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TRANSFORMING DEMENTIA CARE

Decision Architecture Randomization Trials: Extremely Low-Cost Trials with Preservation of Clinician and Patient Choice

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Housekeeping

- All participants will be muted
- Enter **all questions** in the Zoom **Q&A/chat box** and send to Everyone
- Moderator will review questions from chat box and ask them at the end
- Want to continue the discussion? Associated podcast released about 2 weeks after Grand Rounds
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@IMPACTcollab1 https://www.linkedin.com/company/65346172

No Conflicts of Interest

Learning Objectives

Upon completion of this presentation, you should be able to:

- Define ‘nudges’, ‘decision architecture’, and ‘A/B testing’
- Describe a decision architecture randomization trial (DART)
- Understand how DART relates to other pragmatic clinical trial designs

Randomized Trials are Challenging to Conduct

- Average cost estimated at > $10,000 per patient
- < 30% of phase 3 trials meet accrual goals
- Take up providers' and patients' limited time
- Disrupts routine care
  - Especially if patient prefers treatment A and is randomized to treatment B

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Vickers AJ. Clinical trials in crisis: Four simple methodologic fixes. Clinical trials (London, England).
Cheng SK, Dietrich MS, Dilts DM. Clin Cancer Res. 2010;16(22):5557.
Dilts DM, Sandler AB, Baker M, et al. J Clin Oncol. 2006/10/01 2006;24(28):4553-4557.
Speich B, von Niederhäusern B, Schur N, et al. Journal of Clinical Epidemiology. 2018/04/01/ 2018;96:1-11.
Lee SJC, et al. Conceptual Model for Accrual to Cancer Clinical Trials. J Clin Oncol. 2019 Aug 10;37(23):1993-1996.

Pragmatic Designs Help But Are Still Big Undertakings

- Focus on standard of care treatments delivered through normal processes
- Use of routinely collected data
- Cluster randomization

- But, we still need far more high-quality evidence than we can get

https://www.pcori.org/research-results/2015/comparing-two-aspirin-doses-prevent-heart-attacks-and-strokes-people-living-heart-disease-adaptable-study

Bynum JPW et al. J Am Geriatr Soc. 2020 Jul;68 Suppl 2(Suppl 2):S49-S54
Brody A, Durga A, Ford A, Lin SY. Innov Aging. 2022 Dec 20;6(Suppl 1):172.

A/B Testing As a Pragmatic Trial Design

News organizations often randomize to two different versions of a headline

"SOUL-SEARCHING IN BALTIMORE, A YEAR AFTER FREDDIE GRAY'S DEATH"

Vs.

"BALTIMORE AFTER FREDDIE GRAY: THE 'MIND-SET HAS CHANGED'"

https://www.nytimes.com/2016/06/13/insider/which-headlines-attract-most-readers.html

A/B Testing As a Pragmatic Trial Design

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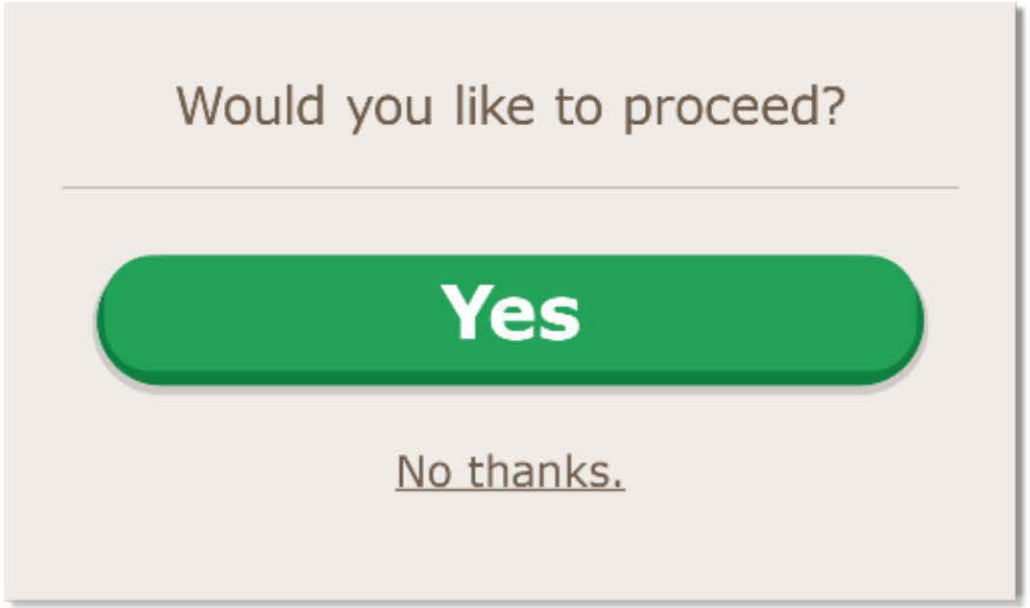
Readership 17 x greater

https://www.nytimes.com/2016/06/13/insider/which-headlines-attract-most-readers.html

Often, A/B Testing is Used to Study Nudges

- Nudges make you more likely to do something but don't force you to do it
  - A headline that makes you want to read an article
  - Making one option the 'default'



Horwitz LI, Kuznetsova M, Jones SA. Creating a learning health system through rapid-cycle,randomized testing. N Engl J Med 2019;381:1175–9.

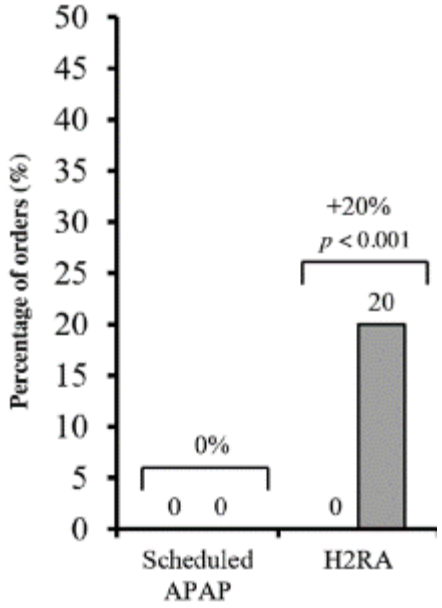
Nudges Can Change Prescribing Decisions

Before
(PPI only option for stress ulcer prophylaxis)

Other medications
Other medications
GI prophylaxis
- Esomeprazole (NexIUM) capsule
  40 mg, Daily before breakfast, Oral
- Esomeprazole (NexIUM) suspension 10 mg
  40 mg, Daily before breakfast, Oral
- Pantoprazole (PROTONIX) injection
  40 mg, Daily before breakfast, IV Push,

After
(H2RA and PPI are options for stress ulcer prophylaxis)

Other medications
Other medications
GI Prophylaxis
- Famotidine (PEPCID) tablet
  20 mg, 2 times daily, Per NG tube
- Famotidine (PF) (PEPCID) injection
  20 mg, 2 times daily, IV Push
- Lansoprazole (PREVACID) suspension
  30 mg, Daily at 0600, Per NG tube



