Medication Adherence: Landscape, Strategies, and Evaluation Methods

Washington Marriott at Metro Center
775 12th St NW, Washington, DC 20005
December 10, 2019

Join the Conversation:

- Twitter: #MedAdherence2019

Welcome & Introductions

Opening Remarks from FDA

Overview of Medication Adherence

USciences
University of the Sciences

Substance Use Disorders Institute

EDUCATION • POLICY • RESEARCH

Setting the Stage

Andrew M. Peterson, PharmD, PhD, FCCP
Executive Director
Professor of Clinical Pharmacy and
Professor of Health Policy


PUSH & TURN TO OPEN
CLOSE TIGHTLY
Call Your Doctor
NO REFILLS
New Rx Required
TO DO
- Refill prescrip
- get oil c
- pick up c

Definitions

- **Adherence**
  - the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a health care provider[1]
- **Compliance**
  - the extent to which patients are **obedient** and follow the instructions of a health care professional[2]
  - Two aspects
    - Initial compliance
    - Ongoing compliance

Sources: 1. World Health Organization. Compliance to Long Term Therapies: Evidence for Action. 2003.
2. Meichenbaum D, Turk DC. Facilitating Treatment Compliance: A Practitioner's Guidebook. Boston: Plenum Press; 1987: 20, 52, 26-29;

Other Terms

- **Persistence**
  - how long a patient remains on therapy, introducing length of treatment as a factor[1]
- **Concordance**
  - concordance implies agreement, trust, and harmony between patient and doctor regarding treatment, and acknowledges the patient as a decision maker, and a cornerstone is professional empathy[2]

1. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. *Value Health.* Jan-Feb 2008;11(1):44-47
2. Johnell K, Lindstron M, Sandquist J, et al. Individual Characteristics, Area Social Participation, and Primary Non-concordance With Medication: A Multilevel Analysis
BMC Public Health. 2006;6

More Terminology

- Abandonment
- Discontinuation
- Implementation
- Initial Medication Adherence
- Initiation
- Pharmionics
- Primary Non-Adherence
- Therapeutic Alliance

ABC Taxonomy

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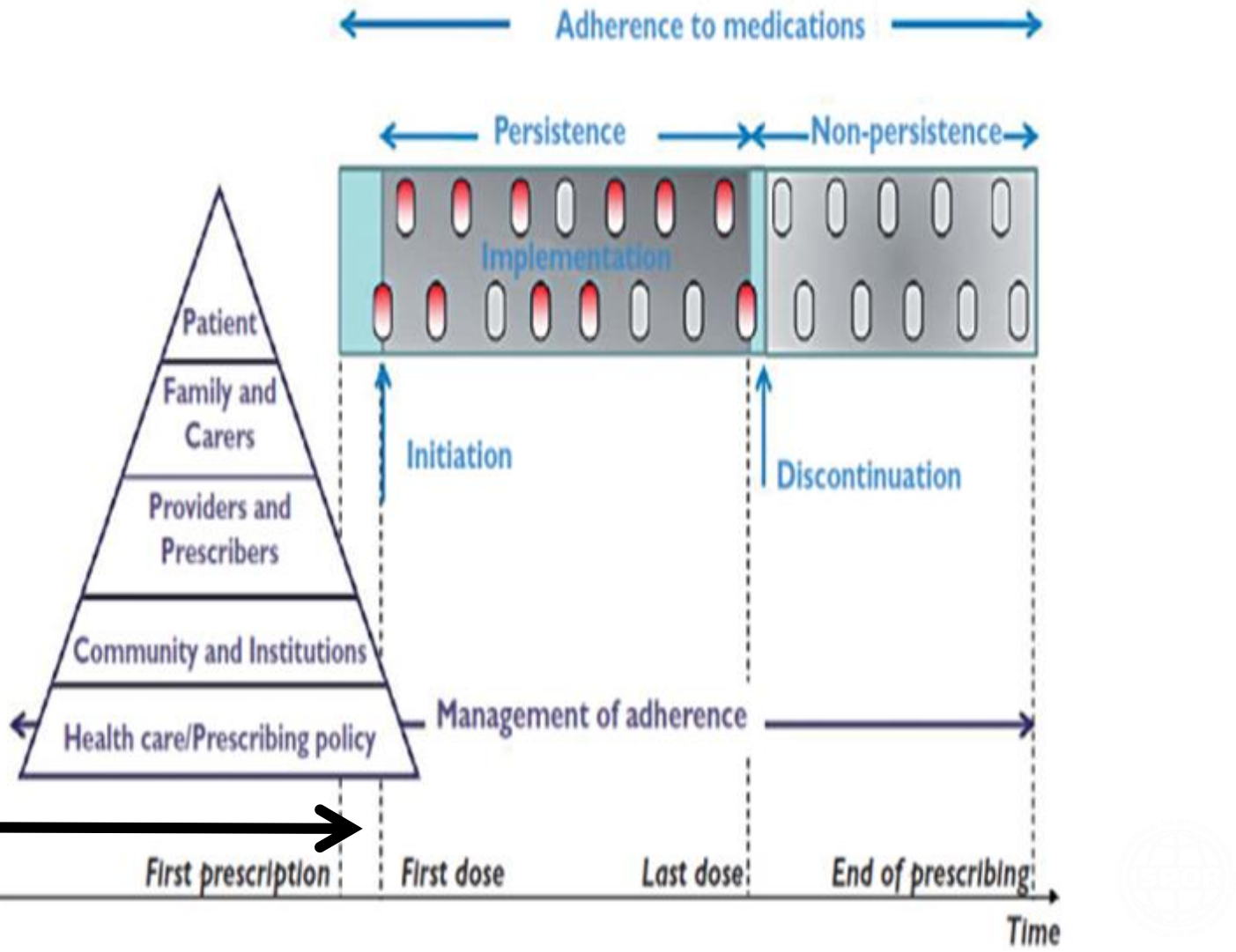
ABC = Ascertaining Barriers for Compliance



Primary Adherence/Initial Adherence

Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. May 2012;73(5):691-705


maker
long
regime
dose
empathy
Two
implies
doctor
period
defined
Synonym
taking
levels
patients
person's
dosing
Manual
behavior
decision
agreed
Blood
Measured
provider1
days
agreement
Adherence
and/or
medication
adherence
concordance
follow
self
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acknowledges
diet
Electronic
Measures
reports
aspects
Subjective
health
prescribed
Refill
executing
treatment
Pill
compliance
Initial
patient
cornerstone
Objective
instructions
remains
discontinuation
Medication
acts
Indirect
corresponds
e.g
Compliance
time
professional
factor
professional2
Health
percentage
trust
care
Persistence
recommendations
per
Direct
Data
Practitioner
accumulation
Patient
therapy
interval
administered
Concordance
initiation
introducing
unit
accordance
lifestyle
Outcomes
regarding
Pharmacy
length
obedient
Ongoing
Counts
changes
harmony
metric
measure
doses

Today's Panel Discussions

- Barriers
- Interventions
- Measurement
- Study Designs

Barriers Panel

- Care coordination
- Medication synchronization
- Pharmacy deserts
- Polypharmacy
- Symptom impact

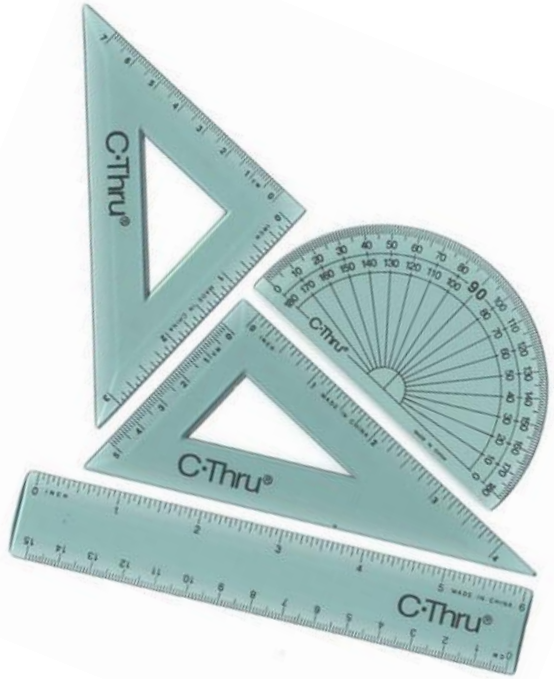
Interventions panel

- Adherence Thresholds
- Analytics
- Behavioral Economics
- Biosensors
- Comparative Effectiveness
- Tailored Interventions

http://vukelani.com/edu/2017/12/05/7-tips-take-panel-discussion-terrible-terrific/

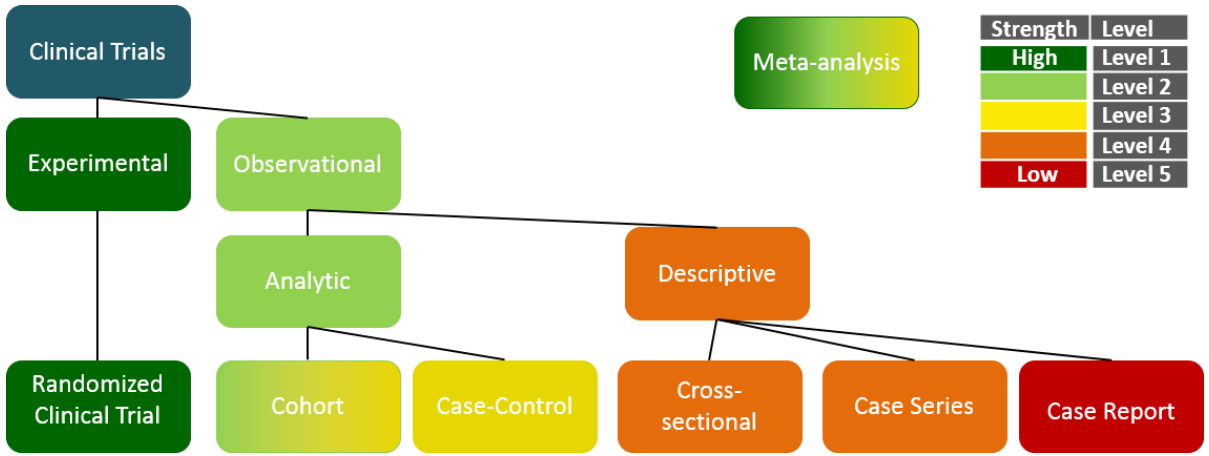
Measurement Panel

- Claims Data
- Data Sources
- Subjective Measures
- Objective Measures
- Electronic Monitoring
- MPR, PDC, Gaps and more



Clinical Trials Panel

- Optimal Study Designs
- Implementation Science
- PRECIS-2
- Chronic vs Acute disease



https://www.hydroassoc.org/research-101-an-explanation-of-clinical-trials-design/

What are we really looking for?

- Improved Outcomes
  - Lower BP
  - Less Pain
  - More mobility
  - Better vision
  - Cure of disease
  - No heart attack
  - Good (better) quality of life

Issues to think about during the day

- Non-adherence is a sign that a bigger problem exists
  - Current measures are only symptoms of the problem
    - Gaps in refills – Money? Lifestyle issues? Insurance? Access issues?
    - Discontinuation – Health belief? Side effect? No effect? Drug shortage?
    - Low PDC – Money? Side effects? Forgetfulness? Insurance problems?
  - Current interventions may be only addressing the symptom that is being measured

Issues to think about during the day

- The complexity of
  - multiple diseases treated with multiple drugs
  - multiple times daily to patients with varying behaviors and
  - varying underlying health beliefs

Other considerations

- Artificial Intelligence/machine learning
- Opioids and adherence
  - Think Medication Based Treatment (methadone/buprenorphine)
- Amazon and Pill Pack


Let's Learn Together!

