Aiming for Impact

What Is the Right Concept to Target?

Moderator:
Steven George, PT, PhD, FAPTA
Duke University

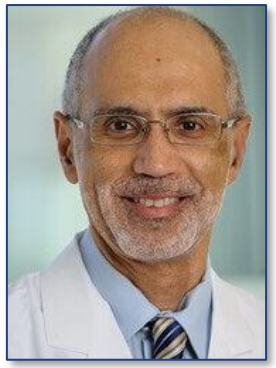
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Participants

Trialists on trial



Michael Ho
Kaiser Permanente Colorado, University of Colorado

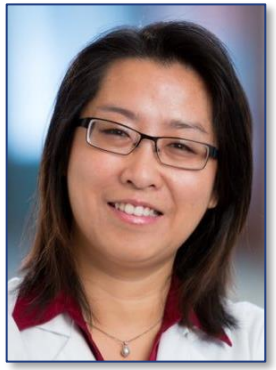


Miguel Vazquez
UT Southwestern

Discussants



Frederick Masoudi
Ascension



Tracy Wang
PCORI



Wendy Weber
NCCIH

Introduction

- Level setting on key terms, concepts, and scope
- Ground rules

Level setting

- In this session, we will use the terms “proximate” and “distal” to differentiate outcomes of PCTs
- Those terms refer to an *intervention and its presumed mechanism of action*, be it biological, behavioral, or operational
- Relative to the intervention and its intended action
  - A ***proximate outcome is closer***
  - While a ***distal outcome is farther away***



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Level setting

- The HPCT (Hypothetical Pragmatic Clinical Trial) trial
- Intervention is a practice alert in the electronic health record
  - Indicating a patient is candidate for referral to specialty clinic
- Potential outcomes of interest
  - Number of referrals to the specialty clinic
    - Proximate to the alert
  - Health status or quality of life for candidate patients
    - Distal to the alert

One-slide tangent

- Please note – we acknowledge that in some cases proximate outcomes may be considered mediators of an outcome

- However, in this session, we are focusing on their use as outcomes, as mediation (while highly interesting) is considered out of scope



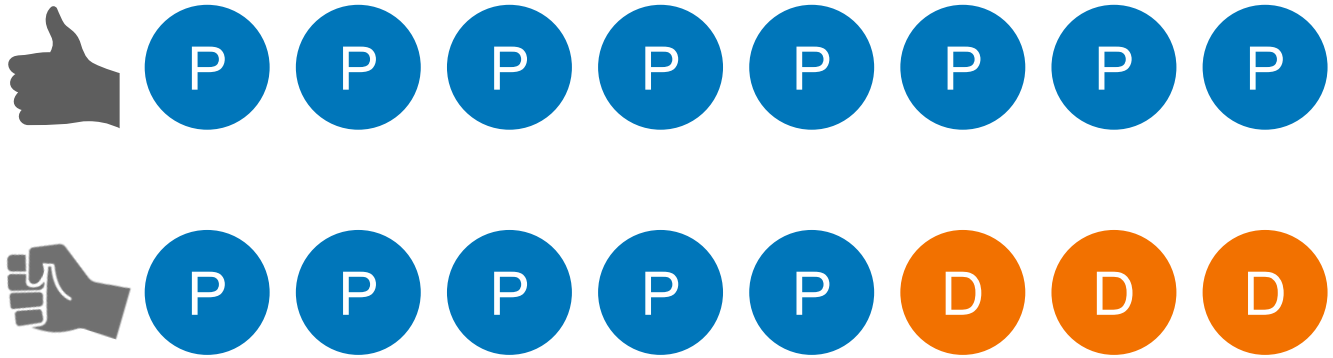
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Level setting

- Why care about this proximate vs. distal distinction?
- Typically, one outcome is designated as a primary outcome for powering the study and conducting statistical analyses
- A pattern emerged with 16 completed NIH Collaboratory Trials
  - Does not include 2 trials stopped early for feasibility reasons

Positive/Null Primary Endpoint vs Location of Outcome on Causal Path

P = Proximate, D = Distal





Level setting

- This pattern becomes more interesting when considering relevance to research partners and interest holders

Outcome Type	Likelihood of an Effect	Relevance to More Partners
Proximate	Higher	Lower
Distal	Lower	Higher

Level setting

- Creates a tension which we hope to fully explore today in the subsequent discussion



Level setting

- What caught our attention was effectiveness outcomes; this concept also applies to implementation outcomes
- And may be especially relevant for hybrid designs
  - **Type 1:** Focuses primarily on clinical effectiveness while secondarily observing implementation context, barriers, and facilitators
  - **Type 2:** Gives equal dual focus to testing the clinical intervention and testing an implementation strategy simultaneously
  - **Type 3:** Focuses primarily on testing an implementation strategy while collecting secondary data on clinical outcomes and uptake fidelity

Ground Rules

- Case studies from the NIH Collaboratory
  - ICD-Pieces → → distal outcome (PI: Vazquez)
  - Nudge → proximate outcome (PIs: Ho and Bull)

- Questions and discussion led by our esteemed panelists
  - Proximate vs. distal considerations
  - Balancing implementation vs. effectiveness outcomes
  - Seeing intervention effects vs. relevance to interest holders

Case Studies



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ICD-Pieces: Improving Chronic Disease Management With Pieces

