of malignancy within 5 years: 30
No history of or planned bariatric surgery, significant weight loss, gastrointestinal surgeries or disease that can affect medication absorption: 27
Not on steroids, weight loss medications, or any other medications that can affect glucose metabolism: 24
BMI 20-40: 19
Age 18-75: **18** **“true potential participants”**

Willing to use contraception for duration of study (males and females): 16
Interested in research (20-50%): 11
Screen for study: 10
Willing to commit to study requirements: 7
Qualify for study after screening: 3
Qualify for study after run-in period: 2
Drop out due to AE or lack of perceived effect: 1

Move to Florida: ☹

Other participants
Study Sponsor
Administration/Institution
Colleagues/Mentors
Staff/Team
Self

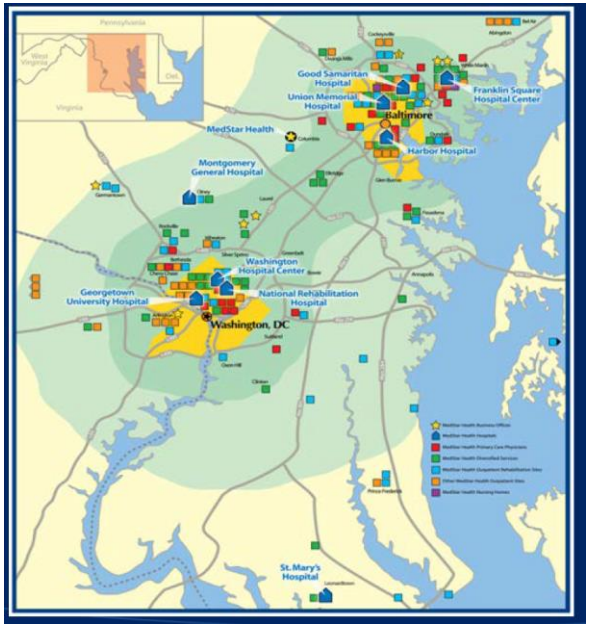
"Clinical Research as Part of the Spectrum of Clinical Care": 2008

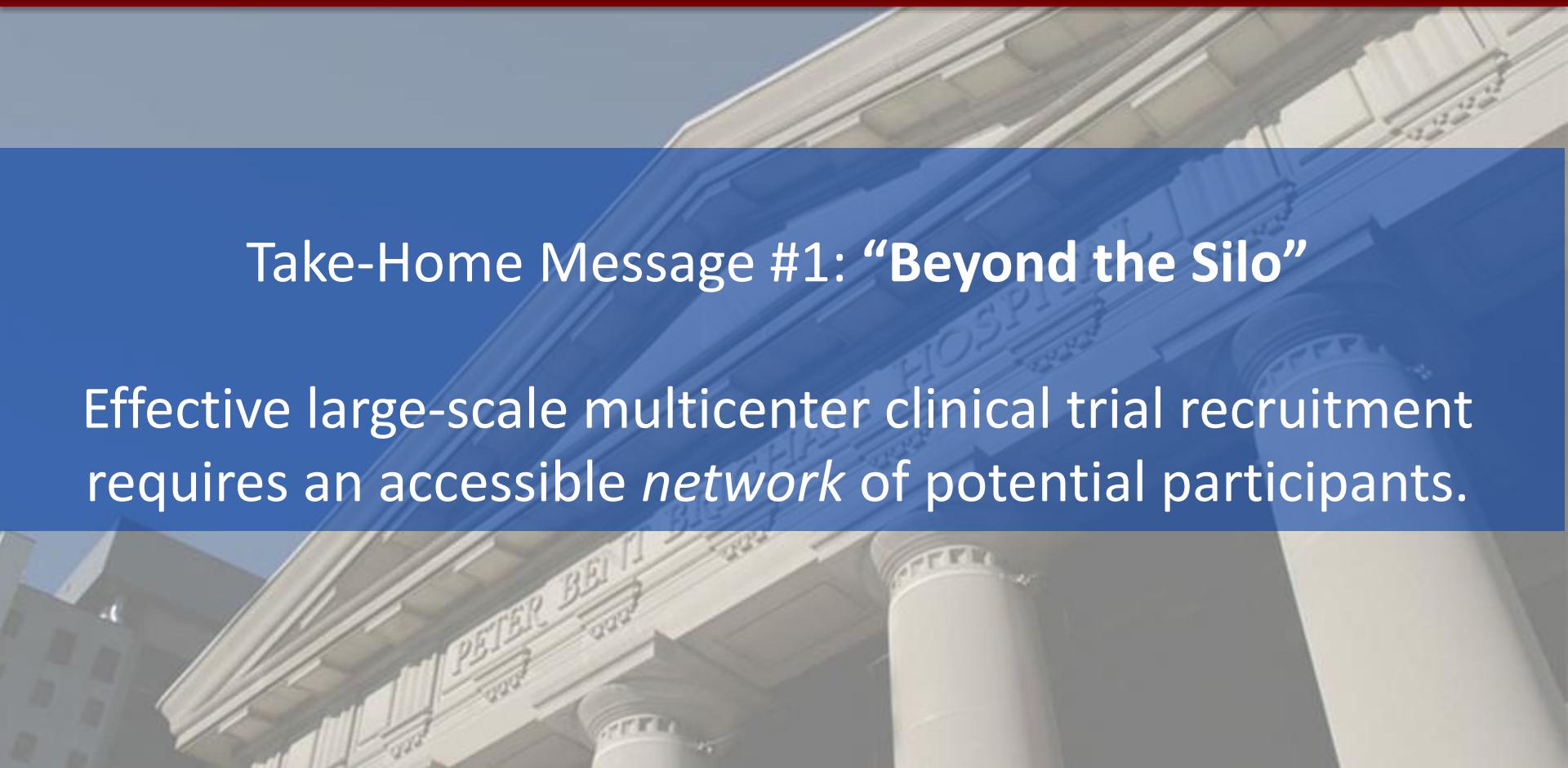
What if we tapped into the potential of 25 MedStar practices?