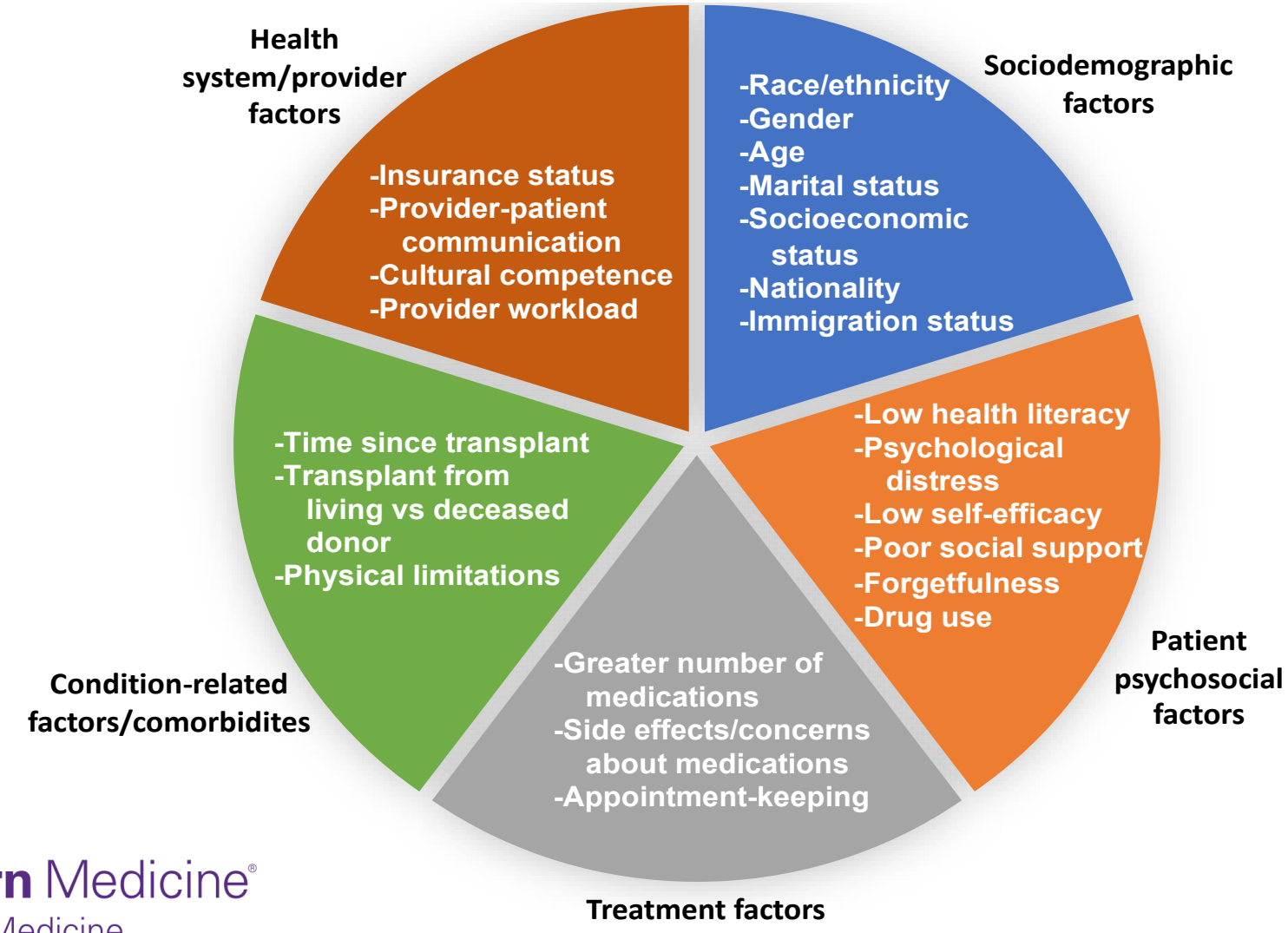

compliance
patient
health
Medication
time
Persistence
therapy

Key Barriers to Effective Medication Adherence

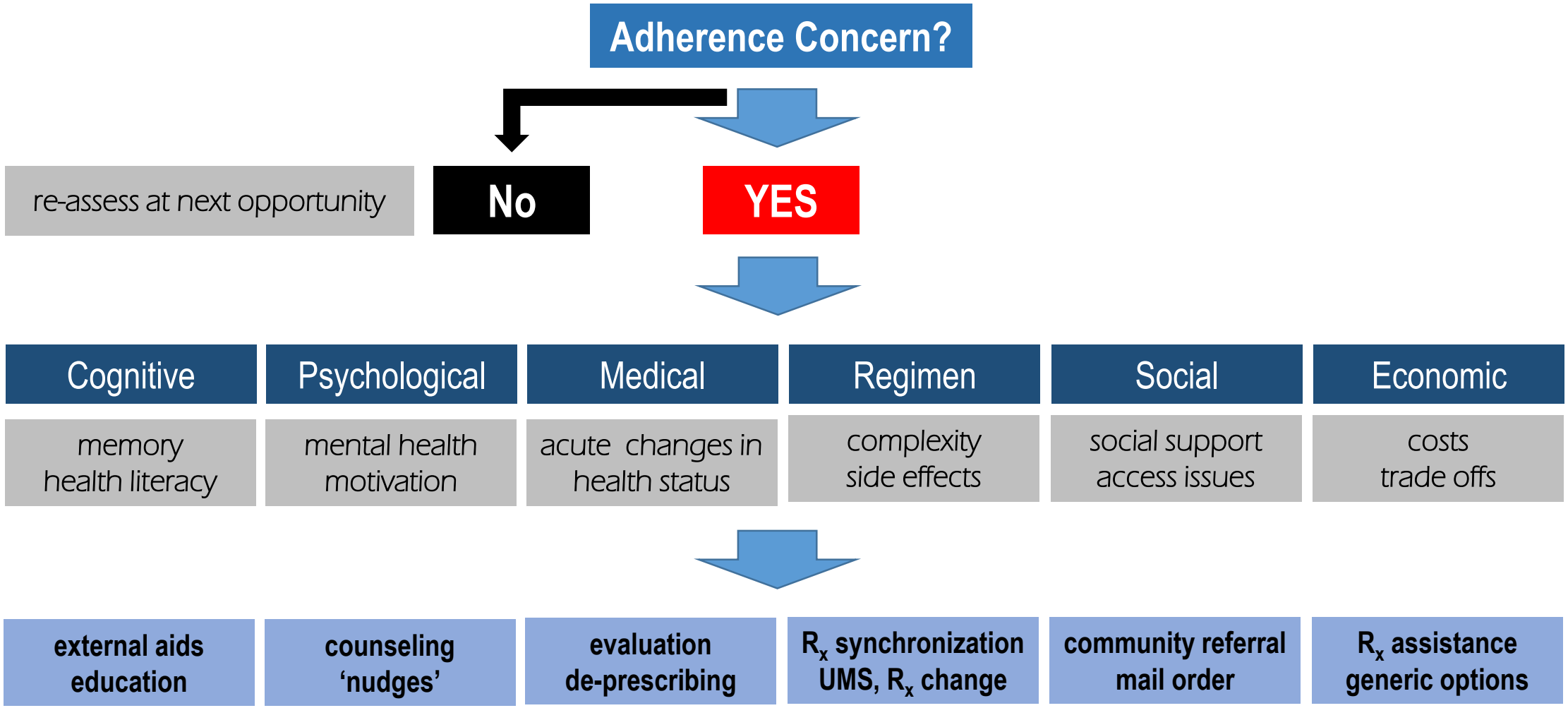
Taking Medicine is Hard

- **A dynamic behavior** *(adding, changing, removing medication)*
- **Multi-drug regimens, variable doses**
- **Multiple devices** *(pill, injection, inhaler, liquid, nasal, eye drops, lotions, etc.)*
- **Tapered and escalating doses**
- **Doses dependent on measurement** *(i.e. weight, blood sugar)*
- **Daily vs. non-daily medicines**
- **Limited duration vs. chronic, extended duration medicines**
- **'PRN' (Pro Re Nata) or 'As Needed' and seasonal medicines**
- **Multiple prescribers, multiple pharmacies, variable instructions**
- **Brand vs. generic drugs** *(variable trade dress)*
- **Unsynchronized fill dates from pharmacy**

WHO Perspective on Medication Adherence Barriers



Adherence 'Phenotypes': Mapping Problems to Appropriate Interventions



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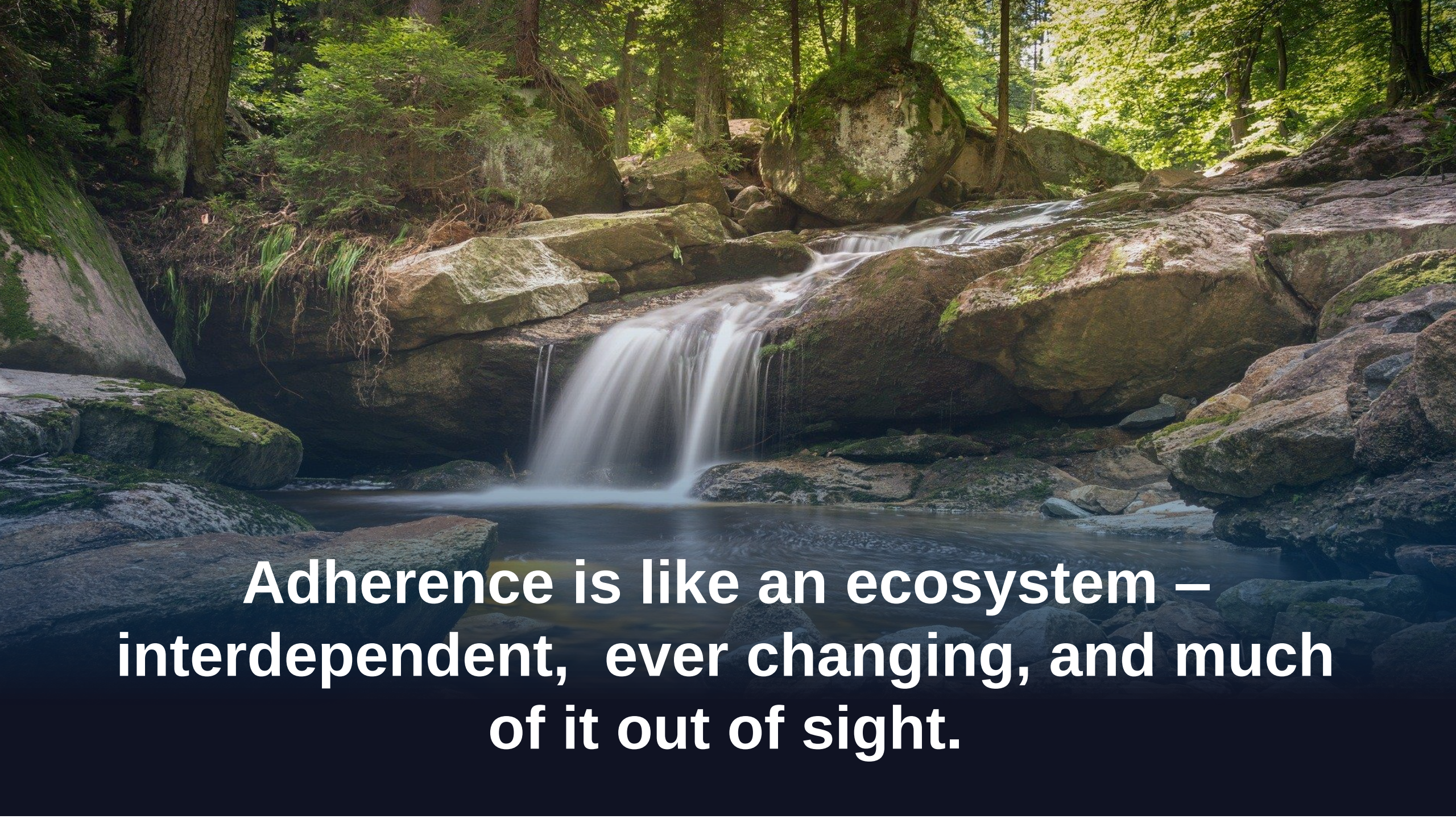
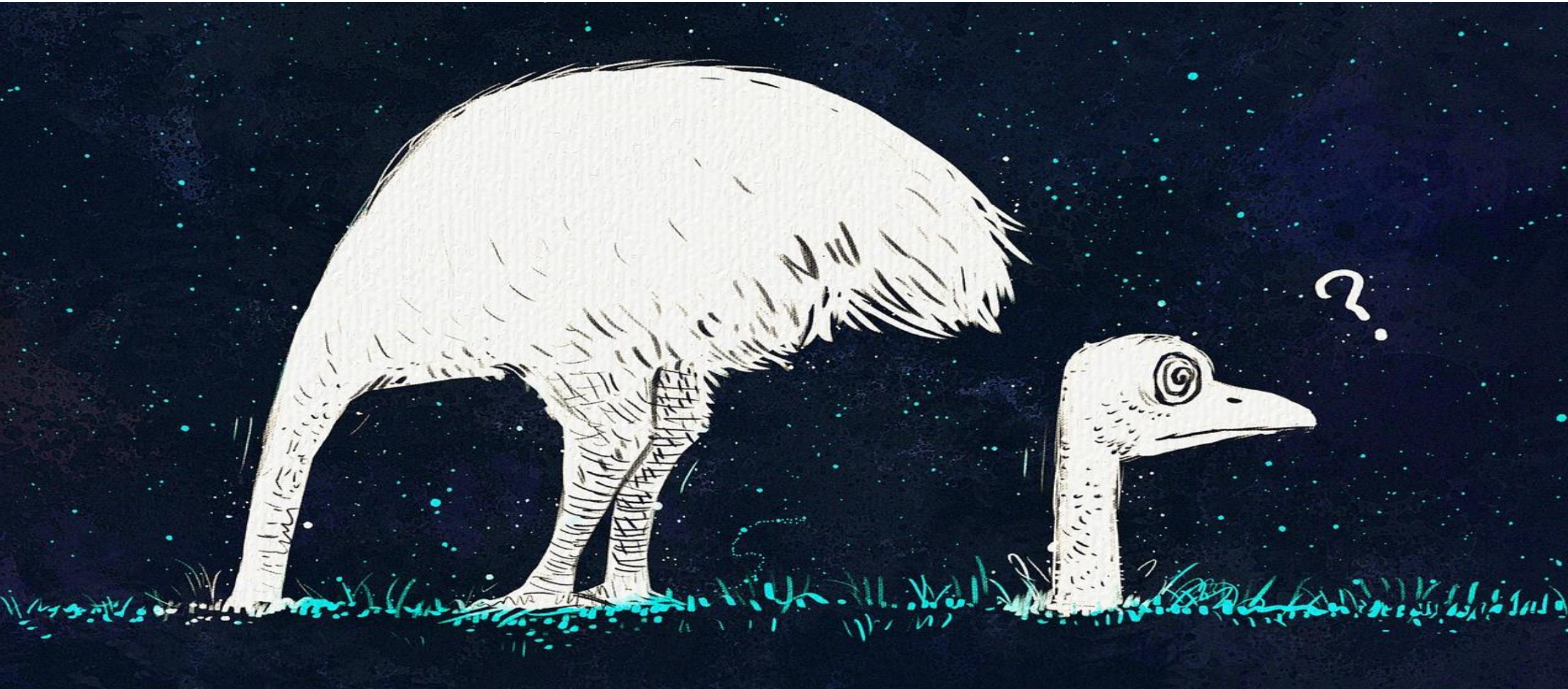
Center for Applied Health Research on Aging

Key Barriers to Effective Medication Adherence



Adherence is like an ecosystem – interdependent, ever changing, and much of it out of sight.

What's beneath the surface?



What's beneath the surface?