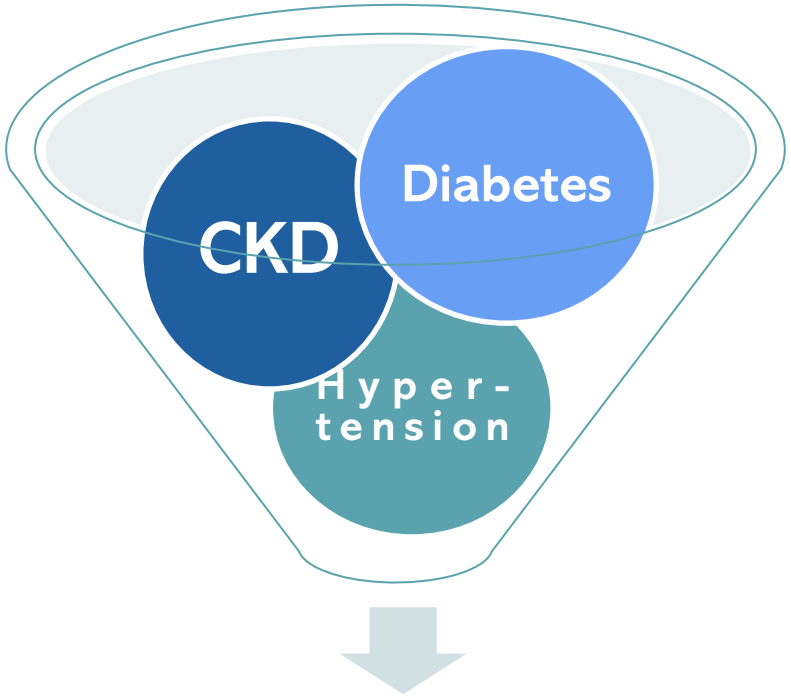
Miguel A. Vazquez, MD
Professor of Internal Medicine
University of Texas Southwestern Medical Center



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Multiple Chronic Conditions

->Common
->Serious Complications



->Under-recognized
->Treatable

Opportunity to
Advance Care

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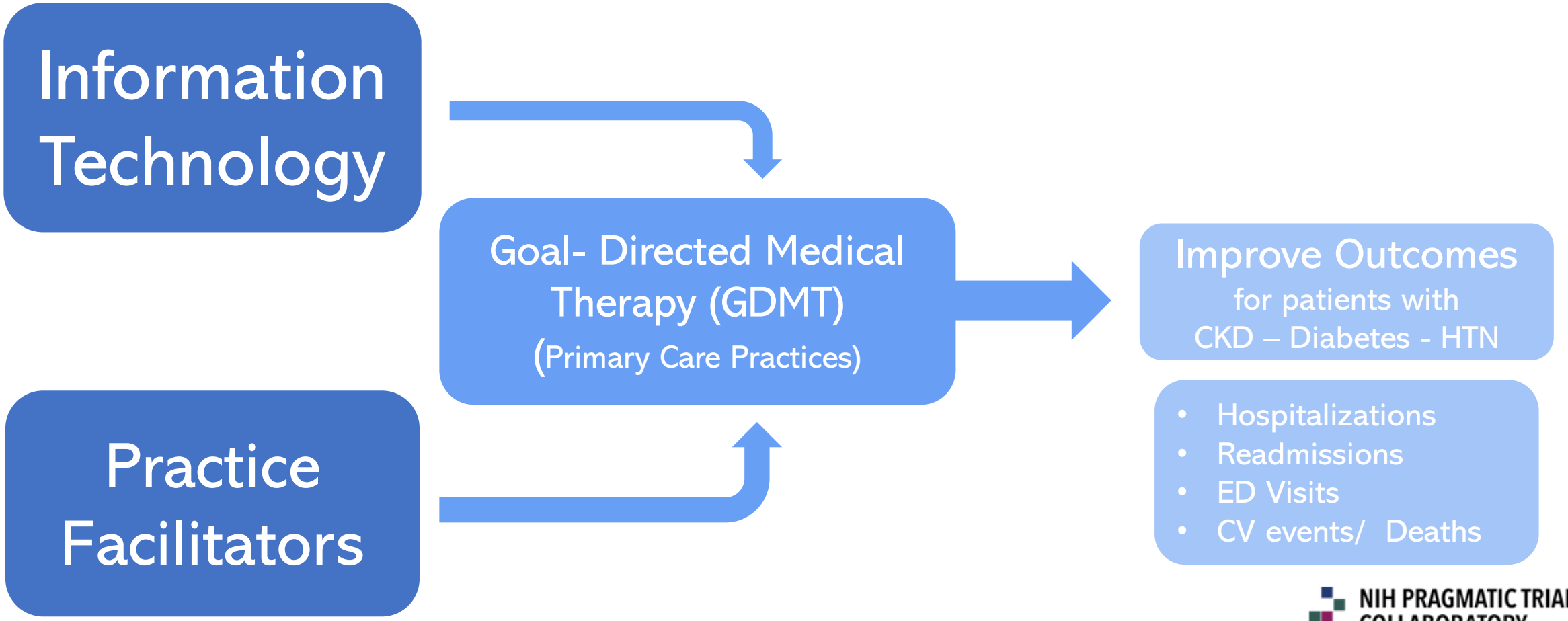
Our Goal: Improve CKD Care

Pragmatic Clinical Trial

WHO	Patients with triad CKD, Diabetes and HTN
WHAT	Identify patients Evidence-based interventions
HOW	Leverage technology Assist personnel in primary practices

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Hypothesis: ICD- Pieces Collaboratory Model of Care