patients in panel: **50,000**
patients with type 2 diabetes: 8,000
patients on metformin only: 4000
patients on at least 1500 mg metformin a day: 2000
patients on stable dose for at least 3 months: 1340
patients on stable antihypertensive and lipid-lowering therapy for at least 1 month: 1206
patients without significant cardiovascular disease, renal disease, hepatic disease, infectious disease: 603
No history of or planned bariatric surgery, significant weight loss, gastrointestinal surgeries or disease that can affect medication absorption: 543
Not on steroids or any other medications that can affect glucose metabolism: 489
BMI 20-40: 391
Age 18-75: **372 "true potential" participants**

Willing to use contraception for duration of study (males and females): 335
Interested in research (20%): 67
Screen for study: 60
Willing to commit to study requirements: 30
Qualify for study after screening: 15
Qualify for study after run-in period: 13
Drop out due to AE or lack of perceived effect: 10

Remainder after move to Florida: **8-10**





Take-Home Message #1: **"Beyond the Silo"**

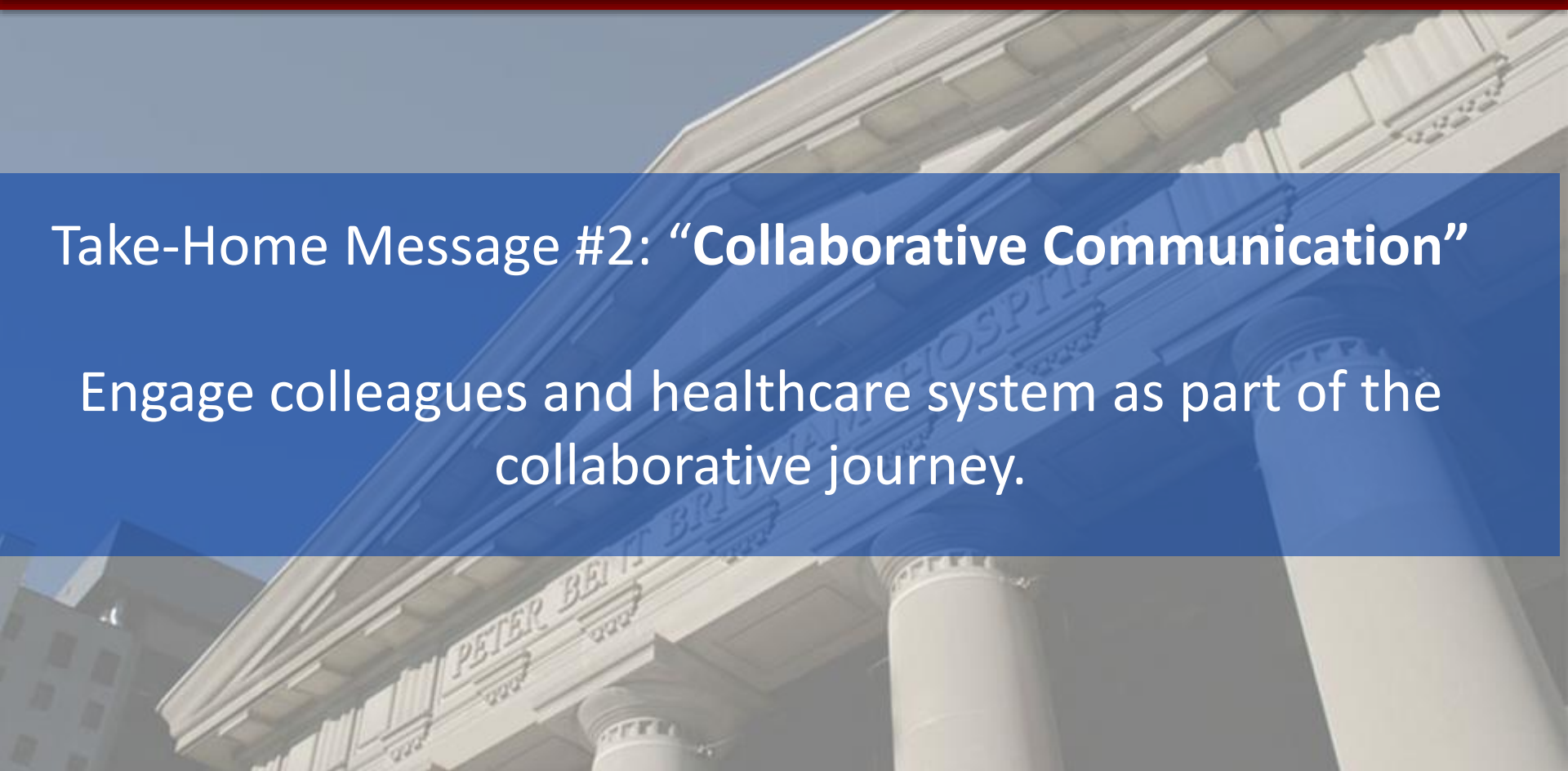
Effective large-scale multicenter clinical trial recruitment requires an accessible *network* of potential participants.