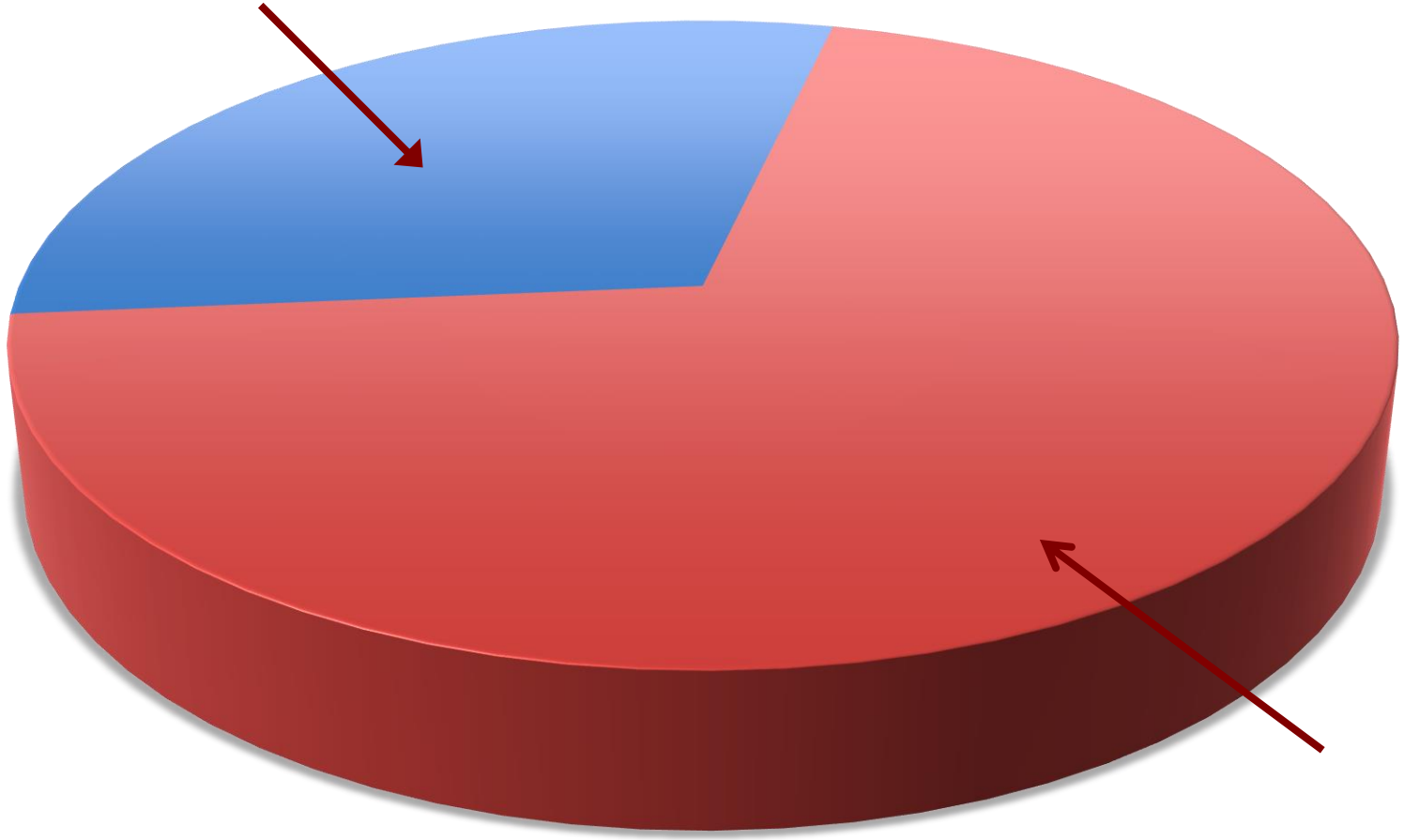
- Social isolation
- Stigma
- Depression & anxiety
- Insurance & provider churn
- Uncoordinated care
- Poor provider relationships
  - Fails to acknowledge and validate medication and care drawbacks

Patients. Providers. Pills. How effective is changing only one?

Key Barriers to Effective Medication Adherence

NONADHERENCE CAUSES

Forgetfulness



Other Causes

Intentional

Emotional

Educational

Other

Osterberg L *N Engl J Med*. 2005;353(5):487-497

Rationale for Hiding Nonadherence

- Social desirability bias
- Fear of being punished, admonished or dismissed
- Fear of embarrassment

ADHERENCE IS DRIVEN BY PATIENTS' BELIEFS

* A 'non-adherent personality' does not exist.

* Adherence to prescription medications is unrelated to adherence to self-care and lifestyle recommendations.

* There is no consistent relationship between demographic characteristics and adherence.

McHorney,C Current Medical Research and Opinion 2009 25:1; 215-238

ADHERENCE IS DRIVEN BY PATIENTS' BELIEFS

* Medication-taking is a decision-making process, and patients actively make decisions about their medications.

- Non-adherence is rational behavior–it is driven by patient beliefs

- Adherence represents shades of grey –
  - patients can be faithfully adherent to one medication,
  - non-fulfill on another, and
  - non-persistent to another because they hold different beliefs about each medication.

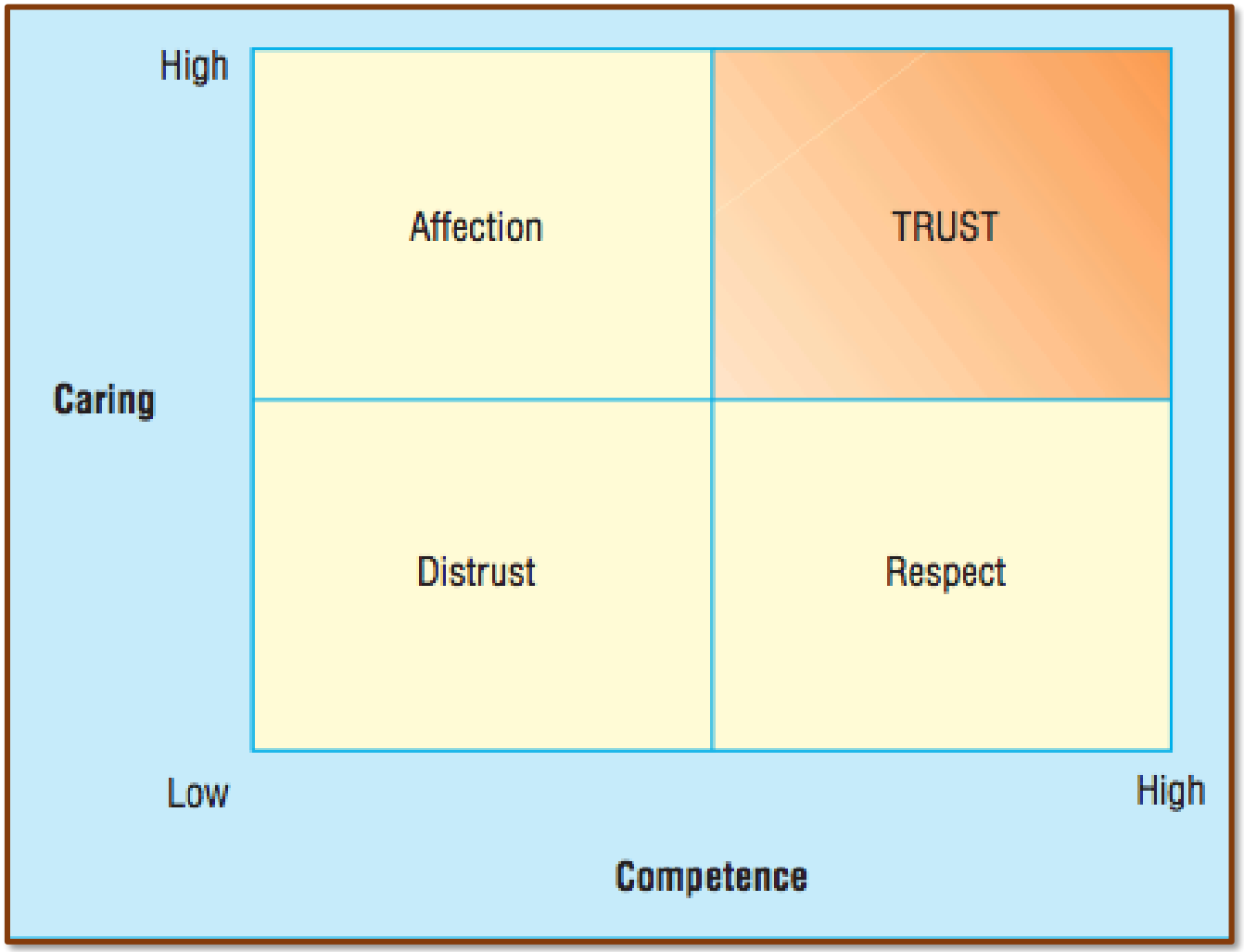
OBSTACLES

UNINTENTIONAL vs INTENTIONAL

- FORGETTING
- SHIFT WORK
- COST/ACCESS
- CONFUSION
- WORK RESTRICTIONS

- MISTRUST
- FEAR OF SIDE EFFECTS
- MENTAL ILLNESS
- LACK OF BELIEF IN BENEFIT
- FEAR OF DEPENDENCY
- FEAR IT IS DANGEROUS
- LACK OF DESIRE
- NO APPARENT BENEFIT
- ALTRUISM

Competence and caring in relation to building trust



Paling,J BMJ 327: 9/27/2003

MEDICINE AND PUBLIC ISSUES | Annals of Internal Medicine

Rethinking Adherence

John F. Steiner, MD, MPH

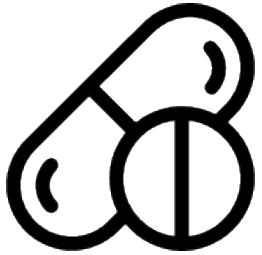
Counseling with a **trusted** clinician needs to be complemented by out-reach interventions and removal of structural and organizational barriers.

Steiner J Ann Intern Med. 2012;157:580-585

Key Barriers to Effective Medication Adherence

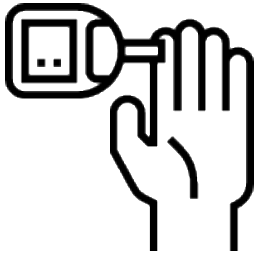
Better adherence & outcomes
with **behavioral economics**

Chronic disease patients don't follow their care plans



MED ADHERENCE

50% don't take meds as prescribed[1]



TRACK METRICS

50% stop measuring in 3 months, if given a device[2]

HIT GOALS

48% of diabetics have A1c > 7%[3]

1. New England Healthcare Institute. (2009). Thinking outside the pillbox.

2. Volpp et al. J Gen Intern Med. 2014 May; 29(5): 770–777.

3. Casagrande et al. Diabetes Care. 2013 Jul; 36(8): 2271–2279.

Why don't patients stick to their care plans?

Present Bias is the reason why patients are not adherent.

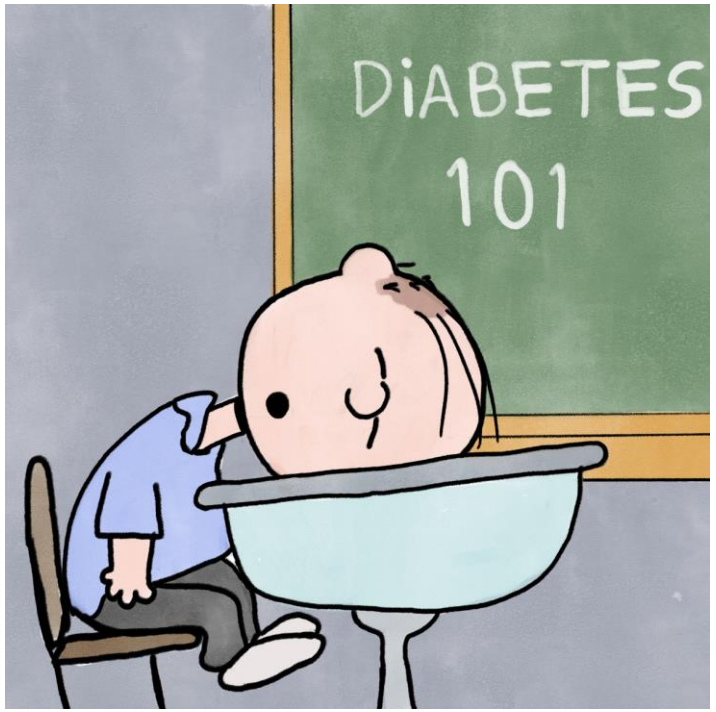
Behavior is motivated by instant gratification.

Previous solutions don't provide the instant gratification necessary to overcome **Present Bias.**

Reminders

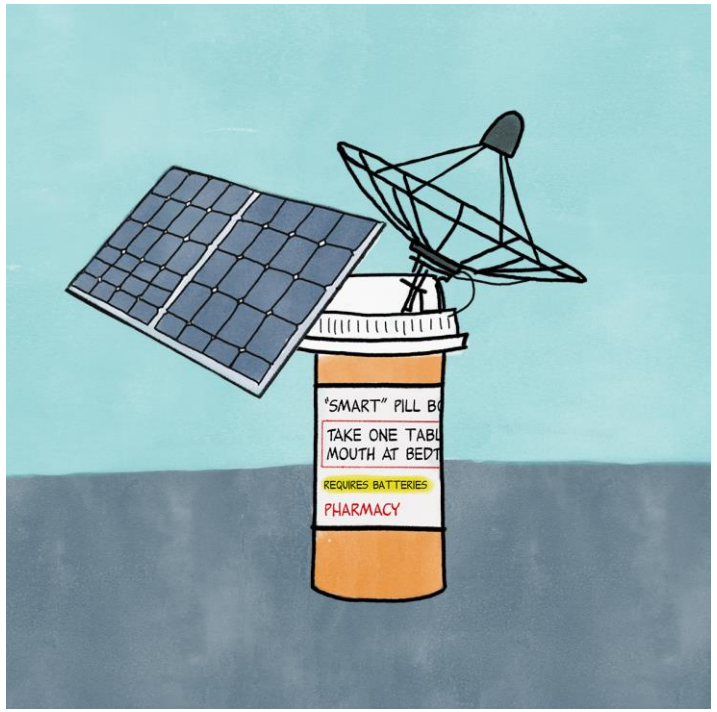
Reminders just become a nuisance over time

Education



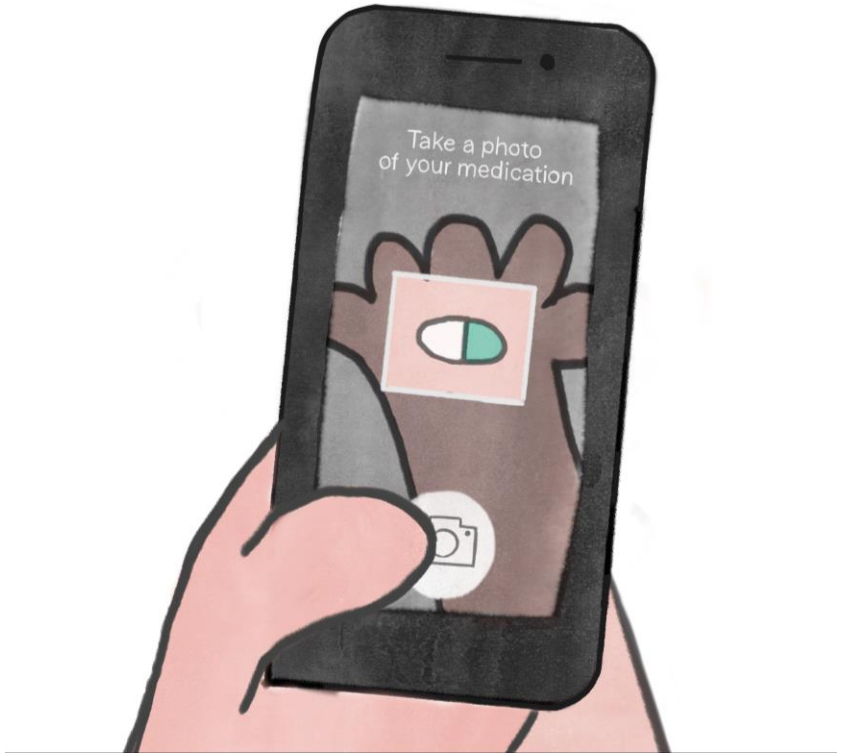
Patients already know they should take their meds.