Adding H2 blockers to an order set increased use by 20%

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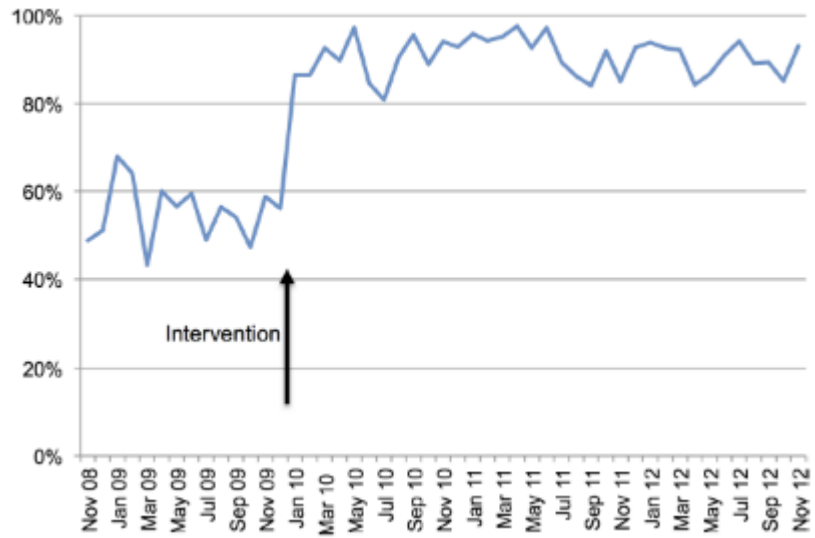
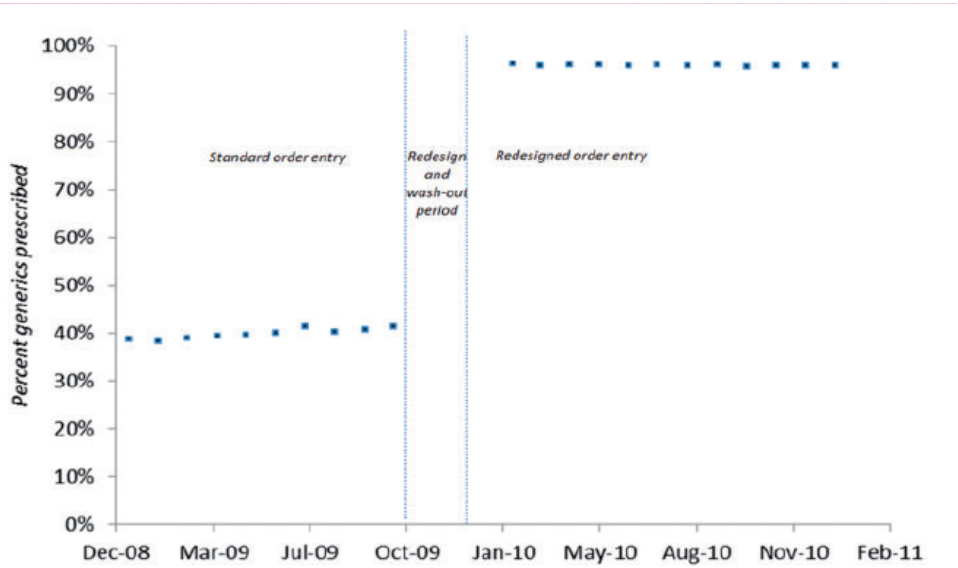
Malhotra S et al. J Am Med Inform Assoc. 2016 Sep;23(5):891-8.
Raban MZ et al. J Am Med Inform Assoc. 2023 Jun 20;30(7):1313-1322.
Bourdeaux CP et al. BMJ Qual Saf 2014; 23 (5): 382–8.
Muniga ET, Walroth TA, Washburn NC. Appl Clin Inform. 2020 Jan;11(1):182-189.

Nudges Can Change Prescribing Decisions



Adding chlorhexidine mouthwash as default to an order set increased use by 35%



Making generic prescribing the default in order entry system increased use of generics by 56%

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Malhotra S et al. J Am Med Inform Assoc. 2016 Sep;23(5):891-8.
Raban MZ et al. J Am Med Inform Assoc. 2023 Jun 20;30(7):1313-1322.
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Muniga ET, Walroth TA, Washburn NC. Appl Clin Inform. 2020 Jan;11(1):182-189.

Order Sets, Decision Architecture, and Nudges

Vs.

Nutritional Status

Eating Clear

- (•) Eating
- ( ) Fasting NPO
- ( ) Tube Feeding Continuous

Insulin Dose

Resistant - Use for obese body type, taking steroids Clear

- ( ) Sensitive - Use for Type 1 Diabetes, lean body type, elderly, renal insufficiency, pancreatectomy
- ( ) Average - Use for average or overweight body type
- (•) Resistant - Use for obese body type, taking steroids
- ( ) Custom

Long-Acting Insulin

Insulin detemir (Levemir) Clear

- ( ) None
- (•) Insulin detemir (Levemir)
- ( ) Insulin glargine (Lantus)

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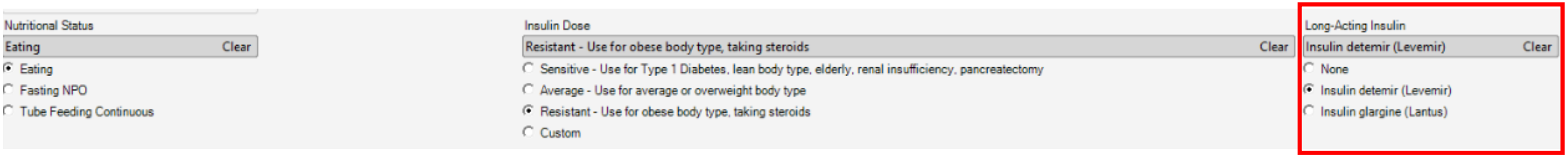
Johnson EJ. The elements of choice: why the way we decide matters. New York: Riverhead Books, an imprint of Penguin Random House LLC, 2021: 390.