Health System and Clinician Engagement Throughout the Entire Life Cycle of the Study

Prior to Study and Initial Contact

"**Collaborative Communication":**
Engage local clinical leaders and colleagues on what the current state of the field is, the question trying to be addressed, and **'our' collective** role in helping to address the question.

- Engage in the **journey -** Don't trivialize the 'ask'
- Dialogue of *continuity*
- Always follow with well-thought through written communication



Take-Home Message #2: "**Collaborative Communication**"

Engage colleagues and healthcare system as part of the collaborative journey.

Health System and Clinician Engagement Throughout the Entire Life Cycle of the Study

Prior to Study and Initial Contact

"Collaborative Communication"

- Ensure right IRB-approved **database query**
  - "Just right" query: Don't over-build or under-build data query (note that this often needs a clinical touch)
  - Spotcheck with team before proceeding!
    - Manually check select number of charts to ensure data query built is best fit for study criteria

Thorough prescreening, consult with each other as needed.

- Ensure compliance with local policies and sensitivity to local culture.

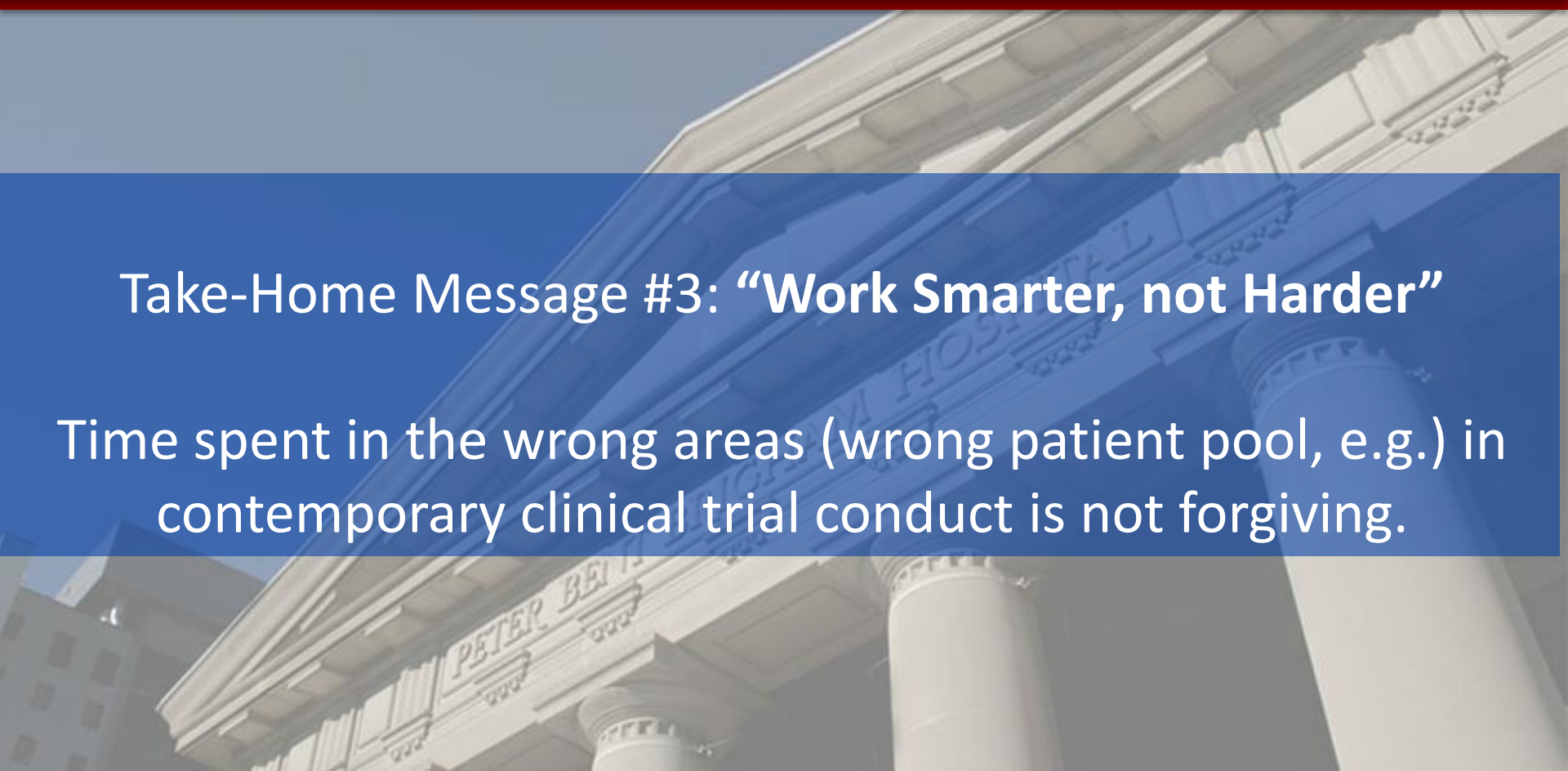
Example:
# of patients that meet criteria: 0

Search criteria:
GHb>7%: 0

GHb?!*?