Connected devices



Devices measure adherence but do not improve it.

Paying patients to adhere to their care plan
does overcome **Present Bias**



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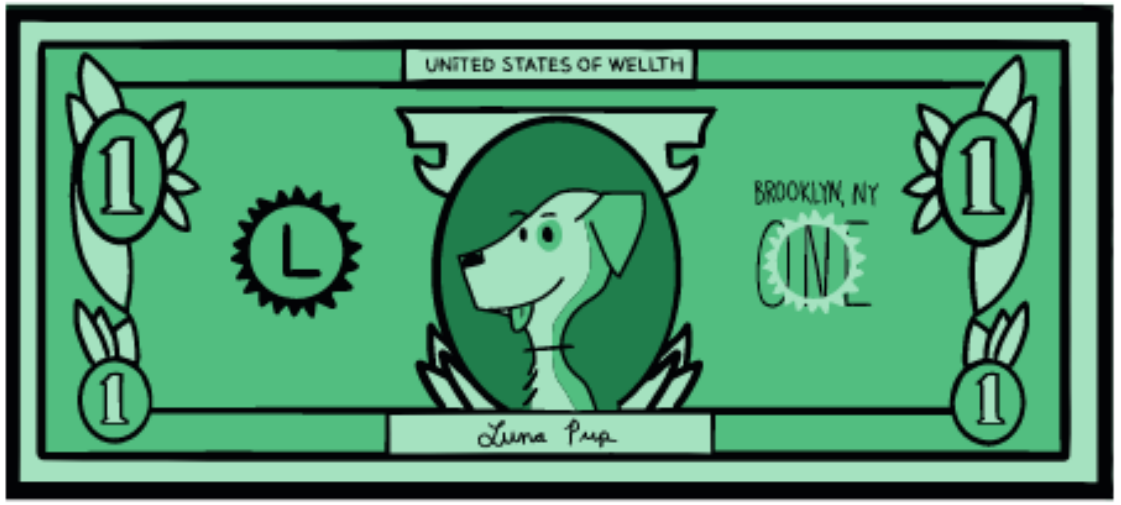
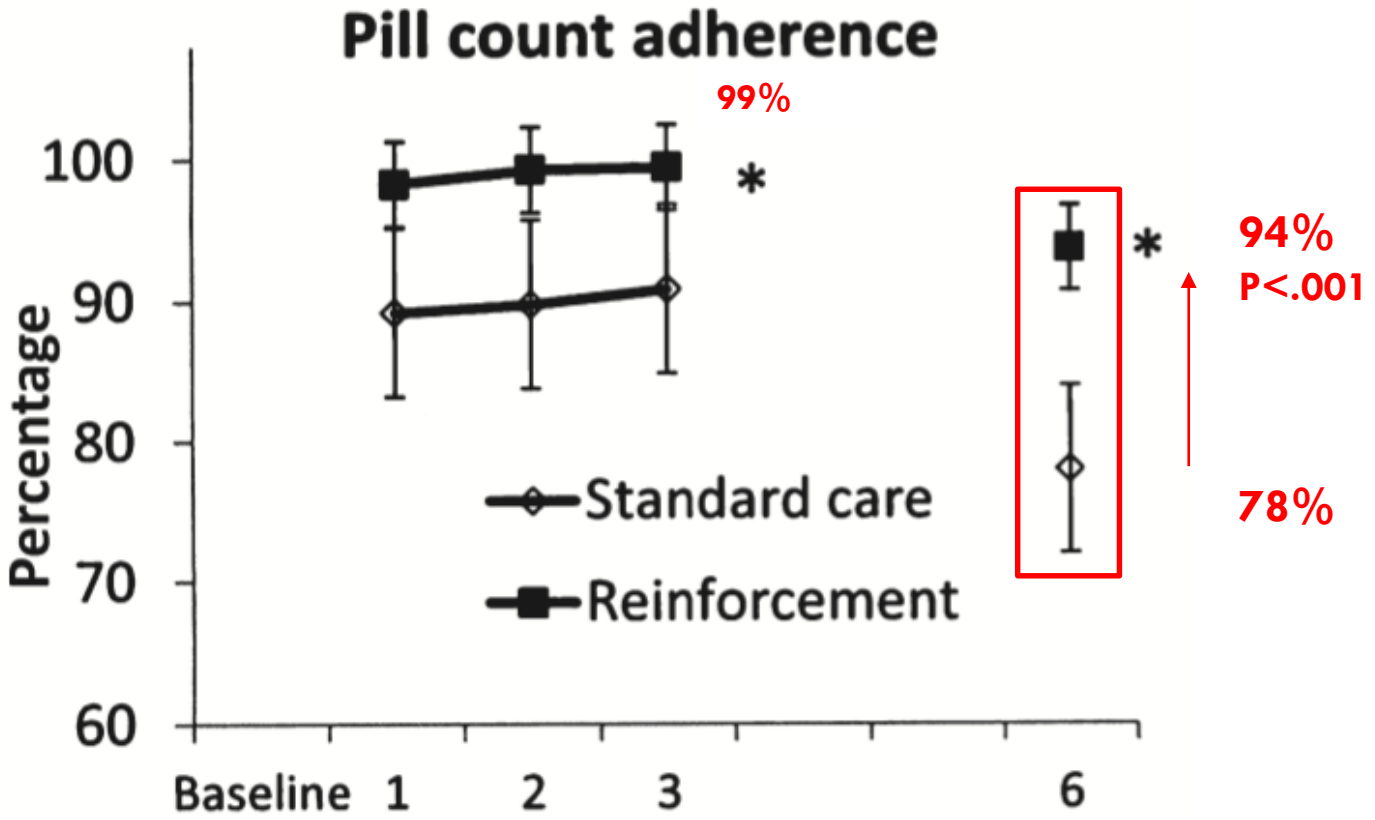


(Well-structured) Incentives produce lasting behavior change

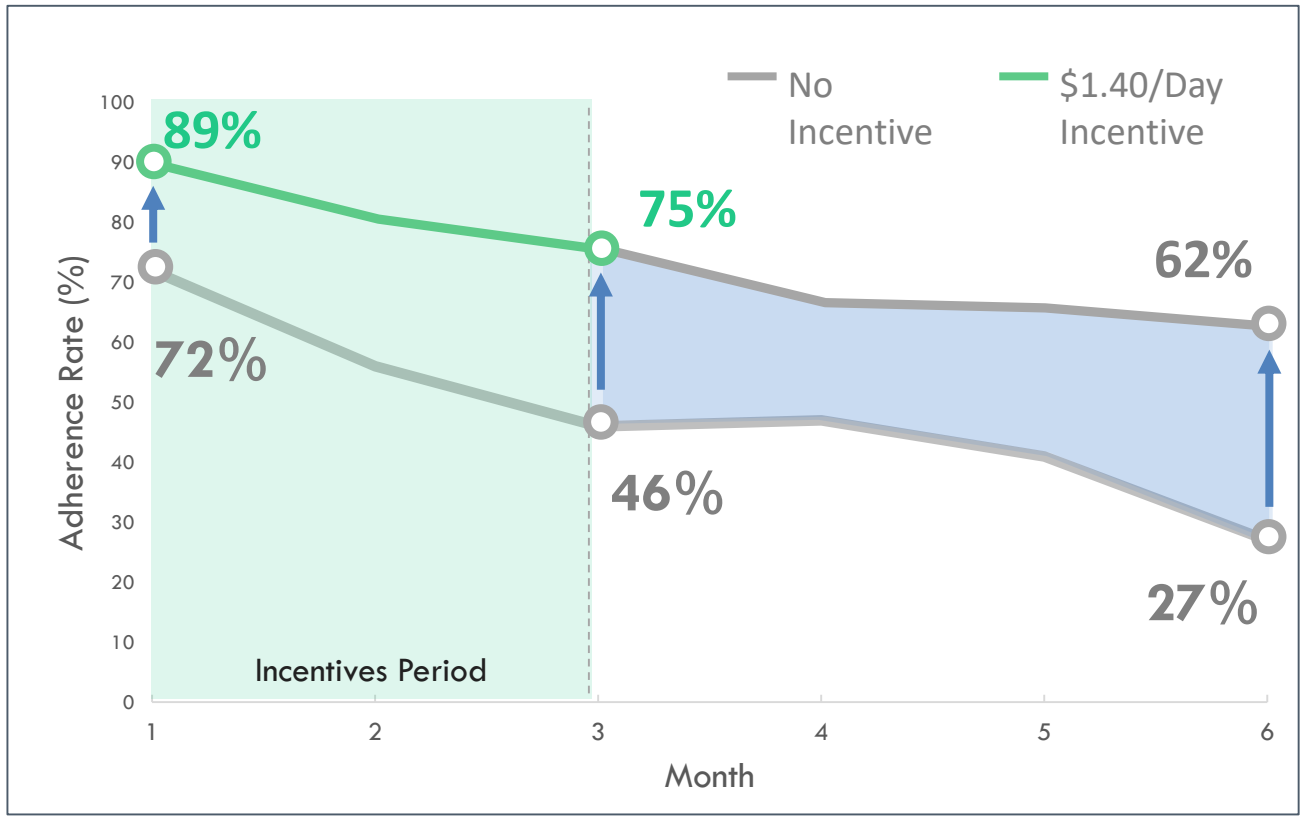
Improvement to med adherence lasts after incentives end



Petry et al. (2015) "Reinforcing adherence to antihypertensive medications." *J Clin Hypertens*. 17.1: 33–38.

Incentives improve adherence for other care plan elements, too

Without incentives, remote monitoring is largely useless



Volpp et al. J Gen Intern Med. 2014 May; 29(5): 770–777.

PATIENT WITH

HEART FAILURE

Roy

Enrollment

$30 deposited into Roy's account; his first month of possible rewards

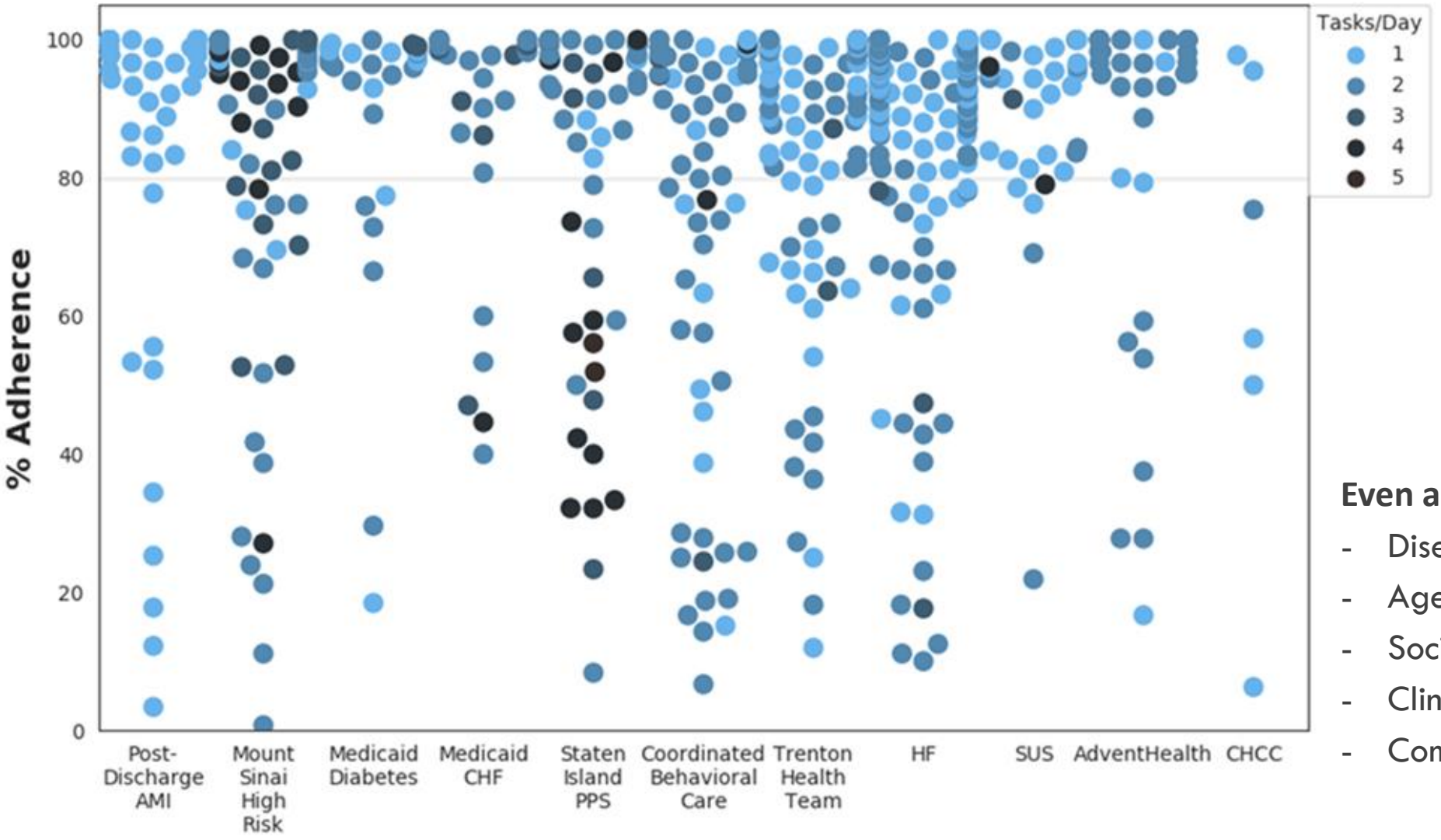
Adherence

Roy becomes 89%+ adherent to his meds and individualized care plan to avoid losing $2/day