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Study design

Population	Adult primary care patients with CKD, diabetes, and hypertension in 4 major health systems (Parkland, Texas Health Resources, VA North Central Texas and ProHealth CT)
Design	Open-label, pragmatic trial randomized by primary care practice (cluster)
Intervention	During primary care clinic visit
ICD-Pieces	Practice facilitator implemented evidence-based care for secondary prevention of HTN, DM, CKD, and CV complications
Control	Usual Care
Waiver of informed consent	(Opt-out)
Outcome	One-year documented hospitalization (claims / EHR)

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ICD–Pieces Implementation

Evidenced-based Care (IT + PF) and Primary Team 4 Health Systems

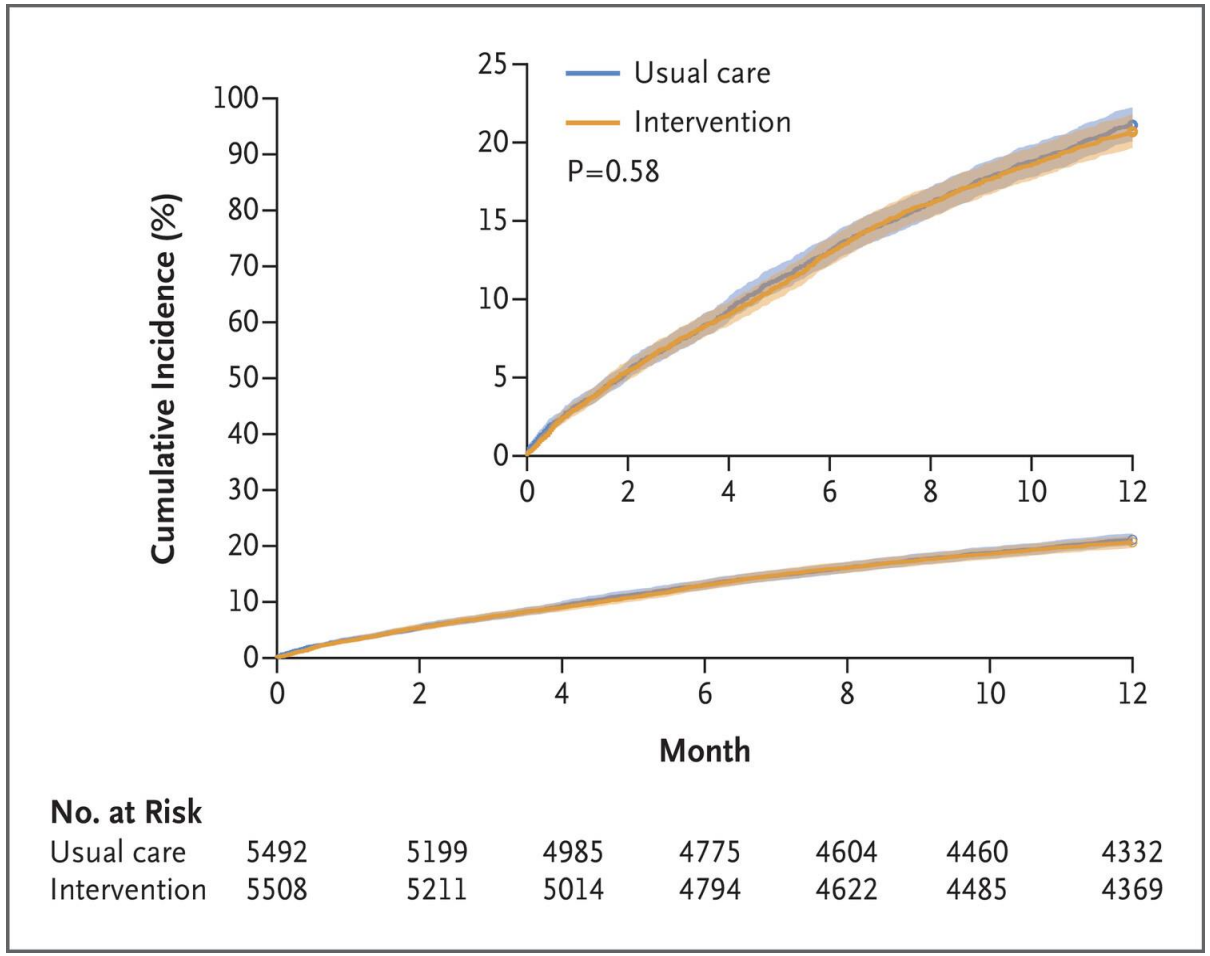
- Update Problem List
- BP control and use ACEI / ARB
- Set HbA1c goal—guidance/ orders
- Avoid hypoglycemia
- Statins
- Avoidance of NSAID
- Immunizations
- Education (visit summary/ NKDEP)
- Document opt-outs

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Pragmatic Trial of Hospitalization Rate in Chronic Kidney Disease

The NEW ENGLAND JOURNAL of MEDICINE

Cumulative Incidence of Hospitalizations



New Engl J Med 2024; 390(13):1196-1206

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Key Outcomes

Table 2. Primary and Key Secondary Outcomes.

Outcome	Intervention (N = 5508)	Usual Care (N = 5492)	P Value*
	no./total no. (%)		
Primary outcome			
Hospitalization at 1 yr	1139/5508 (20.7)	1160/5492 (21.1)	0.58
Secondary outcomes			
Emergency department visit	1336/5508 (24.3)	1242/5492 (22.6)	
Hospital readmission ≤30 days after first inpatient treatment	429/1139 (37.7)	433/1160 (37.3)	
Cardiovascular events†	1020/5508 (18.5)	1065/5492 (19.4)	
Cardiovascular procedures‡	104/5508 (1.9)	99/5492 (1.8)	
Dialysis	37/5508 (0.7)	32/5492 (0.6)	
Death	129/5508 (2.3)	148/5492 (2.7)	

* P values were not reported for secondary outcomes.
† Cardiovascular events included acute coronary syndrome, heart failure, and stroke.
‡ Cardiovascular procedures included cardiac catheterization and revascularization.