HbA1c > 7%: 6388

Image from http://www.knowledgeproduction.com/Research for educational purposes, Accessed 22 Aug, 2019



Take-Home Message #3: **"Work Smarter, not Harder"**

Time spent in the wrong areas (wrong patient pool, e.g.) in contemporary clinical trial conduct is not forgiving.

Recruitment/Engagement Conversations (Team Role-Play): My Top 10…

1. Patients are going to have a lot of questions. More important than actually answering all of their questions in that instant is making sure they feel comfortable that we are going to answer all of their questions throughout the entire **journey**.
2. Don't break into jail – don't even think about going down the nitty gritty detail pathway (which is an easy copout) until there is initial engagement and interest in the higher goals of research and care.
3. Work for the open and **continued dialogue** option. This point in time is part of a bigger continuity.
4. Engage in initial interest of the why, and why it is relevant to them as a **person** in their point in time of their disease.
5. But then always make sure to bring it to the bigger, more **global picture** of what "we" are hoping to achieve, should we proceed on the collaborative journey.
6. Recruitment is, in itself, another form of **informed consent** – where we are getting their permission to have them think about the option.
7. Don't be afraid to share what excites/engages **you** in this study in your role.
8. Never forget context. **Like writing a grant**, it is ok to share what we know, what we don't know, and where we want to go, and what each respective role encompasses in order to get there.
9. **RETENTION** starts with recruitment. Repeat. Research is always voluntary, but consider the **"All in"** handshake (on both sides).

Recruitment/Engagement Conversations (Team Role-Play): My Top 10…

10. What we are doing isn't "recruitment" (like come join the army, let me convince you), but is actually **health engagement** (or I like to call it that)—sharing with patients the **broader health journey** they are a part of and that we are all a part of. That no matter where we are, there is still more we can learn to help advance health and knowledge, and they, as we, are part of that discovery.

"Thank you, Vanita for the thoughtful session, inspiration, and motivation. Will save this for future reference and to ultimately pass along to the next generation."

Health System and Clinician Engagement Throughout the Entire Life Cycle of the Study

Prior to Study and Initial Contact

- **"Collaborative Communication"**
- **Appropriate data queries for right participant**
- **Thorough prescreening, consult as needed.**
- **Sensitivity to local culture and policies**

From Screening to Randomization

Vetting beyond the participant:
-Participant
-Family members
-**Clinical care team**

Materials: Highlight values, mission, and the required collaboration to address the higher goals

-Highlight the bigger picture
-Convey the collaborative "we" in the process
-Build off of local internal guiding mission and values

Health System and Clinician Engagement Throughout the Entire Life Cycle of the Study

Study issues arise, for which the clinical partnership remains essential:

- Enforcing standard of care
- Managing adverse events
- Adherence to protocol
- Retention!

D2d: a contemporary, scaled example in multicenter clinical trial recruitment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vitamin D Supplementation and Prevention of Type 2 Diabetes

Anastassios G. Pittas, M.D., Bess Dawson-Hughes, M.D., Patricia Sheehan, R.N., M.P.H., M.S., James H. Ware, Ph.D.,* William C. Knowler, M.D., Dr.P.H., Vanita R. Aroda, M.D., Irwin Brodsky, M.D., Lisa Ceglia, M.D., Chhavi Chadha, M.D., Ranee Chatterjee, M.D., M.P.H., Cyrus Desouza, M.B., B.S., Rowena Dolor, M.D., John Foreyt, Ph.D., Paul Fuss, B.A., Adline Ghazi, M.D., Daniel S. Hsia, M.D., Karen C. Johnson, M.D., M.P.H., Sangeeta R. Kashyap, M.D., Sun Kim, M.D., Erin S. LeBlanc, M.D., M.P.H., Michael R. Lewis, M.D., Emilia Liao, M.D., Lisa M. Neff, M.D., Jason Nelson, M.P.H., Patrick O'Neil, Ph.D., Jean Park, M.D., Anne Peters, M.D., Lawrence S. Phillips, M.D., Richard Pratley, M.D., Philip Raskin, M.D., Neda Rasouli, M.D., David Robbins, M.D., Clifford Rosen, M.D., Ellen M. Vickery, M.S., and Myrlene Staten, M.D., for the D2d Research Group†