Outcome

Roy improves adherence & health, lowers his utilization, produces 4x+ ROI to payer

Wellth produces lasting adherence habits



89%

Average Daily Adherence

Even across different…

- Disease states & co-morbidities
- Age groups
- Socioeconomic status
- Clinical settings
- Complexity of care plans

Wellth's Adherence Results Yield Strong Clinical and Quality Outcomes

89%

Average Daily Adherence

Care plan behaviors include:

- Medications
- Glucometer Readings
- Blood Pressure Readings
- CPAP Therapy
- Low sodium meals

Wellth Core Disease Areas

Heart Failure | **CV Disease** | **Type 2 Diabetes** | **COPD / Asthma** | **Behavioral Health**

- ✓ 0.96% reduction in A1c levels in poorly controlled, elderly diabetics over a full year
- ✓ Up to 46% reduction to readmissions over 90 days post heart attack
- ✓ 100% appointment attendance at an outpatient behavioral health clinic in enrolled Serious Mental Illness population
- ✓ 92% decrease in avoidable ER utilization in diabetics (24 reduced to 2)
- ✓ 88% Net Promoter Score

Key Barriers to Effective Medication Adherence

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System Barriers

Andrew M. Peterson, PharmD, PhD, FCCP
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Professor of Health Policy

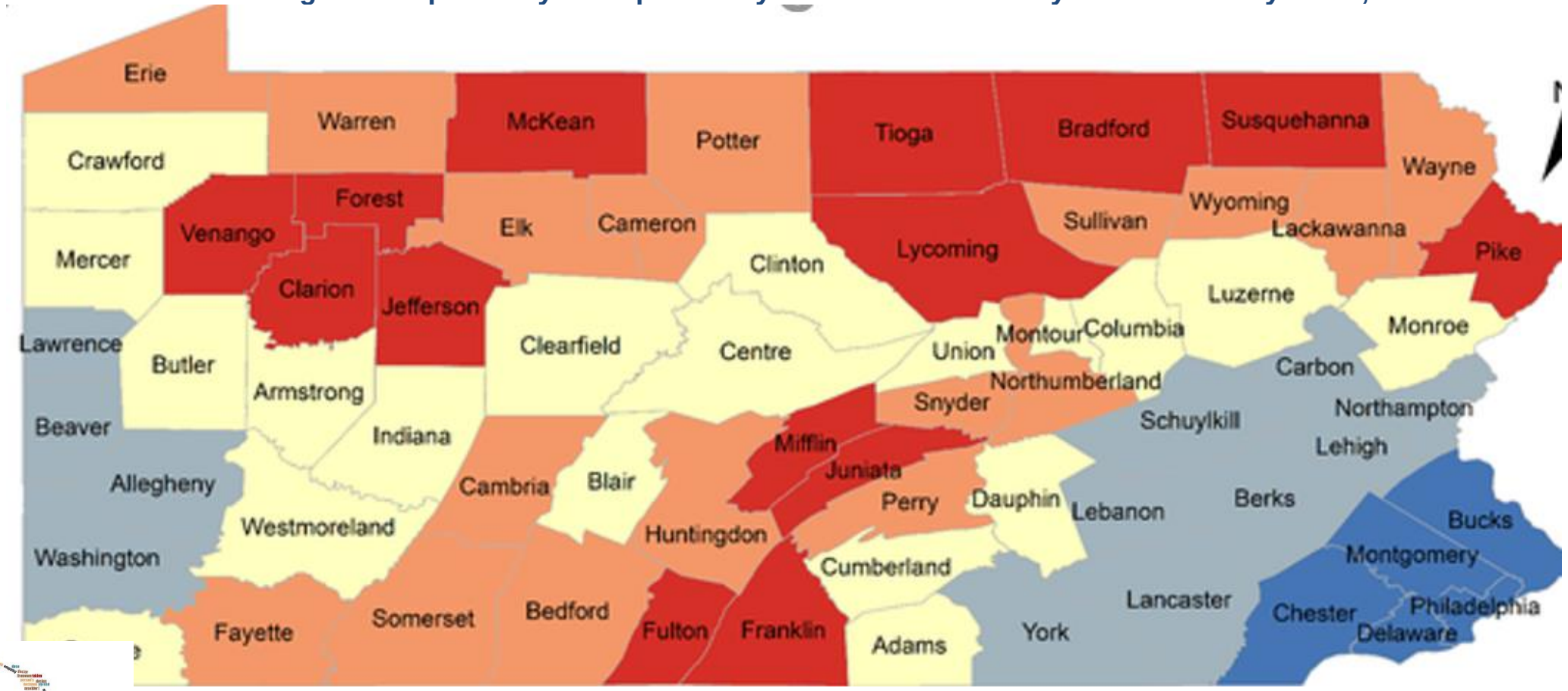
Systems Level Issues

- Pharmacy deserts
- Care coordination/transitions of care
- Medication synchronization

Pharmacy Deserts

- Pharmacy deserts are geographic areas which lack access to a nearby pharmacy and where pharmacy services are scarce or difficult to obtain.

Fig 4. Hot spot analysis of pharmacy deserts at the county level in Pennsylvania, 2015.



Pednekar P, Peterson A (2018) Mapping pharmacy deserts and determining accessibility to community pharmacy services for elderly enrolled in a State Pharmaceutical Assistance Program. PLOS ONE 13(6): e0198173. https://doi.org/10.1371/journal.pone.0198173
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0198173

PLOS ONE

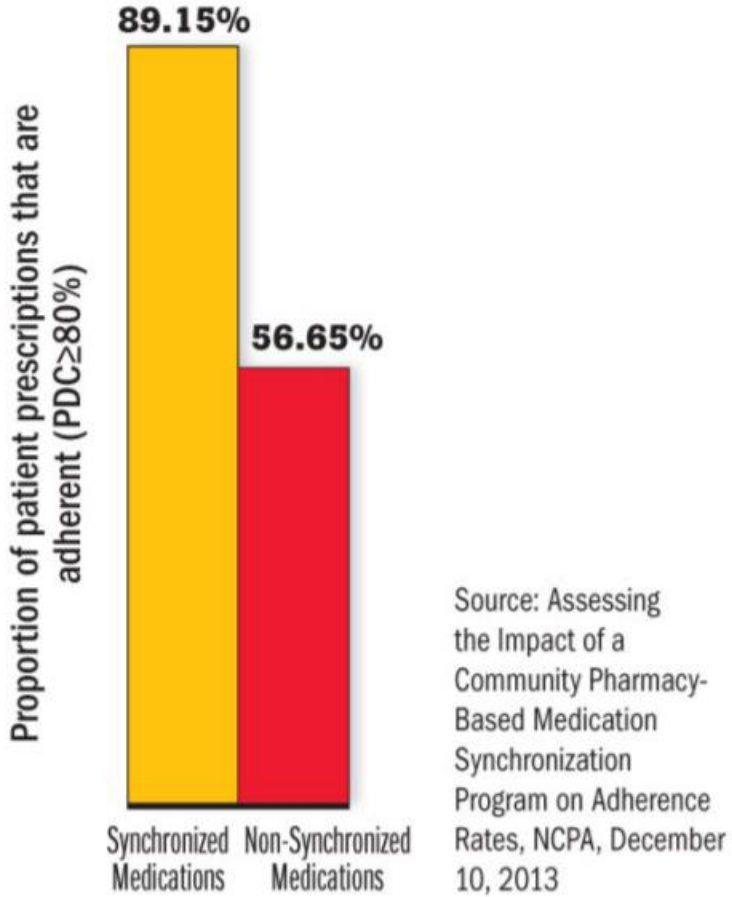
Coordination of Care

- Fragmentation of care
  - Multiple sites of care
    - Hospital/Ambulatory Care/Assisted Care
  - Multiple practitioners
    - Primary care provider/specialists
  - Multiple medications
    - Asynchronized refills/uncoordinated refills

Medication Synchronization

- Aligning prescription refills to occur at the same time each month/quarter

OVERALL IMPACT OF MEDICATION SYNCHRONIZATION ON ADHERENCE (MEASURED AS PDC)



Source: Assessing the Impact of a Community Pharmacy-Based Medication Synchronization Program on Adherence Rates, NCPA, December 10, 2013

Barriers Panel Summary

Key Barriers to Effective Medication Adherence

Break

Interventions to Track and/or Improve Medication Adherence

Topics

1. Medicare's Part D Star Ratings for medication adherence
2. Managing adherence interventions at the population level
3. Effects of some real-world adherence improvement programs
4. Using patient-reported barrier data to design better interventions
5. Important questions about adherence and interventions

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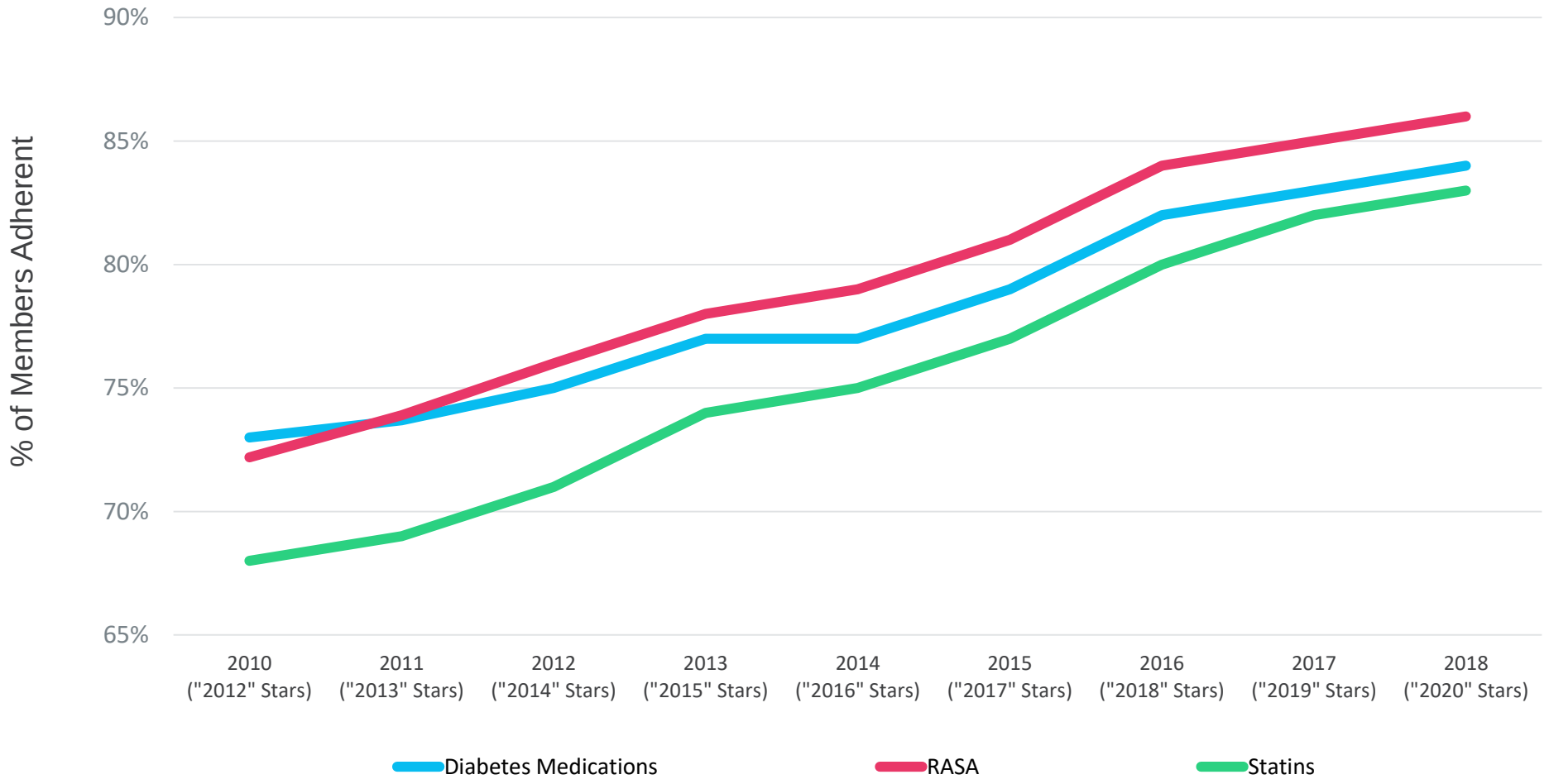
Adherence Rates among Medicare Advantage Members (2010 - 2018)