NEJM 2024; 390(13):1196-1206

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Table 3. Implementation of Assigned Treatment in a 10% Random Sample

Criteria	Processes of Care	Intervention N=582	Usual Care N=531	P-value	Total N=1,113
Chronic Kidney Disease care	Problem list - existing	56%	48%	0.01	52%
	Problem list - updated	15%	5%	<0.01	10%
	Patient education	79%	48%	<0.01	64%
	Met all criteria (Problem list updated & Patient education)	64%	39%	<0.01	52%
Hypertension Management	Problem list - existing	96%	93%	0.02	95%
	Problem list - updated	1%	2%	0.18	2%
	Hypertension/BP goal set	50%	29%	< 0.01	40%
	Use of ACEI/ARB - existing	74%	75%	0.58	74%
	Use of ACEI/ARB - added new	11%	6%	< 0.01	8%
	Patient education	93%	88%	< 0.01	90%
	Met all criteria (Problem list updated, Goal set, ACEI/ARB - added new & Patient education)	40%	22%	<0.01	31%
Blood Pressure Outcomes	Blood pressure < 140/90 mmHg before enrollment	50%	47%	0.39	48%
	Blood pressure < 140/90 mmHg within 1 year after enrollment	73%	66%	0.01	69%

. N Engl J Med 2024;390:1196-1206

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Table 3. Implementation of Assigned Treatment in a 10% Random Sample (continued)

Criteria	Processes of Care	Intervention N=582	Usual Care N=531	P-value	Total N=1,113
Diabetes Management	Problem list - existing	96%	96%	1	96%
	Problem list - updated	2%	1%	0.05	2%
	Diabetes/HbA1c goal set	55%	33%	<0.01	45%
	Patient education	96%	93%	0.07	94%
	Met all criteria (Problem list updated, Goal set & Patient education)	52%	32%	<0.01	43%
Blood Glucose Outcomes	HbA1c < 7.5% before enrollment	52%	55%	0.25	53%
	HbA1c < 7.5% within 1 year after enrollment	55%	57%	0.57	56%
CV risk reduction	Use of Statin - existing	79%	79%	0.9	79%
	Use of Statin - added new	7%	5%	0.08	6%
	Patient education	86%	83%	0.16	84%
	Met all criteria (Statin - added new &Patient education)	77%	73%	0.1	75%

N Engl J Med 2024;390:1196-1206

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Lessons from ICD-Pieces

- Intervention did not reduce hospitalizations
- Identified and enrolled target population
- Delivered intervention with fidelity across 4 health systems
- Captured relevant outcomes data
- Provided model for delivery guideline-directed therapy
- Showed feasible approach future pragmatic trials

ICD-Pieces and Primary Outcome: Hospitalizations

- Relevance: participants, relatives, health system, payors
- Clinically meaningful
- Ascertainment: objective ➔claims data/ EHR
- Limitations:
  - Duration intervention
  - Changes practices: health systems, treatment options CKD
- Secondary outcomes: relation to primary outcome
- Other considerations: changes (improvements) in care

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Endpoint Selection

Lessons learned across 2 pragmatic trials

P. Michael Ho, MD, PhD
Institute for Health Research
Kaiser Permanente of Colorado



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Completed

Nudge *Personalized Patient Data and Behavioral Nudges to Improve Adherence to Chronic Cardiovascular Medications*

- Patient-level randomized pragmatic trial comparing the effects of digital interventions (text messages and chat bot) on **medication adherence** in patients with chronic cardiovascular conditions
- 3 health systems

Nudge

JAMA | Original Investigation

Personalized Patient Data and Behavioral Nudges to Improve Adherence to Chronic Cardiovascular Medications
A Randomized Pragmatic Trial