Recruitment and Retention

CLINICAL TRIALS

Clinical Trials
2019, Vol. 16(3) 306–315

DOI: 10.1177/1740774519839062
journals.sagepub.com/home/ctj
SAGE

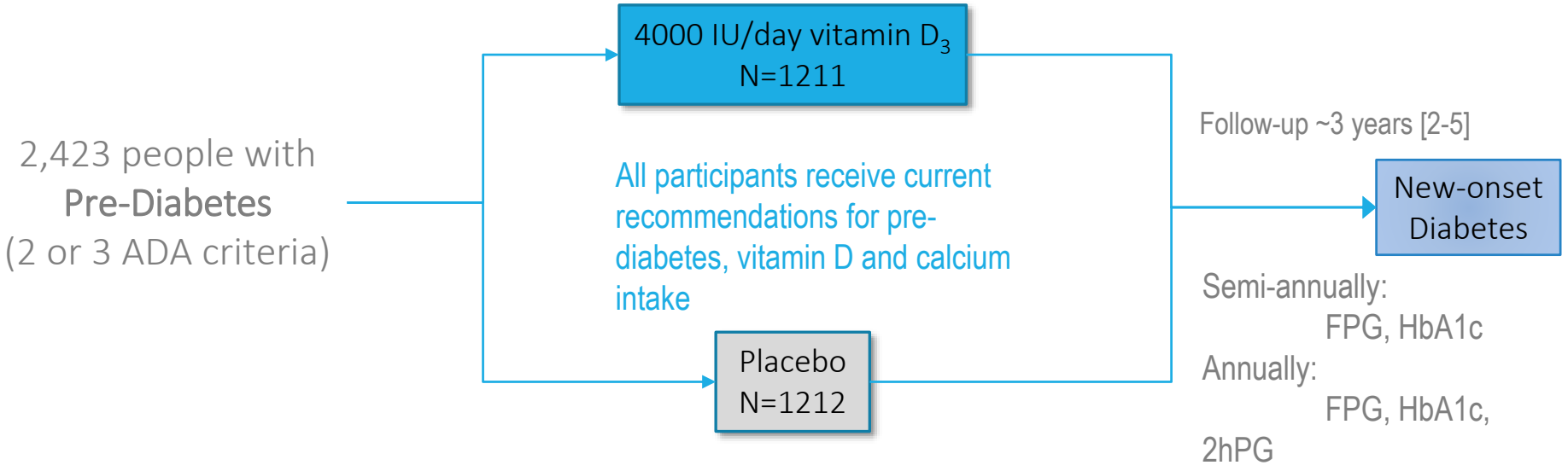
Establishing an electronic health record–supported approach for outreach to and recruitment of persons at high risk of type 2 diabetes in clinical trials: The vitamin D and type 2 diabetes (D2d) study experience

Vanita R Aroda[1,2], Patricia R Sheehan[3], Ellen M Vickery[3], Myrlene A Staten[4], Erin S LeBlanc[5], Lawrence S Phillips[6,7], Irwin G Brodsky[8], Chhavi Chadha[9], Ranee Chatterjee[10], Miranda G Ouellette[11,12], Cyrus Desouza[13] and Anastassios G Pittas[3]; for the D2d Research Group*

Pittas AG et al; *N Engl J Med*. 2019 Aug 8;381(6):520-530

Aroda VR *et al*; *Clinical Trials* 2019; 16:306-315

A ***diabetes prevention multi-center trial*** to determine whether vitamin D supplementation delays the onset of diabetes in people at risk for diabetes.