Source: RxAnte analysis of publicly available CMS data

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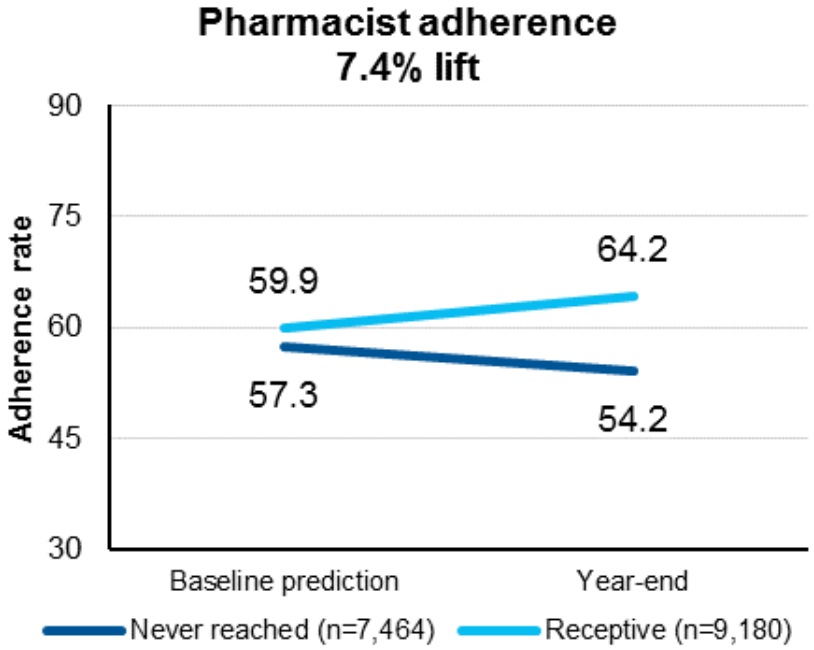
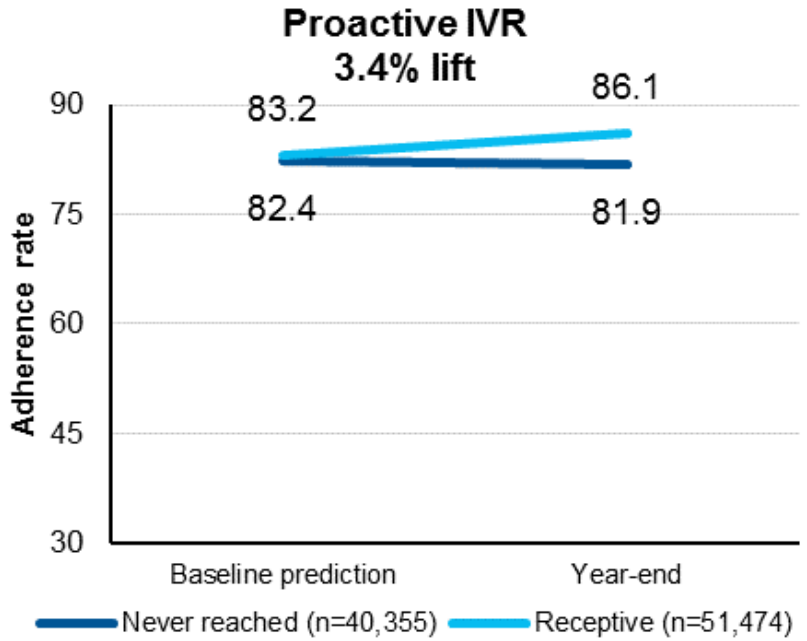
Effects on adherence of some health plan direct-to-member outreach



Operational performance

- 41,600 recommendations
- 91% deployed, 42% reached



Operational performance

- 108,441 recommendations
- 99% deployed, 42% reached

Adherence lift represents an intervention's ability to increase the percentage of members with PDC >80%. It is calculated as the difference between the predicted adherence rate and the actual year-end adherence rate, in patients who were receptive to the intervention vs. those who were never reached (difference-of-differences).

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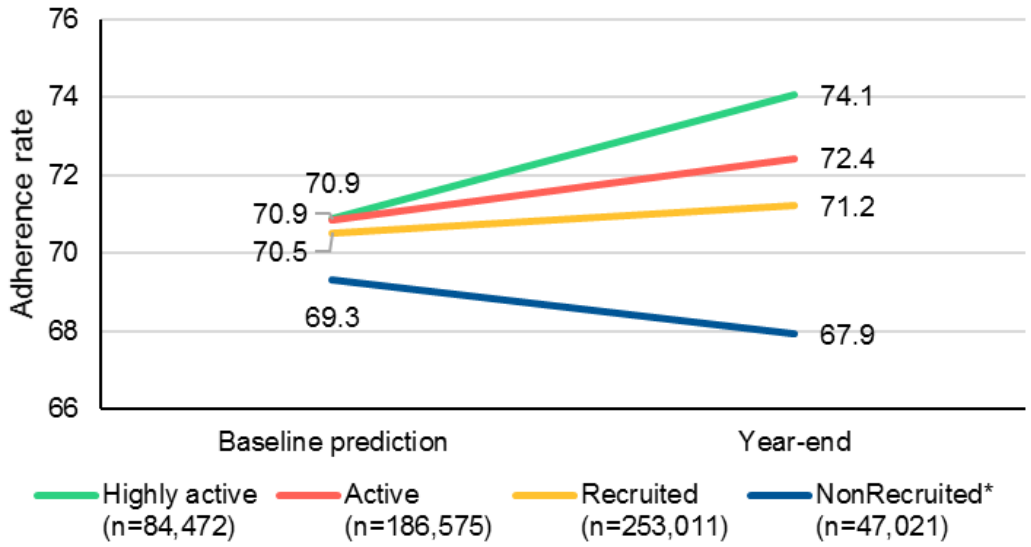
Effects on adherence of provider and pharmacy incentive programs

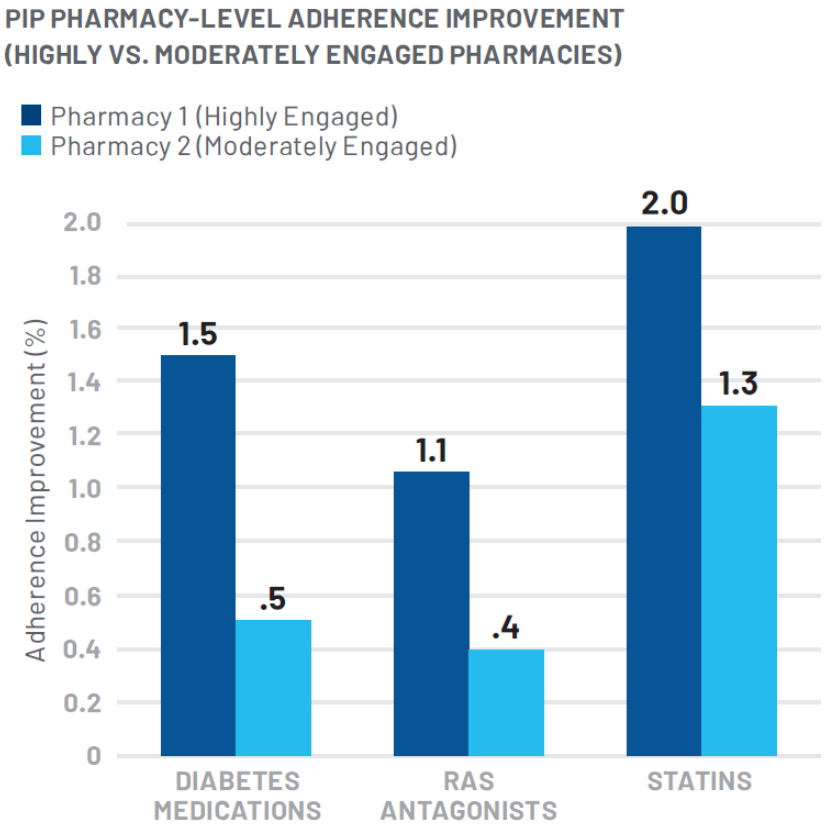
Provider P4P lift stratified by level of provider engagement



Key Year-end Outcomes

- Highly active: 28% of opportunities, **4.5% lift**
- Active: 62% of opportunities, **3.0% lift**
- Recruited: 84% of opportunities, **2.1% lift**

Pharmacy P4P lift stratified by pharmacy engagement status



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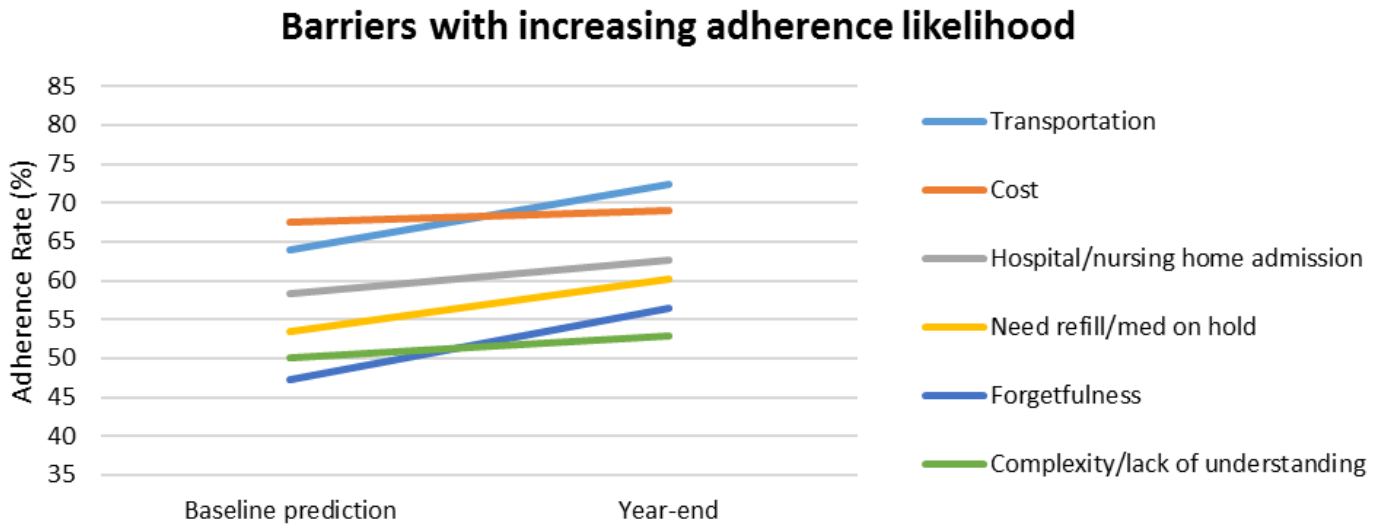
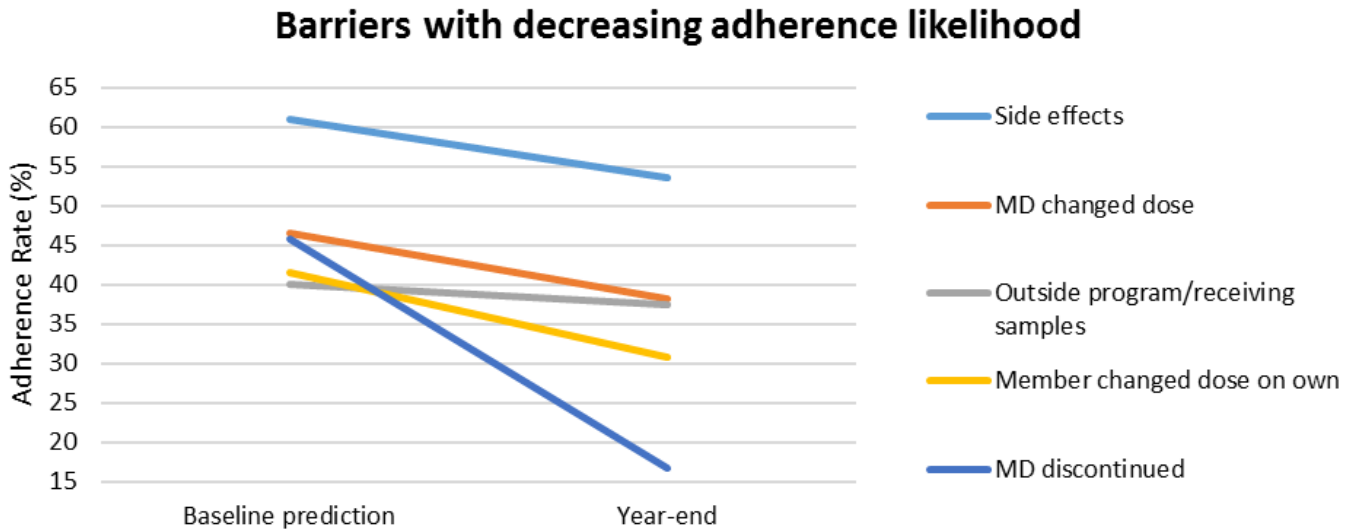
Patient-reported barriers and adherence trajectory over time





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Important questions

- Q: How should we define and measure medication adherence?
  A: Depends on use case and consequences of being wrong. “Measuring fills vs. eaten pills”

- Q: How much adherence is enough?
  A: Need strong population-level data on adherence-response

- Q: What’s the “nuclear option” intervention?
  A: I’m working on it, but am convinced it involves helping complex and vulnerable patients at home…