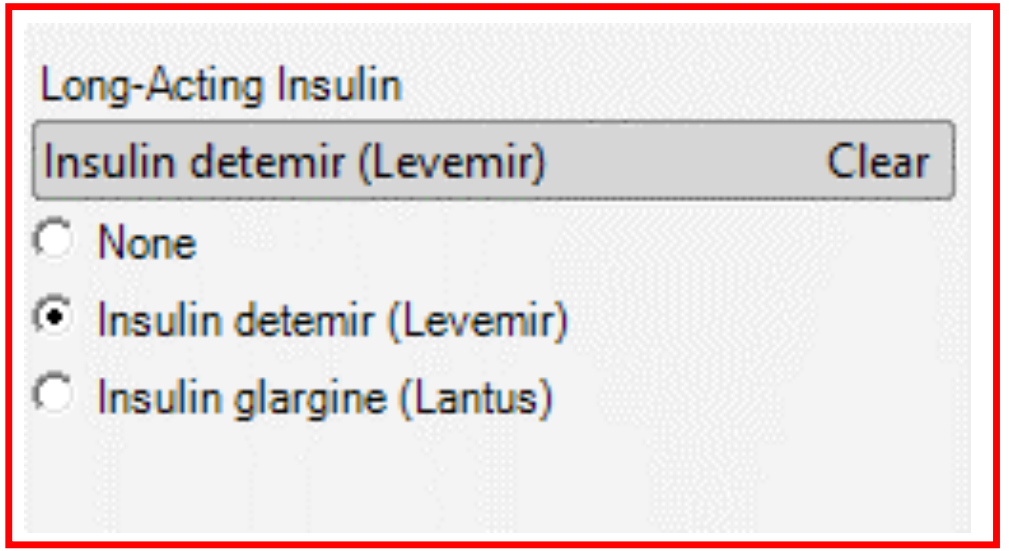
Thaler RH, Sunstein CR. Nudge: the final edition. New Haven: Yale University Press, 2021: 366.

Order Sets, Decision Architecture, and Nudges



Example of a Nudge

- There are two kinds of long-acting insulin at our hospital
- The one that is pre-checked may be more likely to be given



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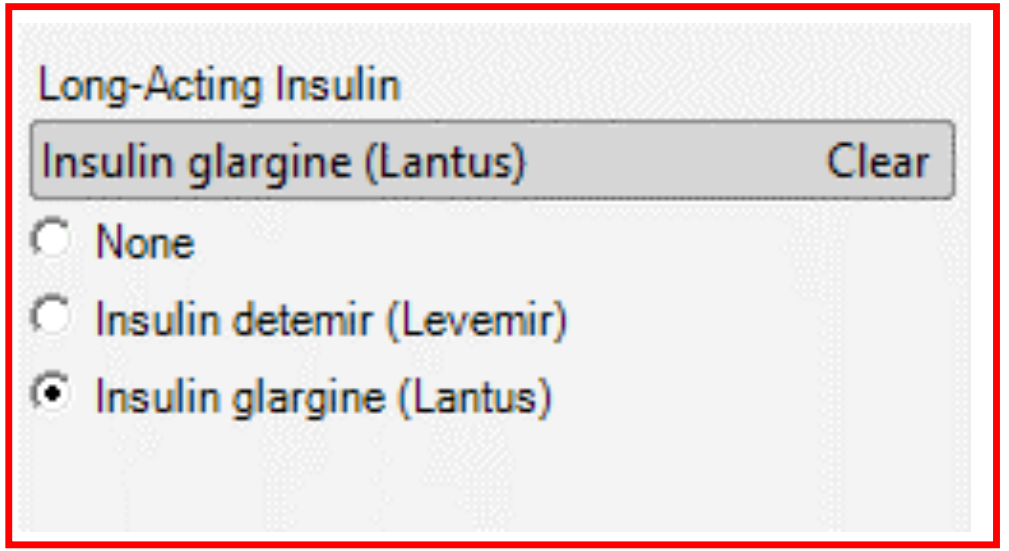
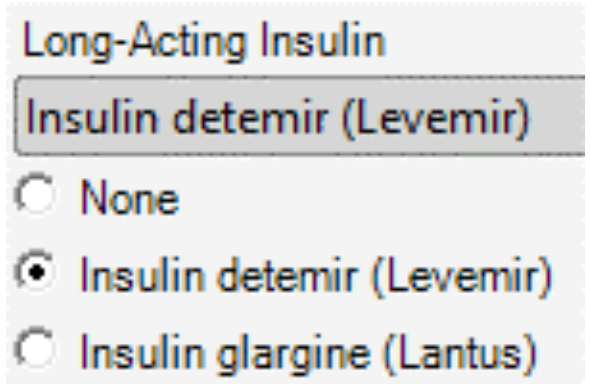