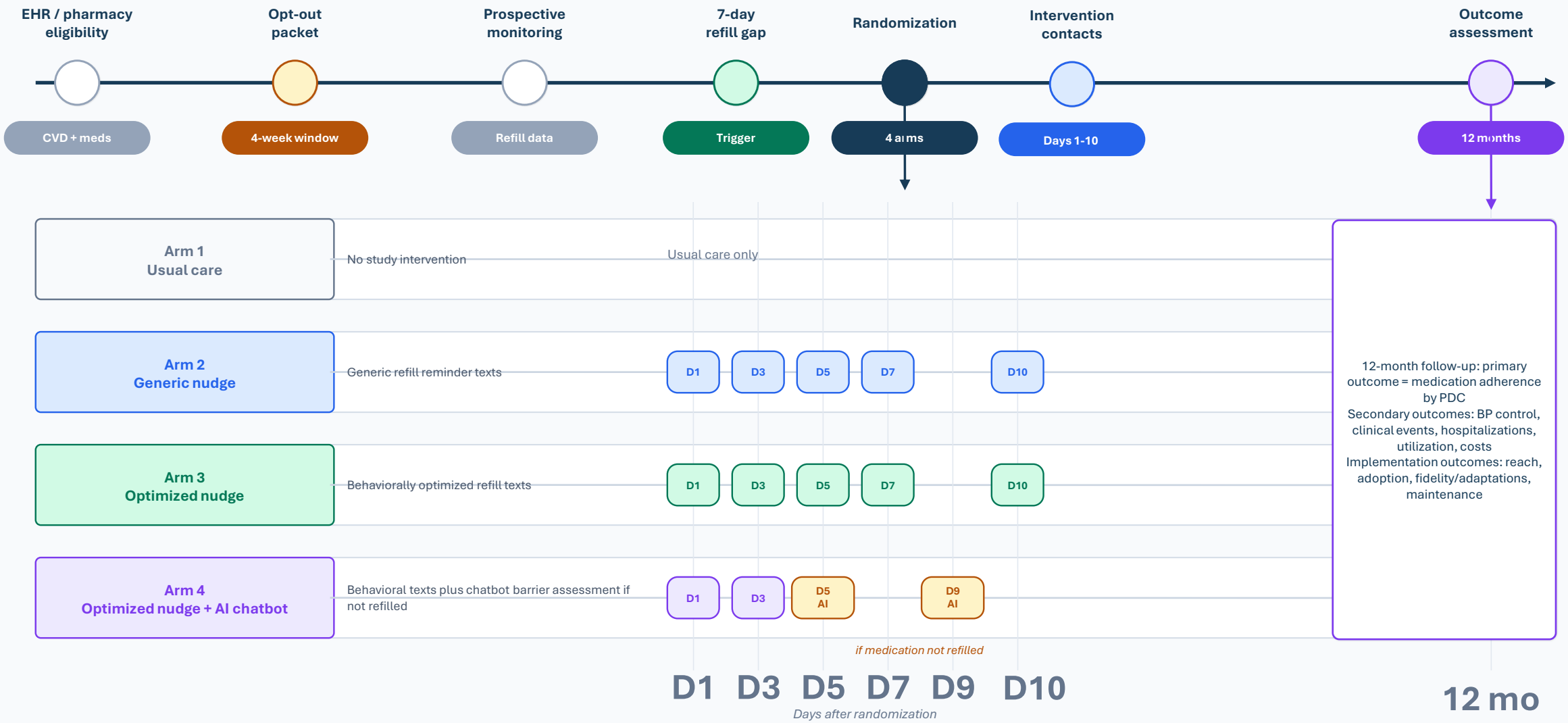
P. Michael Ho, MD, PhD; Thomas J. Glorioso, MS; Larry A. Allen, MD, MHS; Richard Blankenhorn, MSDA, BSF; Russell E. Glasgow, PhD; Gary K. Grunwald, PhD; Amber Khanna, MD; David J. Magid, MD, MPH; Joel Marrs, PharmD, MPH; Sylvie Novins-Montague, BA; Steven Orlando, PharmD; Pamela Peterson, MD, MSPH; Mary E. Plomondon, PhD; Lisa M. Sandy, MA; Joseph J. Saseen, PharmD; Katy E. Trinkley, PharmD, PhD; Shawni Vaughn, MAS; Joy Waughtal, MPH; Sheana Bull, PhD

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NUDGE Trial Timeline

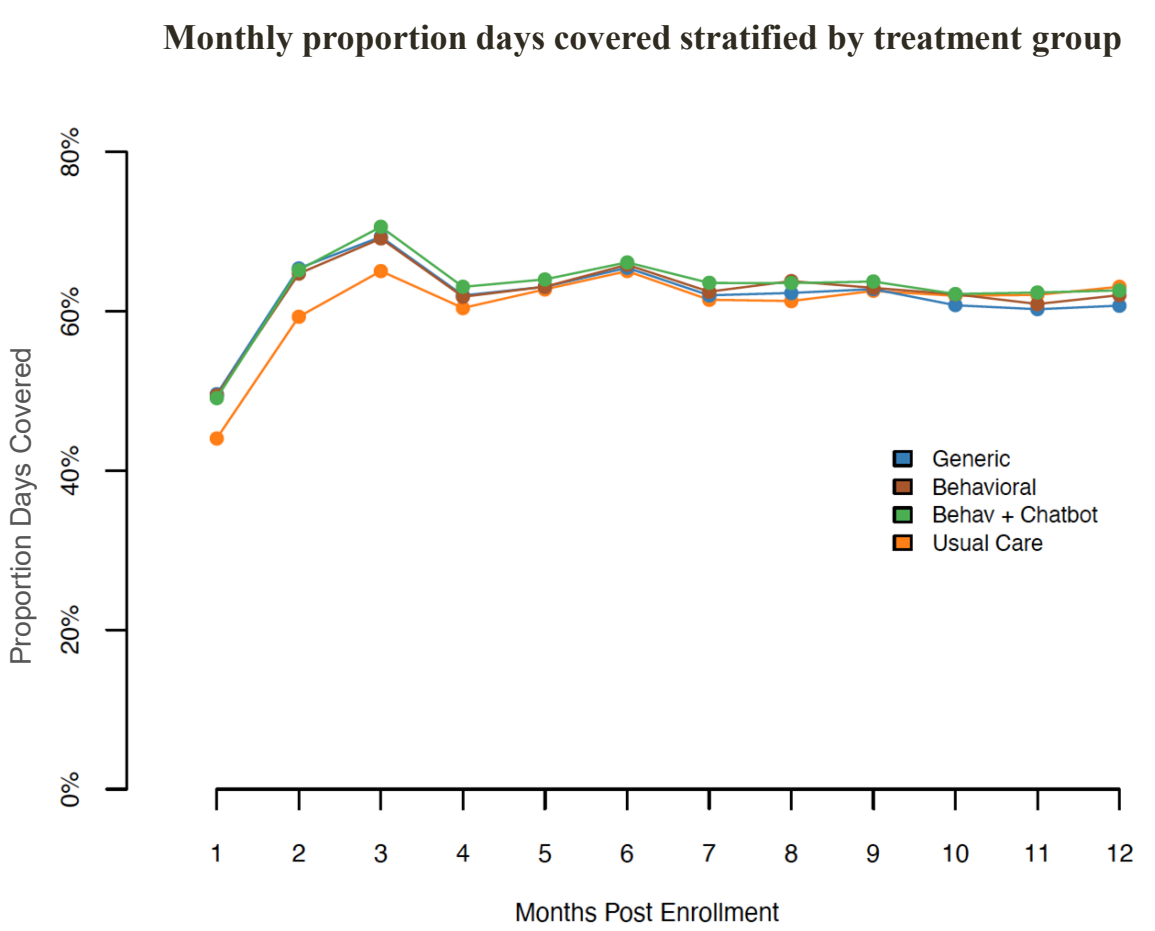
Patient flow from eligibility through randomized intervention timing and 12-month outcome assessment