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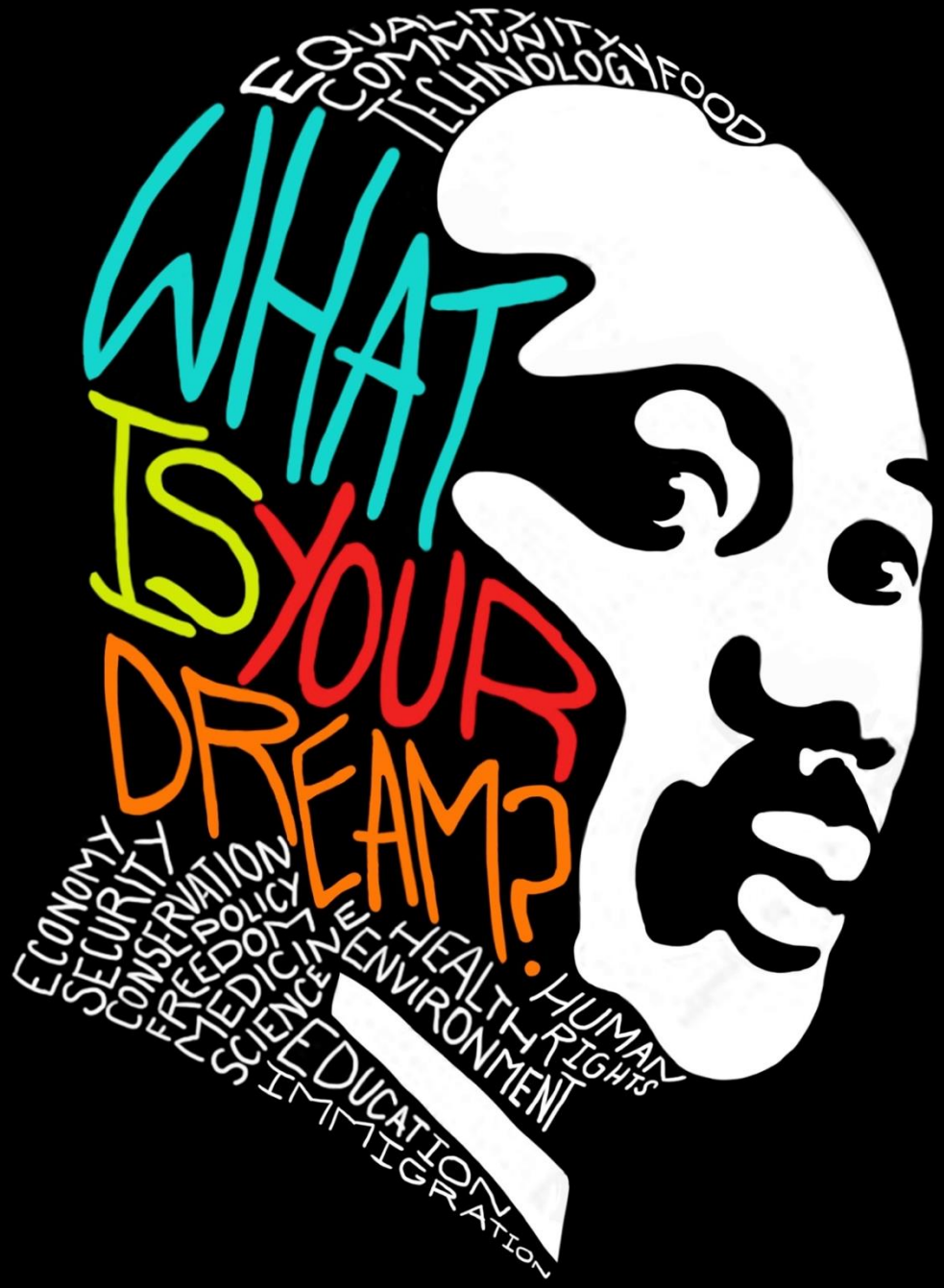
Interventions to Track and/or Improve Medication Adherence



Less Talk More ACTION Research: Toward a 4th Generation of Disparities Research to Achieve Health Equity

Stephen B. Thomas, Ph.D.
Professor Health Policy & Management
School of Public Health
Director, Maryland Center for Health Equity
PI, NIH-NIMHD Center of Excellence on Race, Ethnicity and Health Disparities Research
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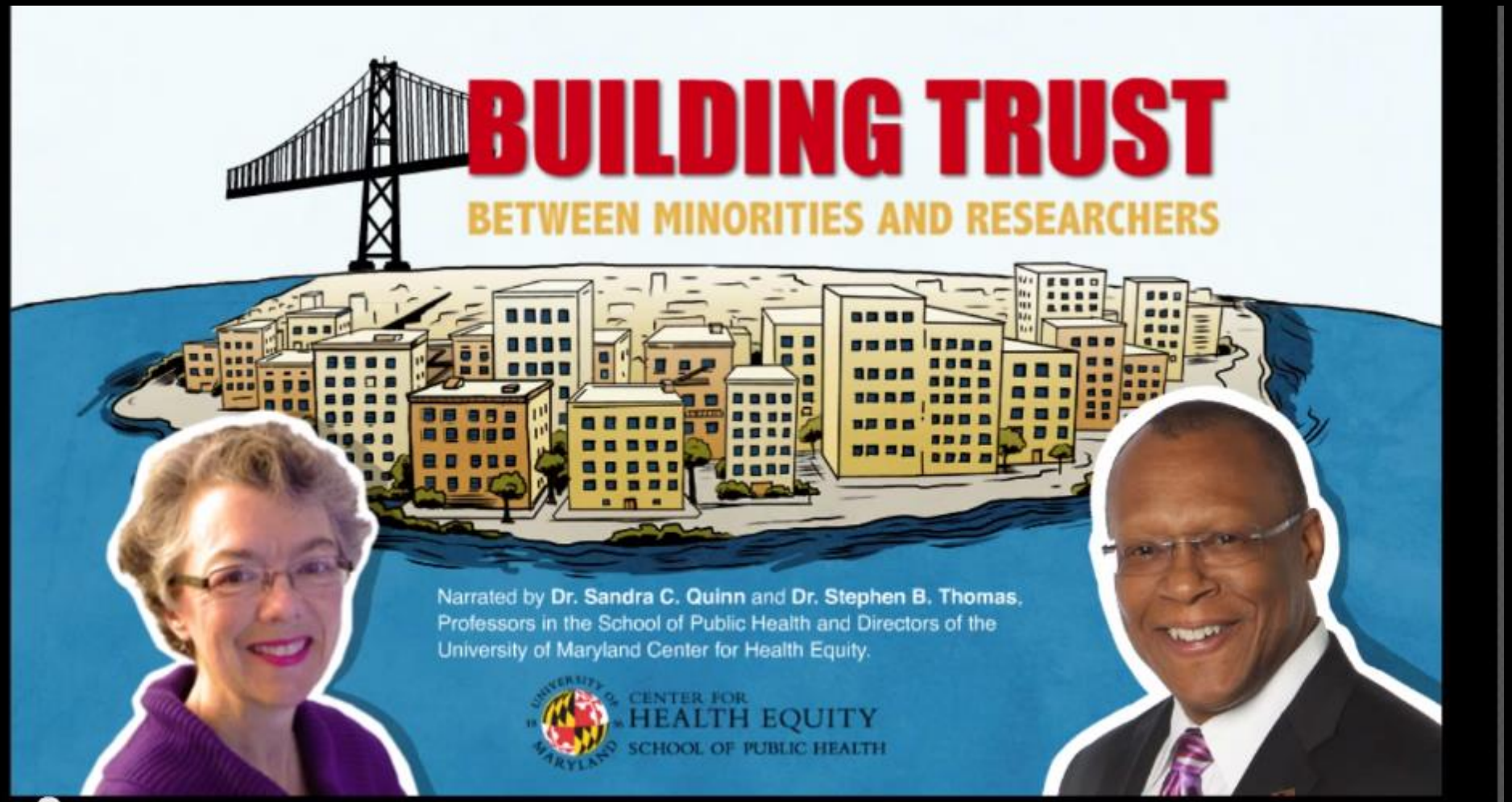
BUILDING BRIDGES
BUILDING TRUST
BUILDING
HEALTHY COMMUNITIES


BUILDING TRUST
BETWEEN MINORITIES AND RESEARCHERS
Narrated by Dr. Sandra C. Quinn and Dr. Stephen B. Thomas,
Professors in the School of Public Health and Directors of the
University of Maryland Center for Health Equity.
CENTER FOR
HEALTH EQUITY
SCHOOL OF PUBLIC HEALTH
0:12 / 3:55

The Social Context of Health Disparities

The ultimate aim is to uncover social, cultural and environmental factors beyond the biomedical model and address a broad range of issues. This approach includes, but not limited to, breaking the cycle of poverty, increasing access to quality health care, eliminating environmental hazards in homes and neighborhoods, and the implementation of effective prevention programs tailored to specific community needs.

The Historical Context of Health Disparities

"..If there is no **struggle**, there is no progress. Those who profess to favor freedom, and yet depreciate agitation, are men who want crops without plowing up the ground. They want rain without thunder and lightning. They want the ocean without the awful roar of its many waters…"

(Fredrick Douglass)

Photo Credit: Sandra Quinn

Cultural Tailoring Matters

2001 FEDERAL DHHS

TAKE A LOVED ONE TO THE DOCTOR DAY

4th GENERATION APPROACH:

TAKE A HEALTH PROFESSIONAL TO THE PEOPLE

Health Advocates In-Research and Research (H.A.I.R.)

National Association of Black Barbershops & Salons for Health

Saturday

February

18

Health Advocates In-Reach and Research

HAIR

Get Your Health Education Check-Up at

Next Level Barber Shop
5910 Riggs Road
Hyattsville, MD 20783

Did you know :"High blood pressure often has no warning signs or symptoms. Once it occurs, it usually lasts a lifetime. If uncontrolled, it can lead to heart and kidney disease, stroke, and blindness" (Guide to Lowering Blood Pressure with DASH Eating Plan, National Institutes of Health, National Heart, Lung and Blood Institute). Come learn what you can do.

Sponsored By:

University of Maryland 18 56

Center for Health Equity
School of Public Health

Linnan, L., **THOMAS, S.,** D'Angelo, H., & Ferguson, Y. (2012). African American barbershops and beauty salons: An innovative approach to reducing health disparities through community building and health education In M. Minkler (Ed.), ***Community Organizing and Community Building for Health and Welfare*** *(3rd Edition)*. New Brunswick, NJ: Rutgers University Press.

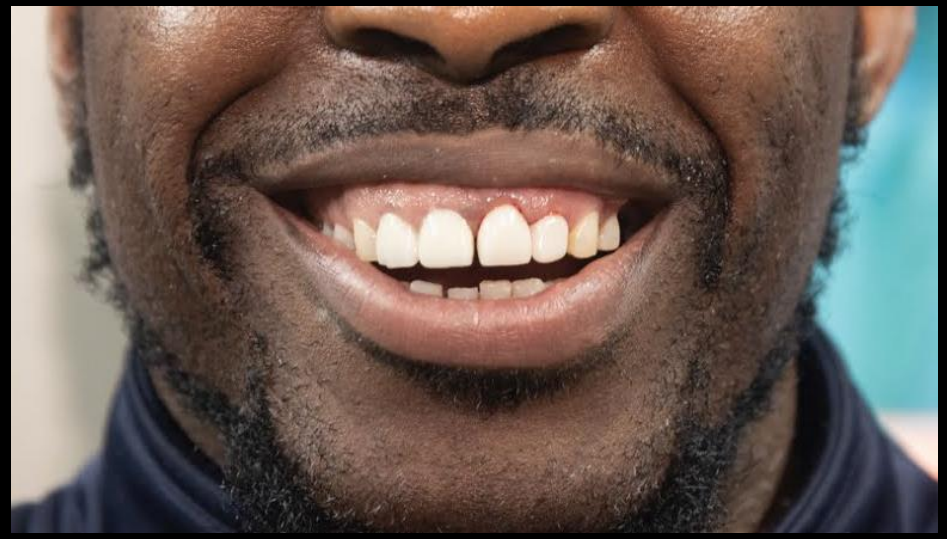
THANK YOU CIGNA !!!

(Photo credit: M-CHE.sph@umd)

"… Because the majority of the dental care is very expensive, and we cannot afford it. If you ask me if I had pain in my tooth, but I have to give my children food, I prefer to buy food for them than take care of my own dental care..." (48-yo Hispanic female)

BUILDING TRUST
BETWEEN MINORITIES AND RESEARCHERS

National Institute on Minority Health and Health Disparities and Office of the Director, National Institutes of Health
American Reinvestment and Recovery Act RC2MD004766; Principal Investigators: Sandra Quinn & Stephen Thomas



(Photo credit: M-CHE.sph@umd)

"… Medical costs are very expensive. So anytime there is something free, as it relates to medical, people will probably take advantage... There's probably 700 people here today, and perhaps not all 700 will be seen. But, the fact that they can come for cleaning and perhaps some of them have not had a cleaning in years. So, I think that this program being offered is a great benefit for the community."
(69-yo old African American male)

National Institute on Minority Health and Health Disparities and Office of the Director, National Institutes of Health
American Reinvestment and Recovery Act RC2MD004766; Principal Investigators: Sandra Quinn & Stephen Thomas

Interventions to Track and/or Improve Medication Adherence

Interventions to Improve Medical Regimen Adherence

Andrea B. Troxel, Sc.D.