Suppose we changed this nudge at random

Random Assignment to Orderset

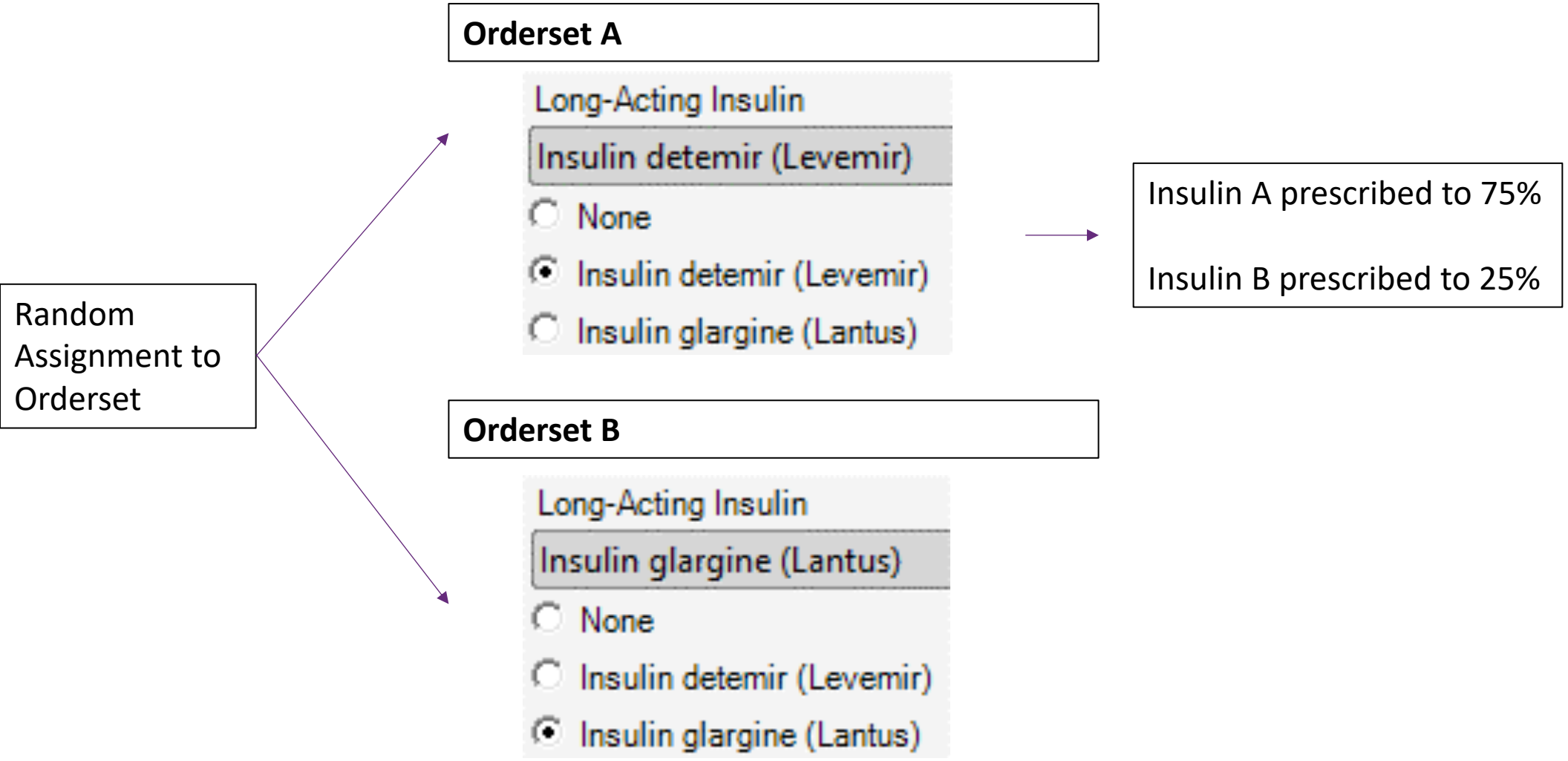
Orderset A



Insulin A prescribed to 75%

Insulin B prescribed to 25%

Suppose we changed this nudge at random



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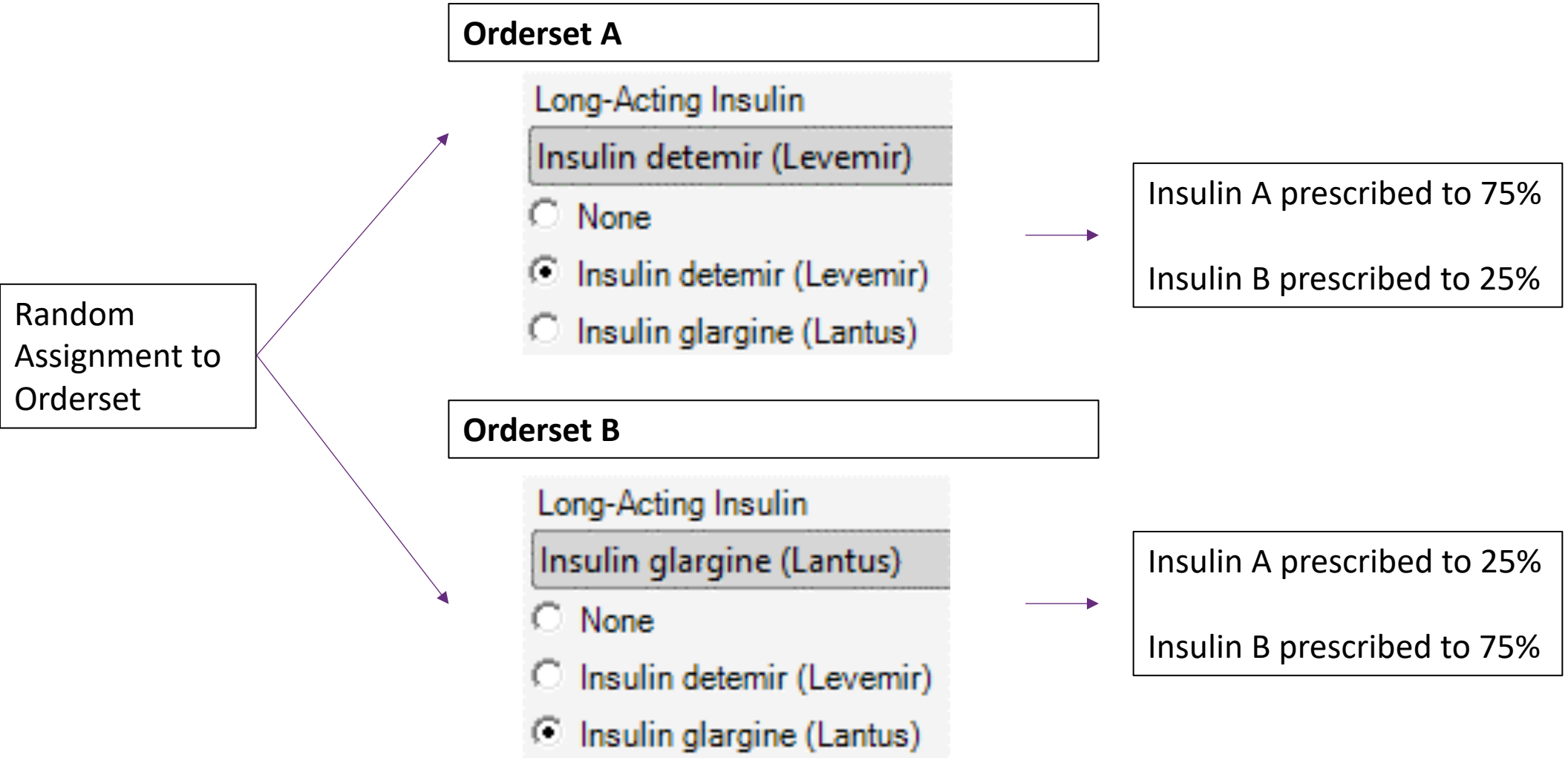

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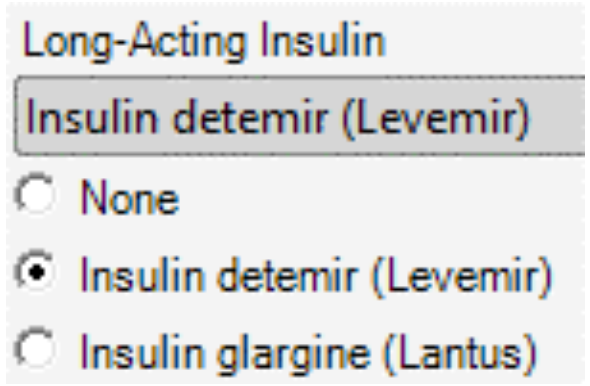
Random Assignment to Orderset

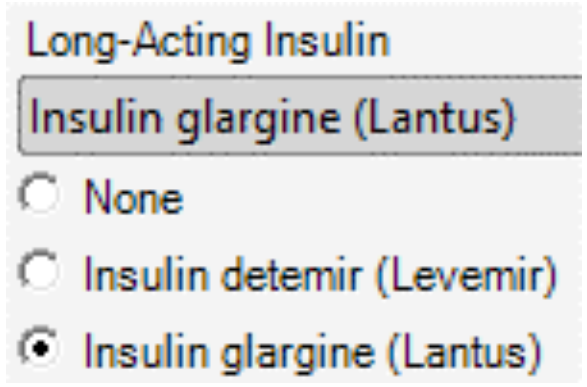
Orderset A



Insulin A prescribed to 75%

Insulin B prescribed to 25%

Orderset B



Insulin A prescribed to 25%

Insulin B prescribed to 75%

50% absolute difference between treatment arms

Ethics and Nudges

Routine Care

Patient/Provider Prefer A	→	Patient Receives A
Patient/Provider Have No Preference	→	Patient Receives A or B (based on arbitrary factors)
Patient/Provider Prefers B	→	Patient Receives B