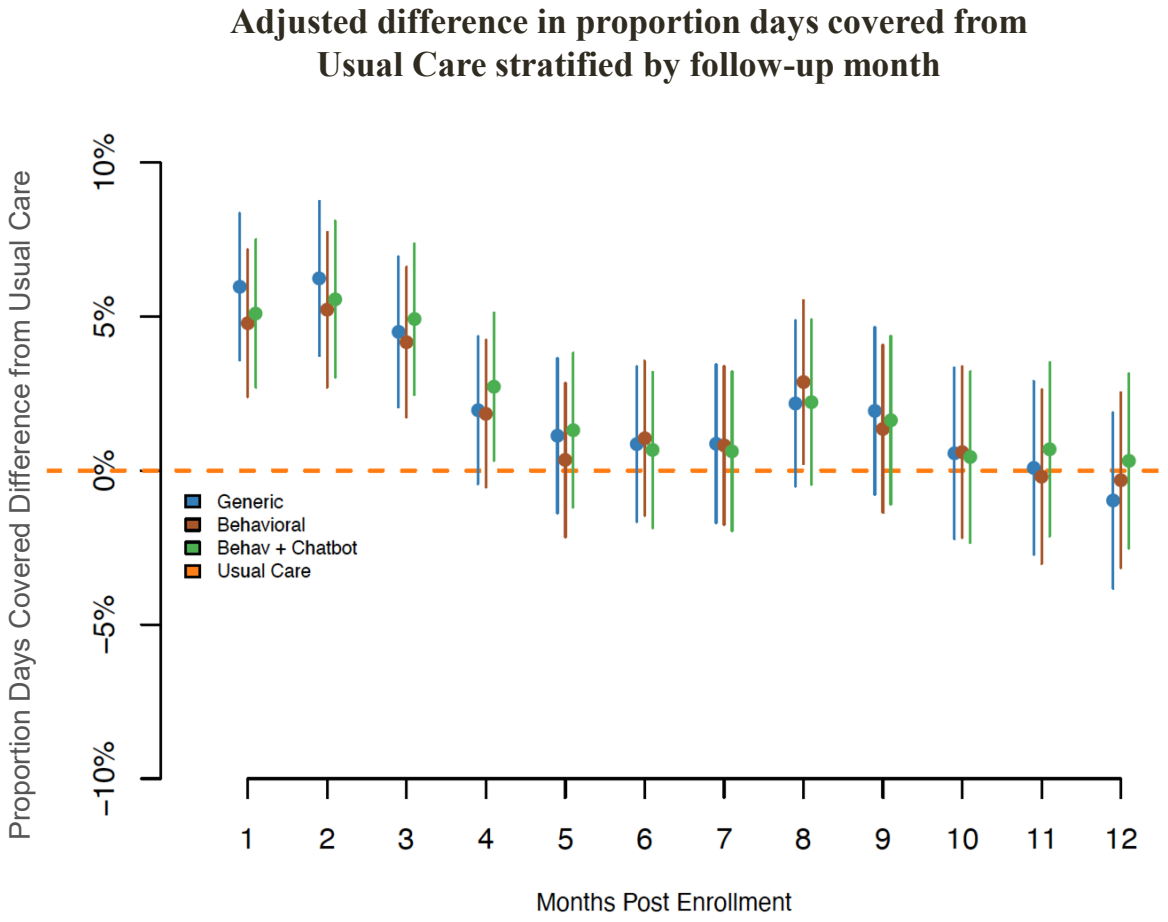
Patient-level pragmatic RCT



Source: NUDGE trial protocol, Glasgow et al., Trials 2021

Main study findings





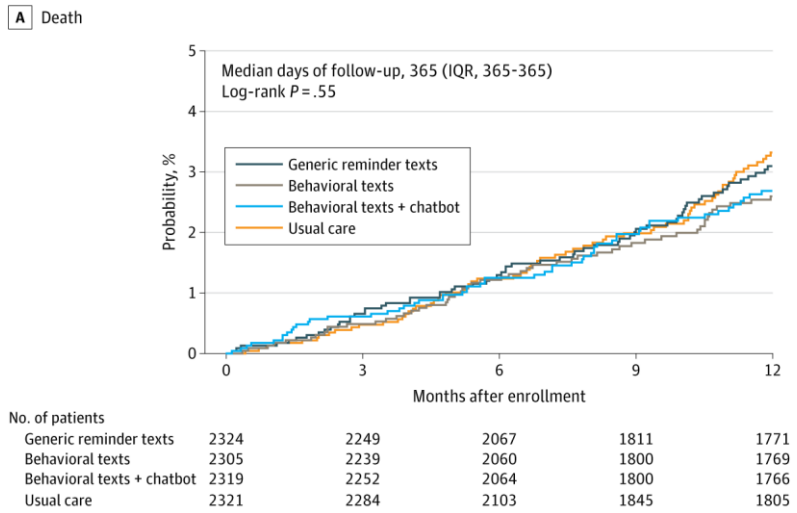
Primary Outcome: PDC at 12-months

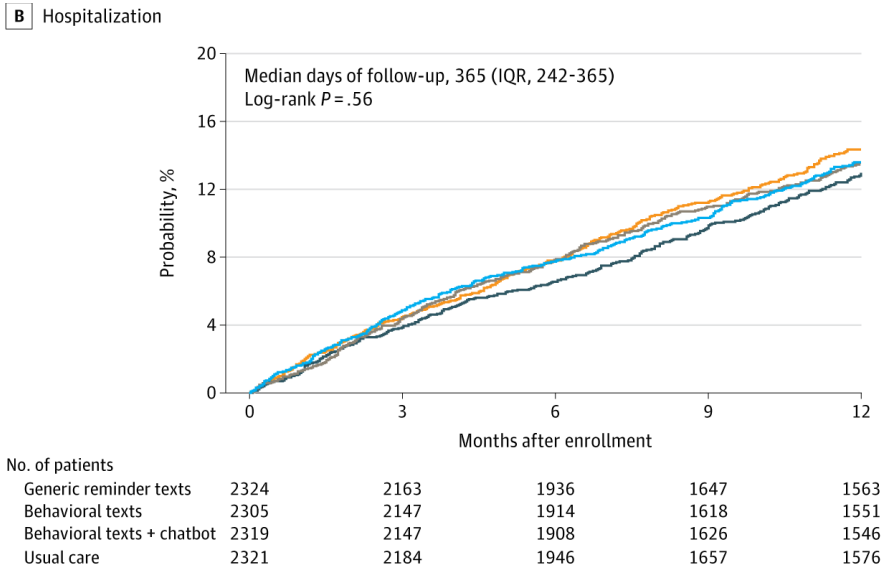
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Nudge

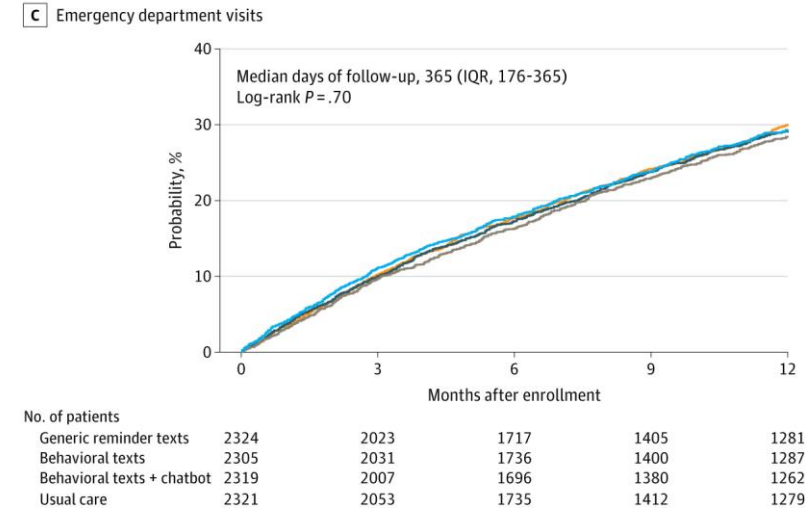
JAMA Network™

From: **Personalized Patient Data and Behavioral Nudges to Improve Adherence to Chronic Cardiovascular Medications: A Randomized Pragmatic Trial**

JAMA. 2025;333(1):49-59. doi:10.1001/jama.2024.21739







Kaplan-Meier Rates for Secondary Clinical Outcomes Stratified by Treatment Group

Enrolling

Chat 4 Heart Health: Using Artificially Intelligent Text Messaging Technology to Improve American Heart Association's Life's Essential 8 Health Behaviors

- Use an artificially intelligent chatbot to deliver text messages and interact with patients to help them improve their control of AHA's Life's Essential 8 (LE8) lifestyle factors: blood glucose, cholesterol, blood pressure, physical activity, weight, diet, sleep, and smoking, and medication adherence
- 3 health systems



Lu et al. Trials (2026) 27:244
https://doi.org/10.1186/s13063-026-09564-z

Trials

STUDY PROTOCOL Open Access

Using artificially intelligent text messaging to improve health behaviors to reduce cardiovascular risk: study protocol for a pragmatic randomized control trial