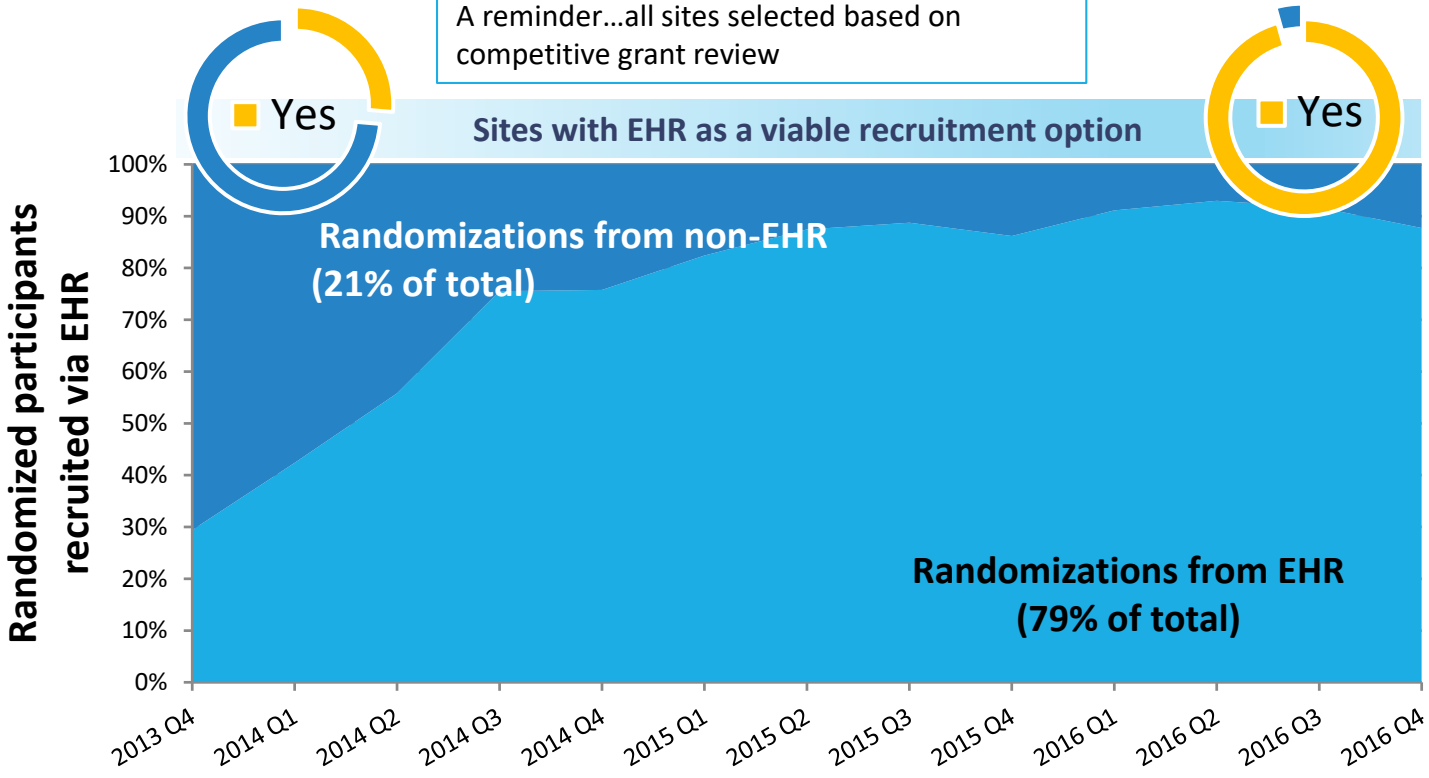
Pittas et al Diabetes Care 2014

Eligibility Criteria

Inclusion criteria	Key exclusion criteria
Overweight: BMI 22.5 – 42 kg/m^2	Taking any diabetes medication
At risk for diabetes: meeting at least two of three ADA 2010 criteria for prediabetes:	Hypercalcemia, Hyperparathyroidism
A1c 5.7 – 6.4%	Kidney stones
Fasting Glucose 100 – 125 mg/dL	Bariatric surgery or obesity treatment
Glucose after OGTT 140 – 199 mg/dL	Vitamin D suppl. > 1000 IU daily
Age: 30+	Calcium suppl. > 600 mg daily

D2d Recruitment: Scalability of EHR approaches across sites

A reminder…all sites selected based on competitive grant review



Aroda et al. Clinical Trials 2019

The Secret?

The “All In” Human Element, Iterative Process, and Commitment to Engagement…with each other (credit: D2d RRS Committee)

Patty Sheehan

Taso Pittas

Sarah Serafin-Dokhan

Chhavi Chadha

Myrlene Staten

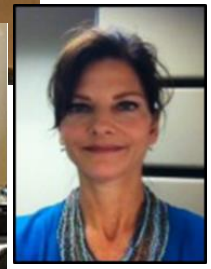
Kim Vo

Cindy Haviet

D2d Vitamin D and type 2 diabetes

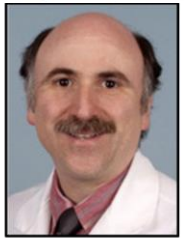
diabetes prevention research matters

HGBA1C (last entry) is greater than 5.9
HGBA1C (last entry) is less than 6.5
Date of Last Observation Entry is before [yesterday's date]
Date of Last Observation Entry is or after [date 90 days before yesterday's date]
Birthdate is before [maximum age bound]
Birthdate is on or after [minimum age bound]
BMI (last entry) is less than 41
BMI (last entry) is greater than 22
Problem Code, Active (Diagnosis lookup) is not DM (ICD-250.00)
Medication Code, Active (Classification lookup) is not ANTIDIABETICS
Medication Code, Active (Classification lookup) is not VITAMIN D
Medication Code, Any (Classification lookup) is not PREDNISONE
Problem Code, Active (Diagnosis lookup) is not CHRONIC KIDNEY DISEASE STAGE V (ICD-585.5)
Problem Code, Active (Diagnosis lookup) is not CHRONIC KIDNEY DISEASE STAGE IV(SEVERE) (ICD-585.4)
Problem Code, Active (Diagnosis lookup) is not HYPERCALCEMIA (ICD-275.42)



Shelly Cook

Vanita Aroda
RRS Chair



Irwin Brodsky
RRS Vice-Chair

Miranda Ouellette
RRS Vice-Chair

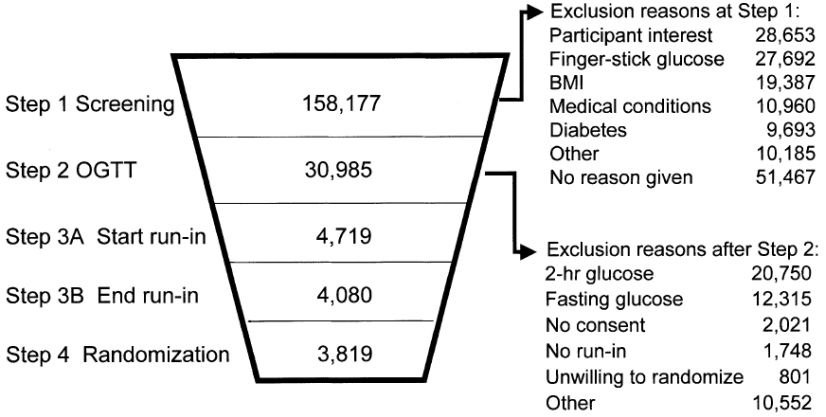
D2d EHR-supported recruitment: The Human Element