Traditional Randomized Trial

Randomized to A

Patient/Provider Prefer A	→	Patient Receives A
Patient/Provider Have No Preference	→	Patient Receives A
Patient/Provider Prefers B	→	**Patient Receives A**

‘Nudge’ Trial

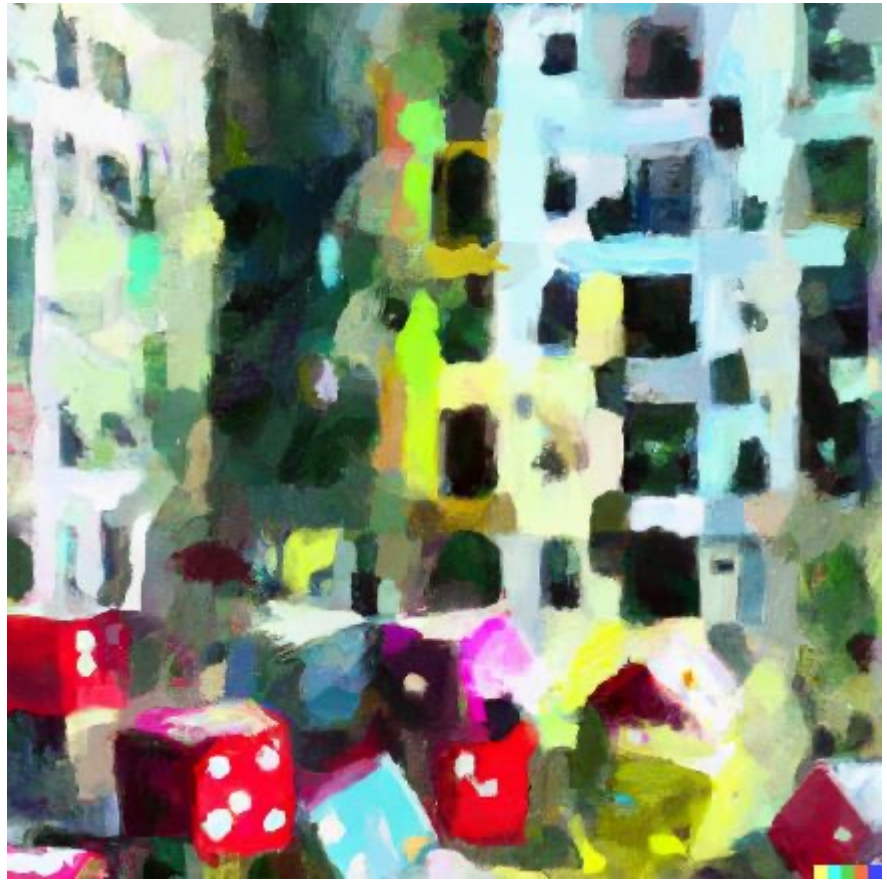
Nudged Towards A

Patient/Provider Prefer A	→	Patient Receives A
Patient/Provider Have No Preference	→	Patient Receives A
Patient/Provider Prefers B	→	**Patient Receives B**

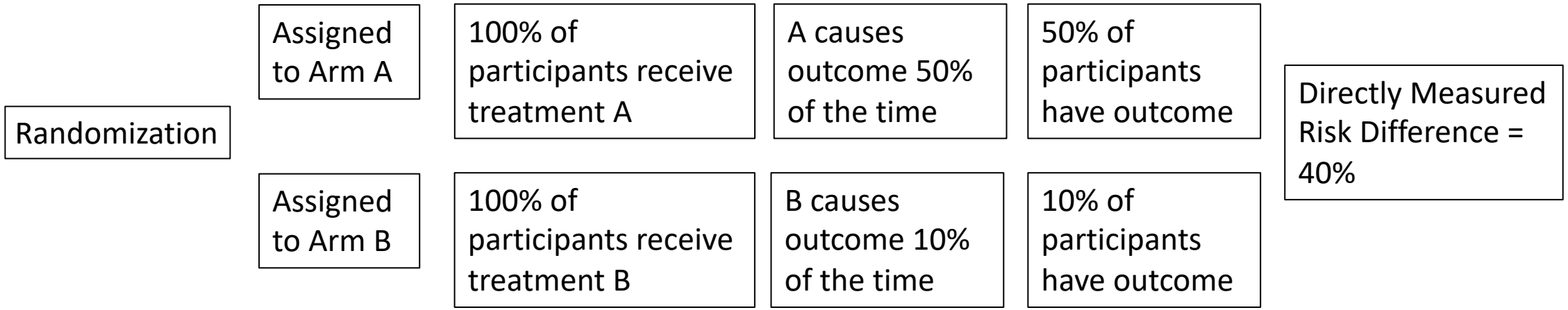
Kim SY, Kimmelman J. Practical steps to identifying the research risk of pragmatic trials. Clin Trials. 2022 Apr;19(2):211-216.

Decision Architecture Randomization Trial

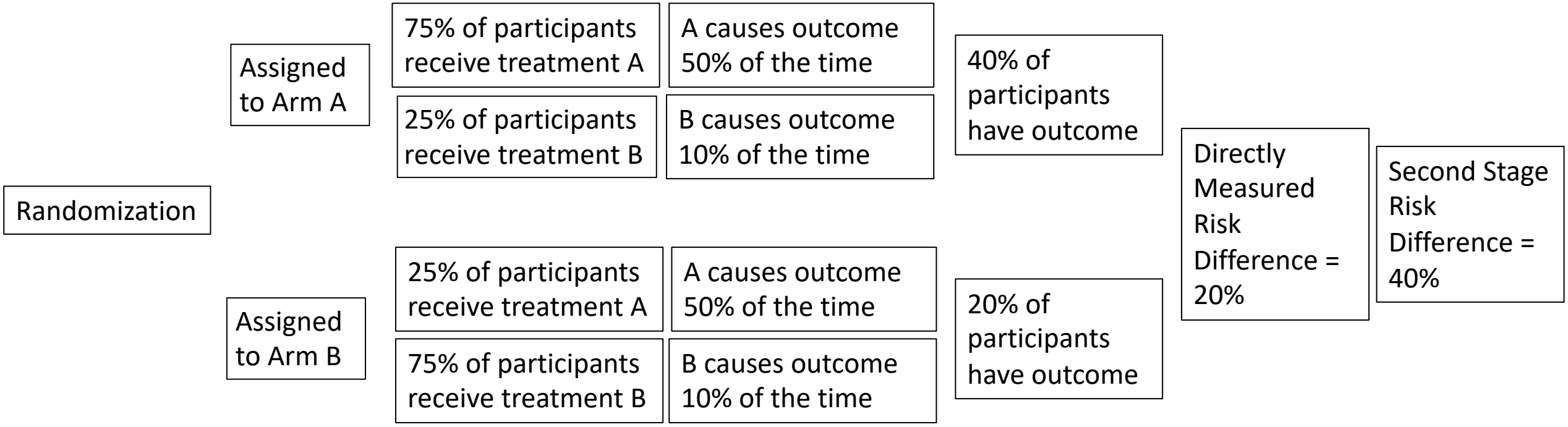
- **Decision architecture**: design choices (e.g., in electronic health records) that affect decision-making
- Decision architecture used to deliver a **nudge**: non-coercive effect making a certain decision more likely
- Use of nudges enables **A/B testing**: unobtrusive, highly scalable randomized trials