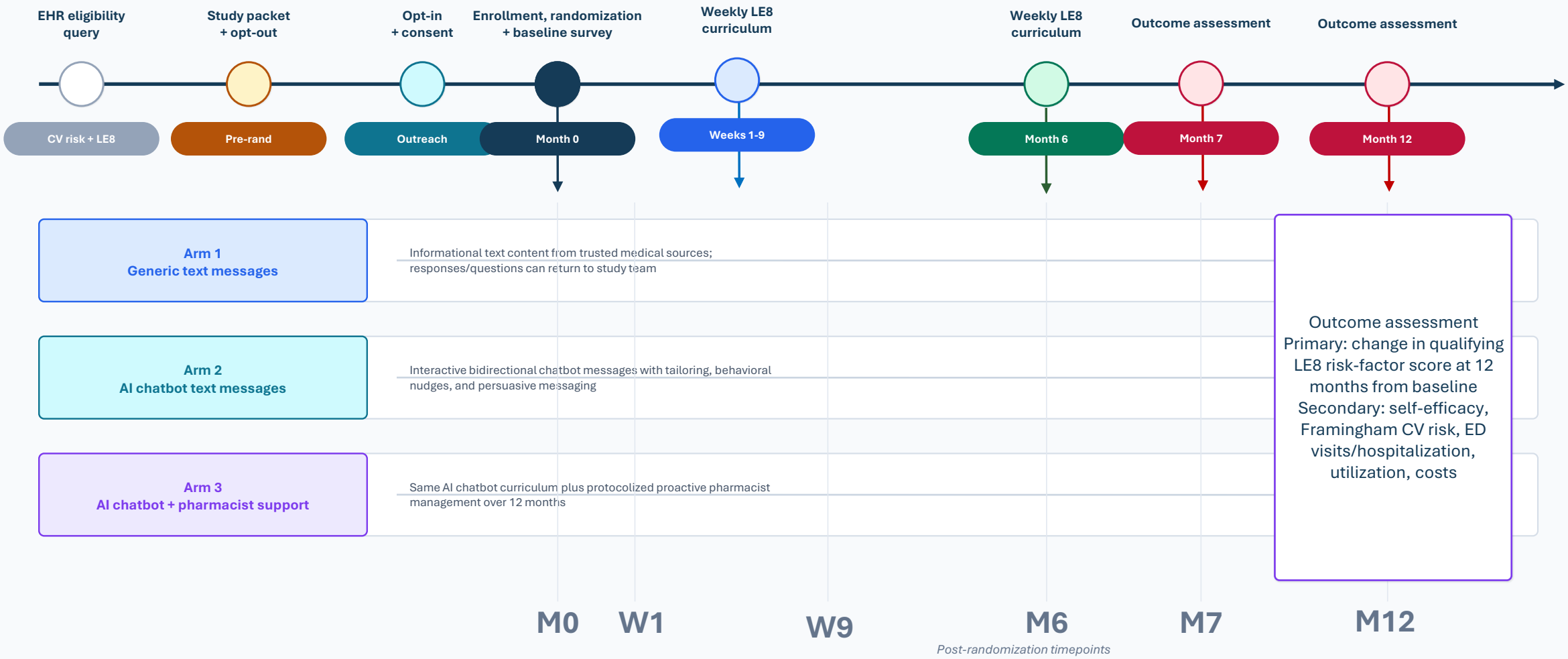
Amy D. Lu[1,2*], Catia Chavez[2,3,5], Stacie L. Daugherty[2,8], Pradeep Dhar[4], Catherine G. Derington[2,3], Rachel Everhart[1,2], Erica F. Morse[8], Sylvie Novins-Montague[3], Katy E. Trinkley[3,5], Joy M. Waughtal[9], Rachel Zucker[8], Evan Carey[10], Sheana Bull[6,9], Pamela N. Peterson[2,7] and P. Michael Ho[2,8]

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Chat for Heart Health Timeline

Patient flow, randomized text-message interventions, pharmacist support, and outcome assessments

Target n = 2,097 | 3 arms | LE8 outcome



Source: NUDGE trial protocol, Glasgow et al., Trials 2021

Justification for change in timing of primary outcome assessment

- Positive impacts of health-related text messaging programs often diminish over time.
- Text messaging interventions typically show strongest positive effects in first 3 to 6 months. Participants are highly engaged at this time and then the effects begin to plateau.
- Prior experience with NUDGE trial showed impacts at 3 months (secondary outcome) but none at 12 months (primary outcome)
- Behavioral survey completion data at 10-week mark was less than 50%
- Better chance at documenting impacts of intervention in a shorter time interval between intervention delivery and outcomes assessment for this low touch intervention.

After discussion with DSMB and NHLBI

- Primary outcome will be assessed at months 7 and 12 (LE8 EHR components measured poor/intermediate at baseline)
- Primary hypothesis comparison: There will be a cascade of 2 then 1 comparisons for the primary hypotheses at 7 months, thus we adjust for multiple comparisons with alpha = (0.5/2). The first two comparisons are below:
  - Group 1 (generic text) versus Group 2 (AI chatbot text messages)
  - Group 1 versus Group 3 (AI chatbot text messages plus proactive pharmacist support)
  - If either of these statistical tests are significant, we will make the final comparison:
  - Group 2 (AI chatbot text messages) versus 3 (AI chatbot text messages plus proactive pharmacist support)
- The second primary outcome of change in LE8 from baseline to 12 months will only be tested if one or both of the statistical tests of the first two comparisons described above are significant.

Reflections on endpoints selection

- In the grant writing phase, our team felt that more distal and clinical endpoints would be more meaningful to grant review panel and funder
- Being realistic about dose/intensity and duration of intervention and its potential impact on outcomes
- Adjusting timing and/or outcomes after UG3 pilot year and before starting UH3 years
- Including BOTH proximal and distal outcomes may be one approach
- Strategically including both effectiveness and implementation outcomes as co-primary outcomes
- Identifying multiple and/or composite outcomes relevant to health systems and advancing the science

Discussion

Proximate vs. distal considerations



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Discussion

Implementation vs. effectiveness outcomes

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Discussion

Seeing intervention effects vs. relevance to interest holders



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