Key Stakeholder	Role
Recruitment and Retention Subcommittee Coordinating Center	Constructive conduit, non-judgmental learning environment, continuous 'all-in' engagement in recruitment and retention
Site principal investigator	Two-way bridge; Relationship-builder; Catalyst Problem solver
Site research staff	Glue Investigator-extender
Institutional review board (IRB)	Opportunity sharer
EHR/health information technology (IT) leadership and liaison	Gatekeeper
Clinicians and patients partners (for sites that engaged primary care providers)	Equal Partners: Our Collective Journey

Aroda VR *et al Clinical Trials* 2019 16(3):306-315.

Putting D2d Enrollment in Perspective

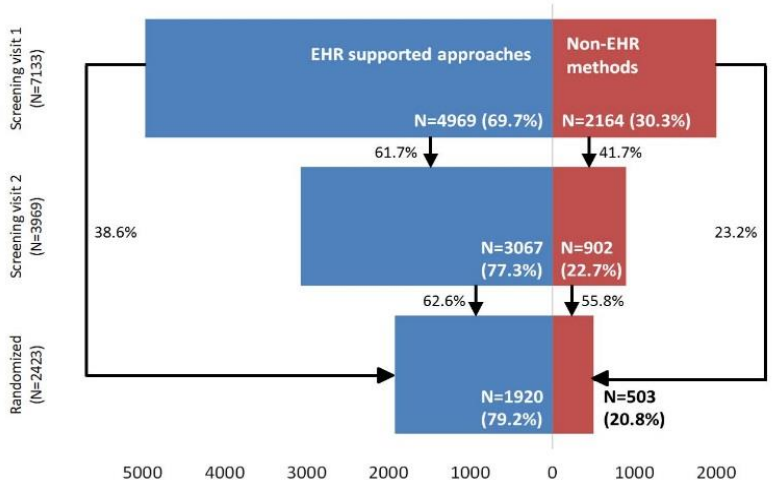
Diabetes Prevention Program Recruitment 1996-1999



Historical perspective

DPP: 41 screened for 1 enrolled/randomized (2%)
[screened an additional 154,358 potential participants]