Analysis of Traditional RCT



Analysis of a DART



Relative Pros and Cons of DART Design

Traditional Randomized Trial	**DART**
Changes process of care	**Imperceptibly integrated into usual care**
Patient & clinician must accept randomly assigned treatment	**Patient & clinician freely choose treatment**
High cost per additional patient accrued	**Potentially no cost per additional patient accrued**
Smaller sample size	Larger sample size

Other Limitations of DART

- Interventions must all be in routine use
- Requires an appropriate nudge that can be randomized
- Assumes baseline characteristics and outcomes can be found in routinely collected data
- Individual patient informed consent likely to be impractical

DART in the Real World

The Great Wave off Kanagawa, Hokusai

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DART in the Real World

PCORI Methodology Contract

- Aim 1: Ethics and stakeholder acceptability
- Aim 2: Statistical and technical feasibility
- Aim 3: Pilot DART study

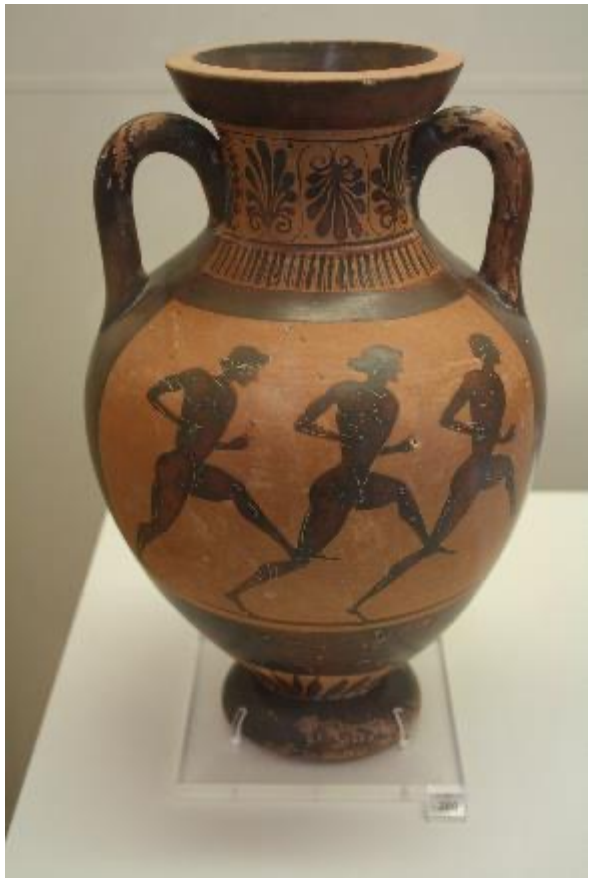
Flory J, Ancker JS, Kim SYH, Kuperman G, Vickers A. Decision architecture randomisation: extremely efficient clinical trials that preserve clinician and patient choice? BMJ Evid Based Med. 2023 Jul 21:bmjebm-2023-112386. doi: 10.1136/bmjebm-2023-112386. Epub ahead of print. PMID: 37479243.

Aim 1: Ethics and Acceptability

- Many DARTs may meet criteria for waiver of traditional informed consent
  - Minimal risk
  - Impracticability with traditional consent
- The scalability of DART should be considered

Moving slowly, not breaking anything

- Facebook used A/B testing to randomize **689,003 people** to positive versus negative emotional content in their feeds
- LinkedIn used A/B testing on over **20 million people** to compare the effectiveness of ‘strong’ and ‘weak’ ties for finding employment
- Both projects were published in high-impact scientific journals
- Both projects attracted concern over research oversight and ethics



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Verma IM. Editorial expression of concern. *Proceedings of the National Academy of Sciences of the United States of America*. 2014;111(29):10779-10779.
Kramer AD, Guillory JE, Hancock JT. Proc Natl Acad Sci U S A. 2014 Jun 17;111(24):8788-90.
https://www.nytimes.com/2022/09/24/business/linkedin-social-experiments.html
Rajkumar K, et al. A causal test of the strength of weak ties. Science. 2022 Sep 16;377(6612):1304-1310.

Stakeholder Engagement

Co-Investigators
- 5 academic researchers
- 3 patient advocates

Diabetes Team
Memorial Sloan Kettering
- 2 MD/DO clinicians
- 2 APP clinicians
- 1 Registered Dietician
- 2 Registered Nurses/Clinical Diabetes Educators

Stakeholder Advisory Board
Coordinated through Vanderbilt and STAR Clinical Research Network
- 3 patient advocates
- 2 clinicians (1 informatician)

Patient and Family Advisory Council for Quality, Memorial Sloan Kettering

Qualitative Research
- 100 members of general public
- 25 institutional review board members
- 25 clinicians

Stakeholder Engagement: Next Steps

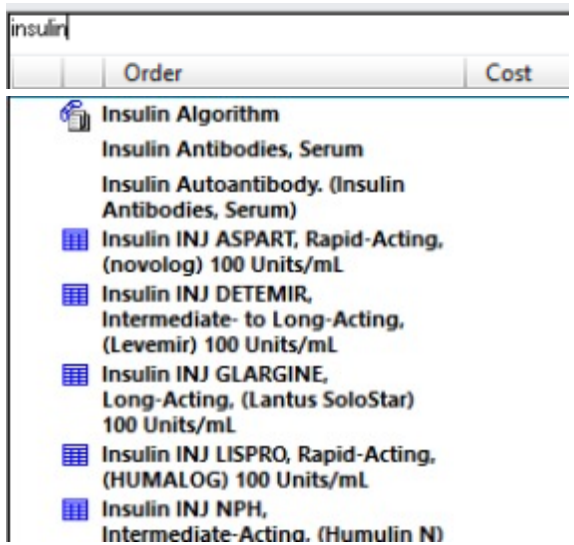
- Moving forward with deliberative democratic sessions with 150 participants
  - Also includes pre-post survey of each participant
- Goals
  - Identify stakeholder concerns about DART
  - Identify potential solutions
    - Including appropriate constraints on how/when DART is done