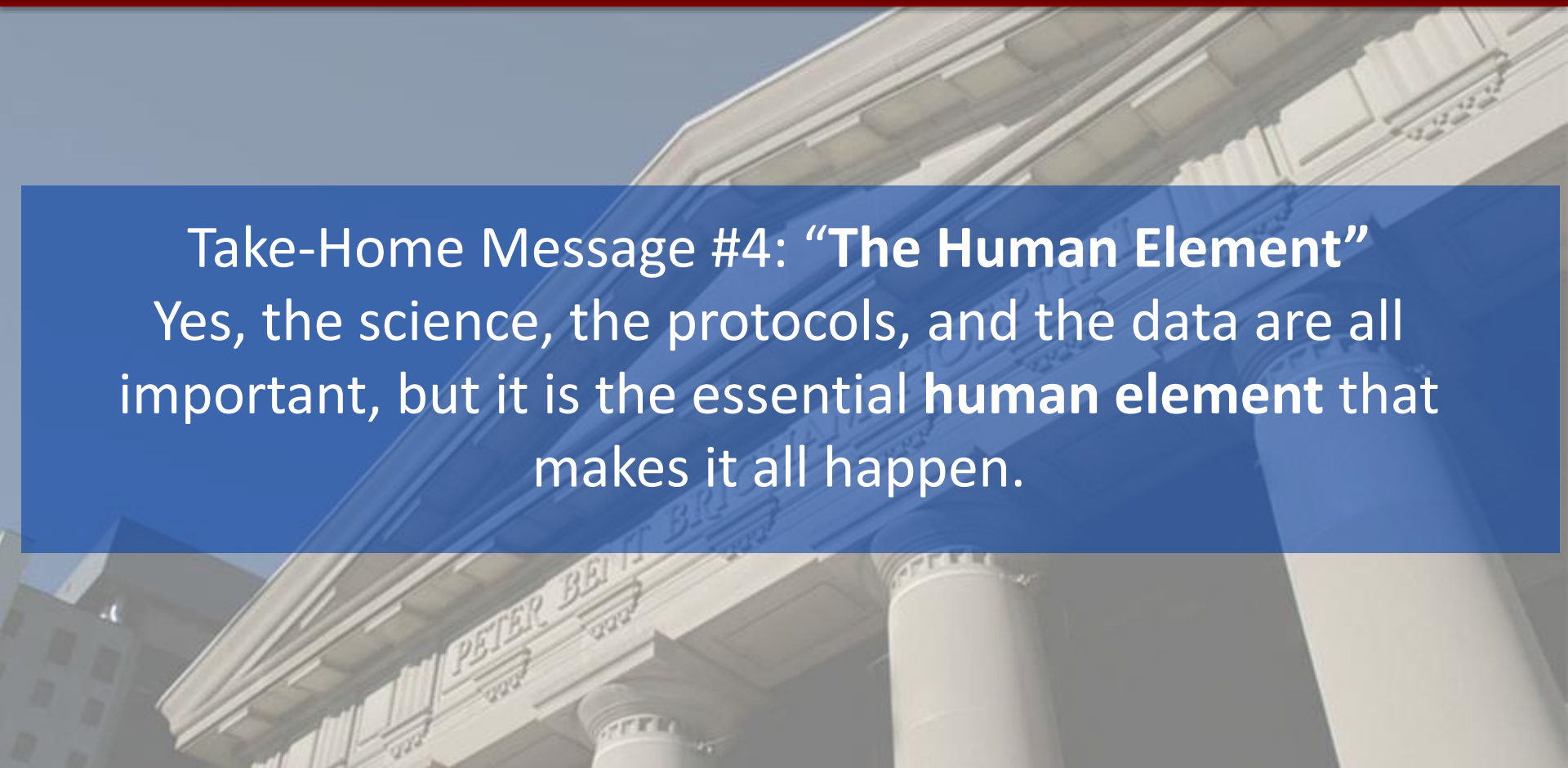
D2d Recruitment: 2014-2016



Contemporary perspective:

D2d: 3 screened for 1 enrolled (33%);

- At historical rates, we would have needed to screen 99,343 individuals, not 7,133 (or taken 10 years!), which would not have been feasible, and we would not have been able to meaningfully address the primary question

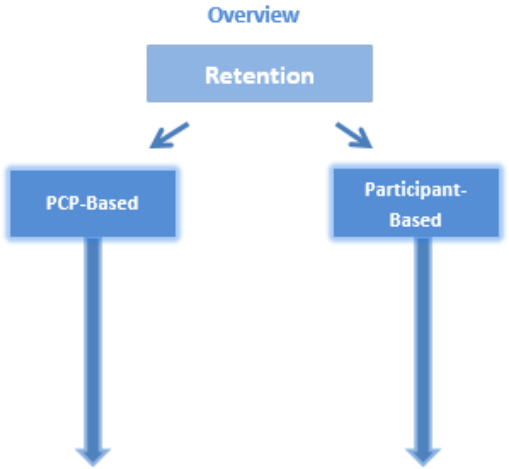


Take-Home Message #4: "**The Human Element**"
Yes, the science, the protocols, and the data are all important, but it is the essential **human element** that makes it all happen.

Retention, a continuation of Recruitment/ Engagement

Overview of Retention Strategies for D2d, July 2015

Objective: To maximize participant retention and adherence to study procedures, the RRS has prepared an overview of retention strategies, structured as a tool to facilitate discussion within your team on how to optimize and individualize your approaches to retention. The RRS encourages you to provide additional examples and ideas that we can incorporate and share study-wide.



PCP-Based:

1. Keep your clinician base informed about general study progress

Tools: Clinician Newsletter

2. Keep participant's PCPs generally informed about medical issues specific to their patients.

This requires direct PCP-INVESTIGATOR-participant communication:

A. Outside labs suggest progression to diabetes, but study labs do not (PCP wants to start metformin)

Tools: example communication template

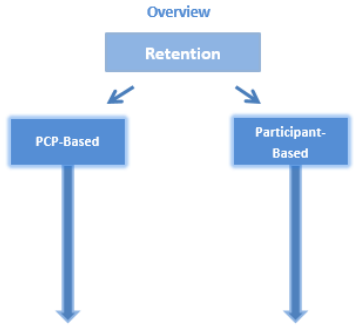
B. Outside vitamin D level is low. PCP wants to give high dose vitamin D (e.g. "My doc checked my levels, I *know* I'm on placebo!")

Tools: handout "Talking points about vitamin D and calcium"

Retention, a continuation of Recruitment/ Engagement

Overview of Retention Strategies for D2d, July 2015

Objective: To maximize participant retention and adherence to study procedures, the RRS has prepared an overview of retention strategies, structured as a tool to facilitate discussion within your team on how to optimize and individualize your approaches to retention. The RRS encourages you to provide additional examples and ideas that we can incorproate and share study-wide.



- Another way to look at RETENTION is our opportunity to **"Give Back"** to participants. They are consistently giving to us during the study – their consent, their blood, their information, and their stories.

  ⇒ *Team discussion:* Think of what we can keep giving back that will keep participants engaged with the study for the long-term.

- Remember, **this is 'our' study**. Participant stories are part of the bigger story being formed. Participants are encouraged to share their own story on the D2d webpage.

"Adele" Letter

Lyrics for cultural reference:
"Hello, it's me
I was wondering if after all these years you'd like to meet…"

"We would like to remind you that it is important for individuals with pre-diabetes to have their sugar levels tested once a year to ensure that they have not progressed to the diabetes range. This can be done by your PCP or D2d Team."

"We value your opinion please let us know if there is anything we can do differently to reconnect with you."

Take-Home Message #5: Essence of Recruitment & Retention? "**The Joy of Clinical Trials**"

"To be able to walk this journey side by side with our participants, teams, peers, and collaborators, knowing that whatever we will learn, we will learn together and contribute to the broader knowledge and advances of care…is **PURE JOY**."

"The Joy of Clinical Trials" – VR Aroda (unpublished)