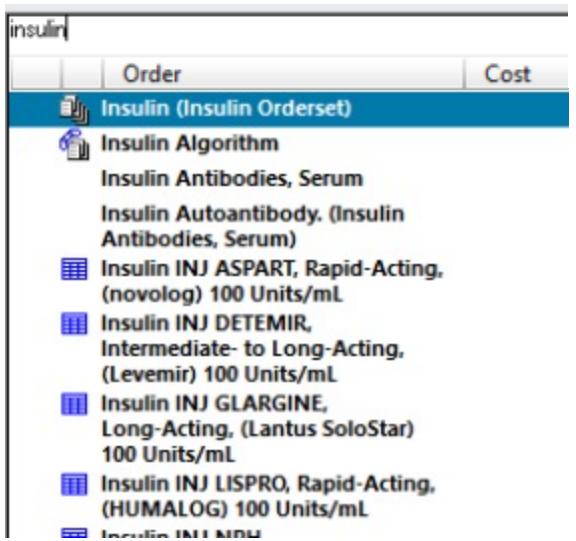
https://commons.wikimedia.org/wiki/File:Assen_Deliberation-Overleg2_Bert_Kiewiet.jpg

Aim 2: Technical Feasibility

Example: Two Insulin Dosing Paradigms

Sliding Scale Only	Fixed + Correction
Give insulin based just on blood sugar	Adds fixed dose before meals
Simpler	More complex
	Preferred by expert guidelines (but little evidence cited)





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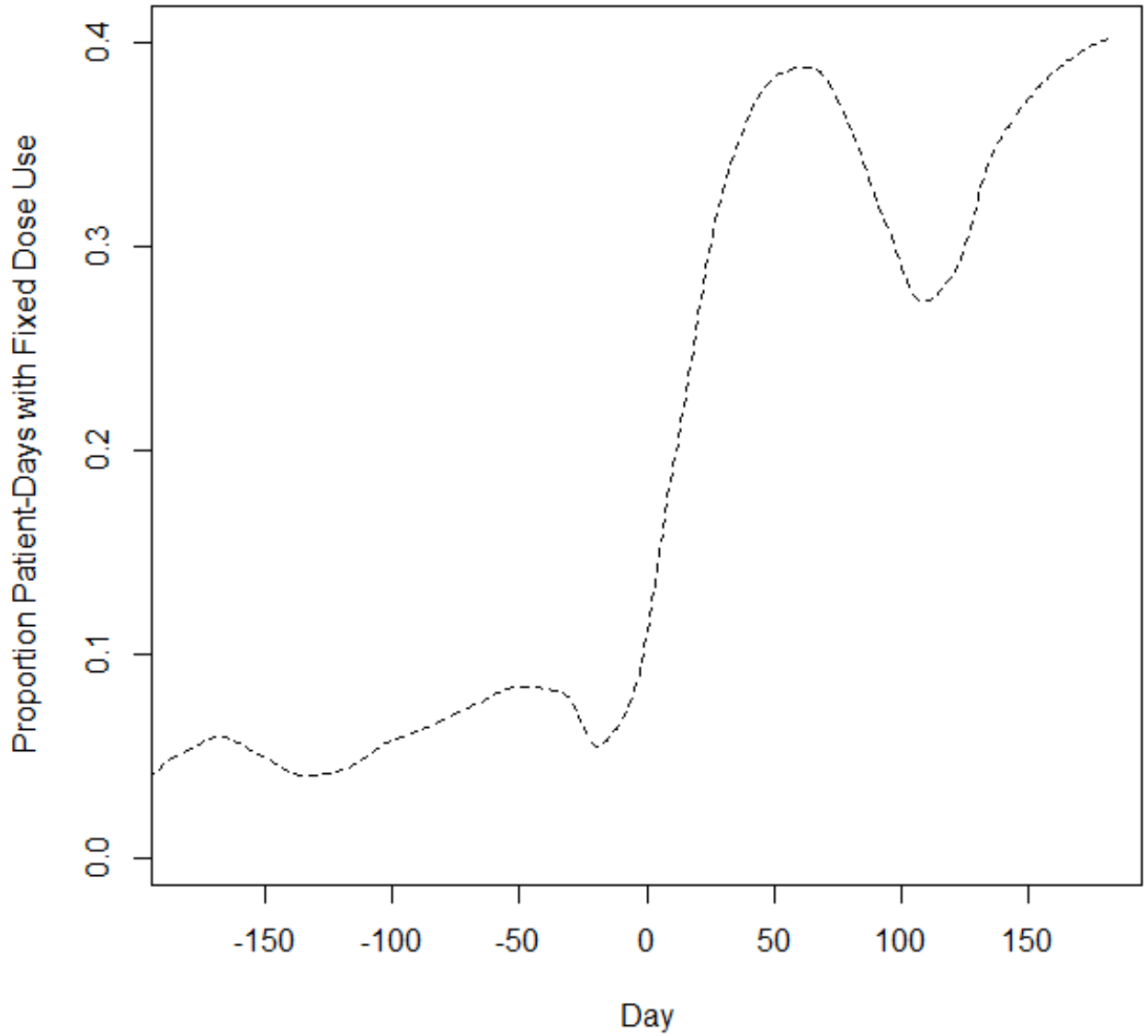
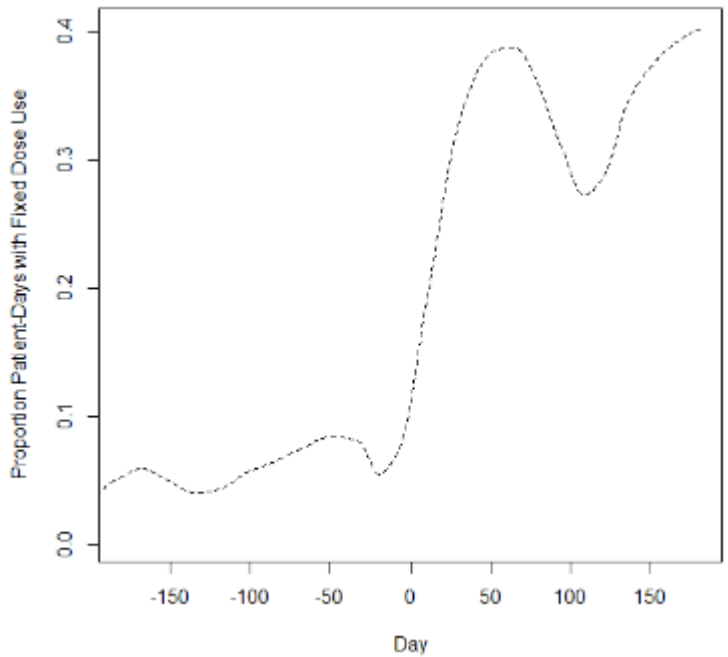
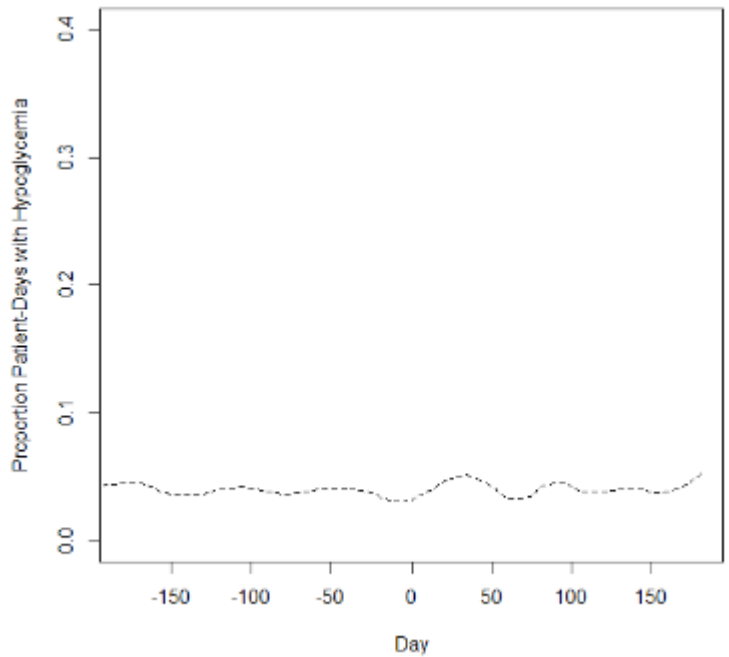
Nuha A. ElSayed, et al; on behalf of the American Diabetes Association, 16. Diabetes Care in the Hospital: *Standards of Care in Diabetes—2023*. *Diabetes Care* 1 January 2023; 46 (Supplement_1): S267–S278.


Proportion Patient-Days with Fixed Dose Use
0.0
0.1
0.2
0.3
0.4
-150
-100
-50
0
50
100
150
Day

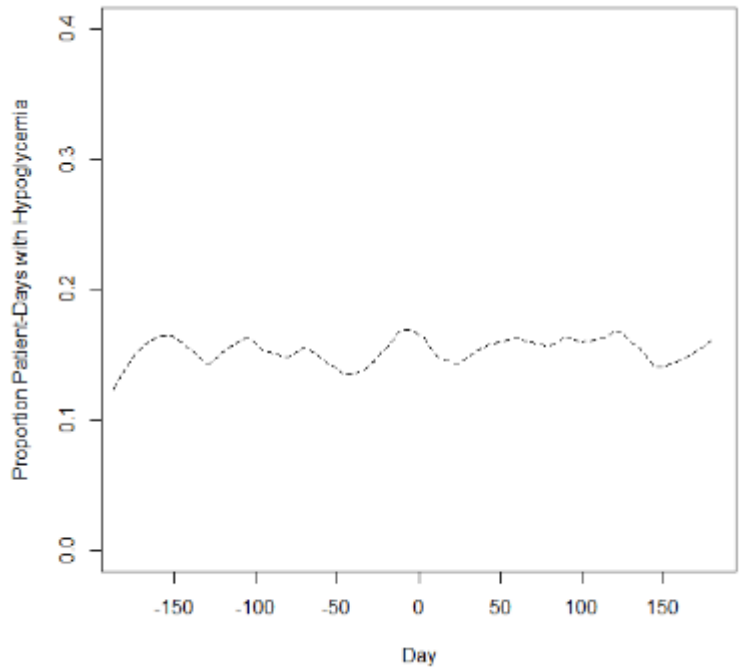
Rate of Fixed-Dose Use



Rate of Hypoglycemia



Rate of Hyperglycemia

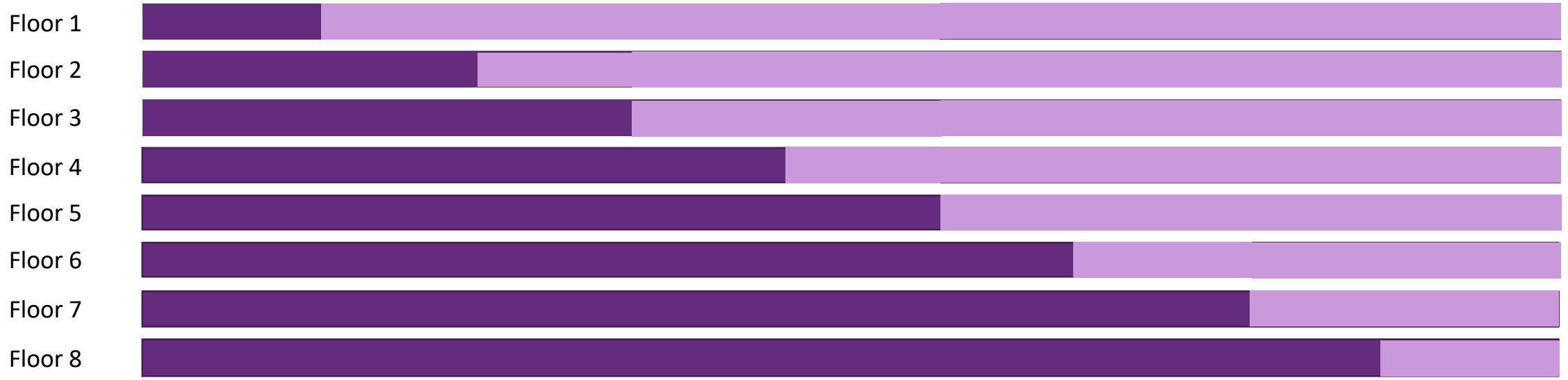


Feasibility: Preliminary Findings

- We can create appropriately strong nudges in our electronic health record
- Close partnership with informatics service is essential
- Randomized or pseudo-randomized deployment of nudges really is needed to draw firm conclusions

Feasibility: Next Steps

- Stepped wedge designs may to be the easiest way to implement DART in many cases
- We are developing approaches to individual patient or provider-level randomization



Aim 3: DARTs Under Development

- **Question:** Which is the better long-acting insulin for hospitalized cancer patients?
- **Nudge:** Default selection in an order set
- **Randomization:** Stepped wedge
- **Outcome:** Glucose control, length of stay

Aim 3: DARTs Under Development

- **Question:** Does tighter glycemic control reduce surgical site infections in colorectal surgery patients?
- **Nudge:** Default selection of correctional insulin in post-surgical order set
- **Randomization:** Individual at level of patient
- **Outcome:** Surgical site infection rate

Aim 3: DARTs Under Development

- **Question:** Does referral to a registered dietician improve outcomes in patients with newly diagnosed type 2 diabetes?
- **Nudge:** One-click option for nutrition service referral in new visit notes
- **Randomization:** Individual at level of provider
- **Outcome:** Glucose control, rate of antidiabetic medication use

Conclusions

- DART is a novel pragmatic trial design intended to:
  - Reduce risk and preserve patient choice
  - Bring the scalability and simplicity of A/B testing to comparative effectiveness research
  - Compare two (or more) standard of care interventions
- Implementation depends on the ability to deliver a randomized nudge (usually through an electronic health record) in a way that is
  - Reasonably strong
  - Not disruptive to care
  - Acceptable to stakeholders

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- Jun Mao
- Patient and Family Advisory Council for Quality
- Clare Relton
- Jason Karlawish

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- Michele Levy

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Questions?