Department of Population Health
NYU School of Medicine

December 10, 2019

Medication Adherence:
Landscape, Strategies, and Evaluation Methods

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NYU Langone Health

Overview

Overview

Medication/Behavior Adherence in Chronic Disease

- Diabetes
  - medication
  - HbA1c monitoring
- Hypertension
  - medication
  - lifestyle changes
- Hyperlipidemia
  - medication
  - lifestyle changes
- Obesity
  - lifestyle changes
- Psychiatric conditions

. . . and many others

Common Elements

- Daily behavior
- Varying degrees of burden
- No immediate benefits
- No tangible benefits
- Often completed privately

Behavioral Economics (BE)

- Integrate theories of economics and psychology
- *Standard* economics
  - rational beings maximize expected value
- *Behavioral* economics
  - decision errors are common
    - present bias
    - (mis)understanding of probability
    - loss aversion
    - social pressure
  - harness these errors to improve decision-making
  - defaults are powerful

Potential Interventions - Patients

Daily lotteries for daily behaviors

- large chance of small reward
- small chance of large reward
- only receive reward if desired behavior occurred
- BE principles
  - variable reinforcement
  - regret aversion
  - entertainment

Potential Interventions - Patients

Deposit contracts

- put down money in advance
- get money back (plus match) if meet goal
- BE principles
  - endowment effect
  - loss aversion

Potential Interventions - Patients

Social incentives

- identify support partner
- partner receives information on progress
- BE principles
  - social incentives
  - actions are witnessable
  - social norming
  - competition

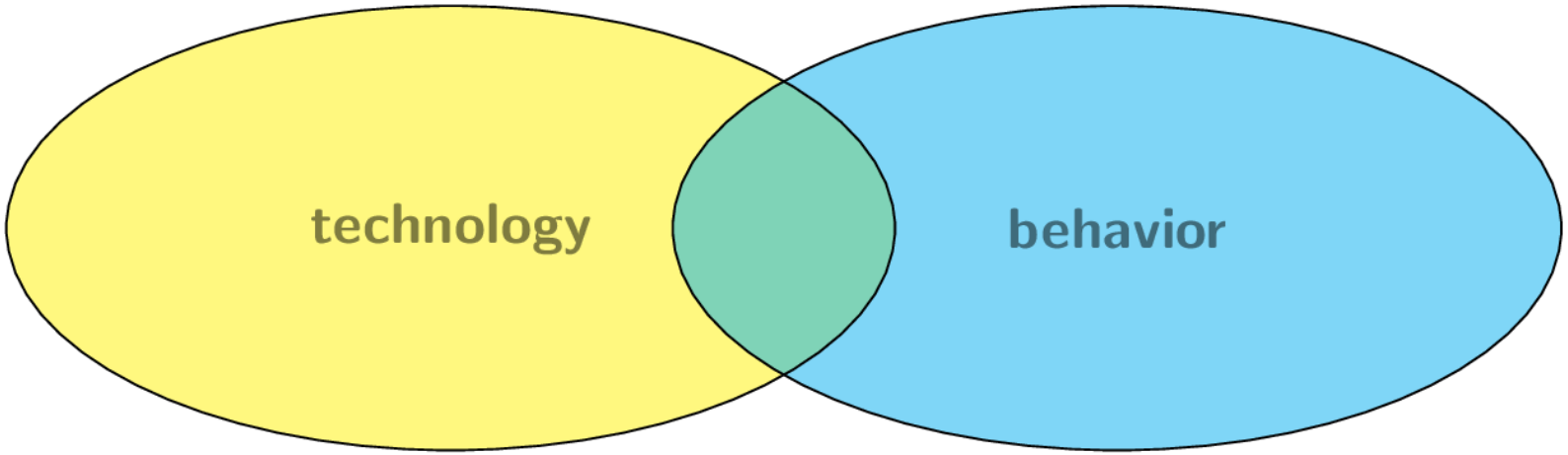
Potential Interventions - Providers

Fixed payments

- separated from general income stream
- tied to particular outcomes
- BE principles
  - competition
  - accountability

Scalability

- Scale is impossible without technology
- Technology is useless unless it engages human behavior



Overview

Shared incentives trial (SI)

1. SI PIs Asch/Volpp

Population	1,500 patients with high cardiac risk and elevated LDL
Interventions	financial incentives
	▶ control
	▶ patient incentives: lottery for daily statin adherence
	▶ physician incentives: payments for meeting quarterly goals
	▶ shared incentives: each at half value
Randomization	cluster-randomized by physician
	balanced by arm
	stratified by study site (Penn, Geisinger, HVMA)
Outcomes	**change in LDL over 12 months**
	daily adherence
	statin initiation/intensification
Analysis	longitudinal mixed effects model for LDL
Side study	compare different consent approaches in diabetics

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Side study compare different consent approaches in diabetics

Shared incentives trial

Asch DA, Troxel AB, Stewart WF, Sequist TD, Hones JB, Hirsch AG, Hoffer K, Zhu J, Wang W, Hodlofski A, Frasch AB, Weiner MG, Finnerty DD, Rosenthal MB, Gangemi K, Volpp KG (2015). Effect of Financial Incentives to Physicians, Patients, or Both on Lipid Levels: A Randomized Clinical Trial. *JAMA* 314(18): 1926-35.

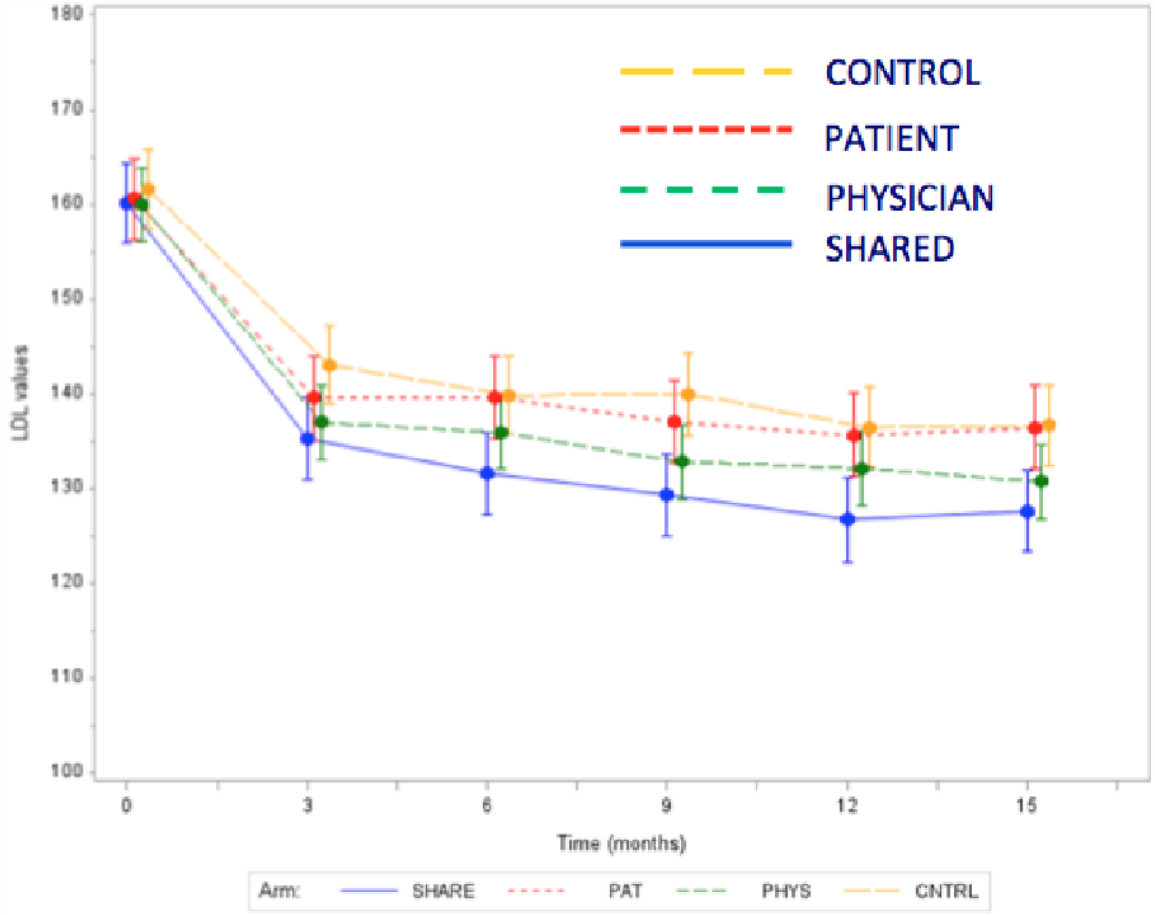
Shared incentives participants

- 238 primary care physicians at 3 sites
- 1,503 patients
  - age $18 - 80$
  - FRS $\geq 20\%$ or CAD with LDL ≥ 120
  - FRS $10 - 20\%$ with LDL ≥ 140

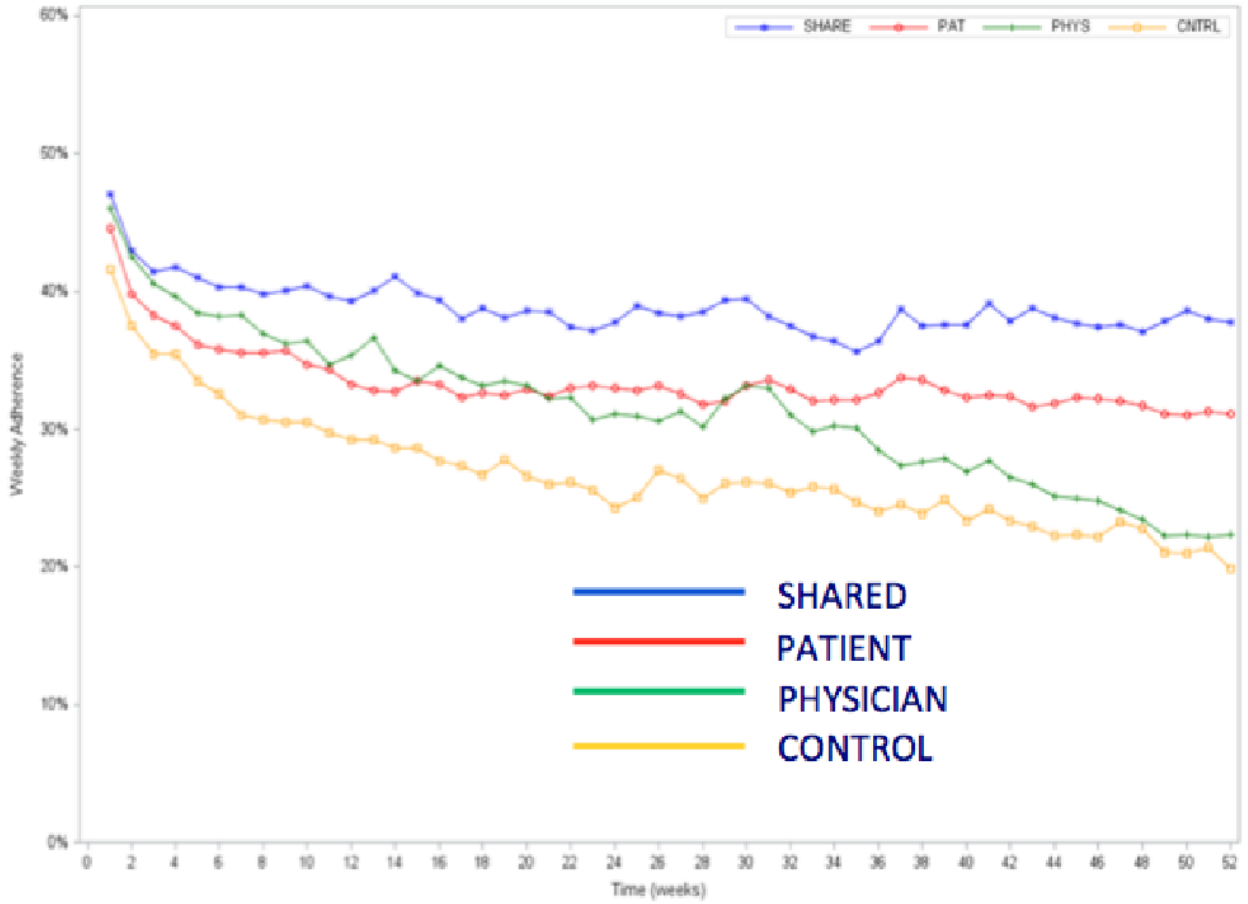
SI: LDL reduction at 12 months

	Control	Patient Incentives	Physician Incentives	Shared Patient and Physician Incentives
Δ LDL	26.6	26.4	30.0	36.8
CI	$22.7 - 30.6$	$22.5 - 30.3$	$26.6 - 33.4$	$32.9 - 40.6$
p	–	0.87	0.20	< 0.001

SI: Average LDL over time



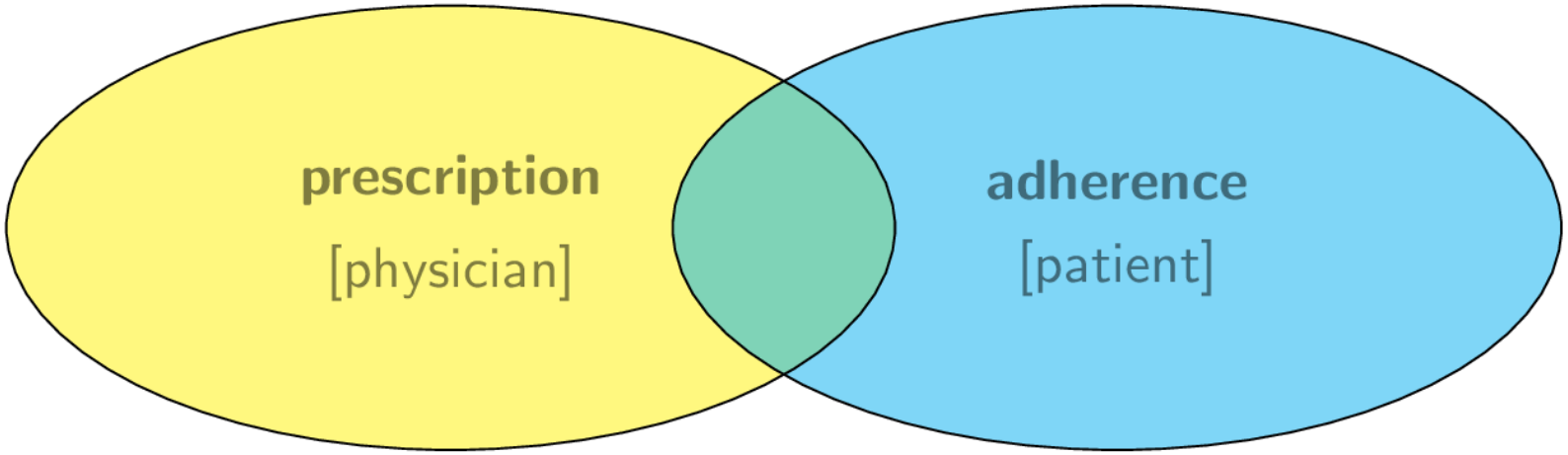
SI: Average adherence over time



SI: Summary

- Physician incentives are no better than control
- Patient incentives are no better than control
- Shared incentives are better than control
  - each at *half value*
- Adherence is disappointingly low

SI: Explanation?



Overview

Summary

- Enormous potential for innovation
  - technology
  - detailed and immediate information
  - understanding of human behavior
  - rapid-cycle innovation
- Optimized interventions
  - must be rigorously tested
  - must address needs of various populations
  - must incorporate multiple partners
    - patients
    - providers
    - community health linkers
    - other social partners

Interventions to Track and/or Improve Medication Adherence

Medication Adherence: Landscape, Strategies, and Evaluation Methods

INTERVENTIONS TO TRACK AND/OR IMPROVE MEDICATION ADHERENCE: INDUSTRY PERSPECTIVE

JOCELYN ULRICH, MPH

DEPUTY VICE PRESIDENT, PHRMA

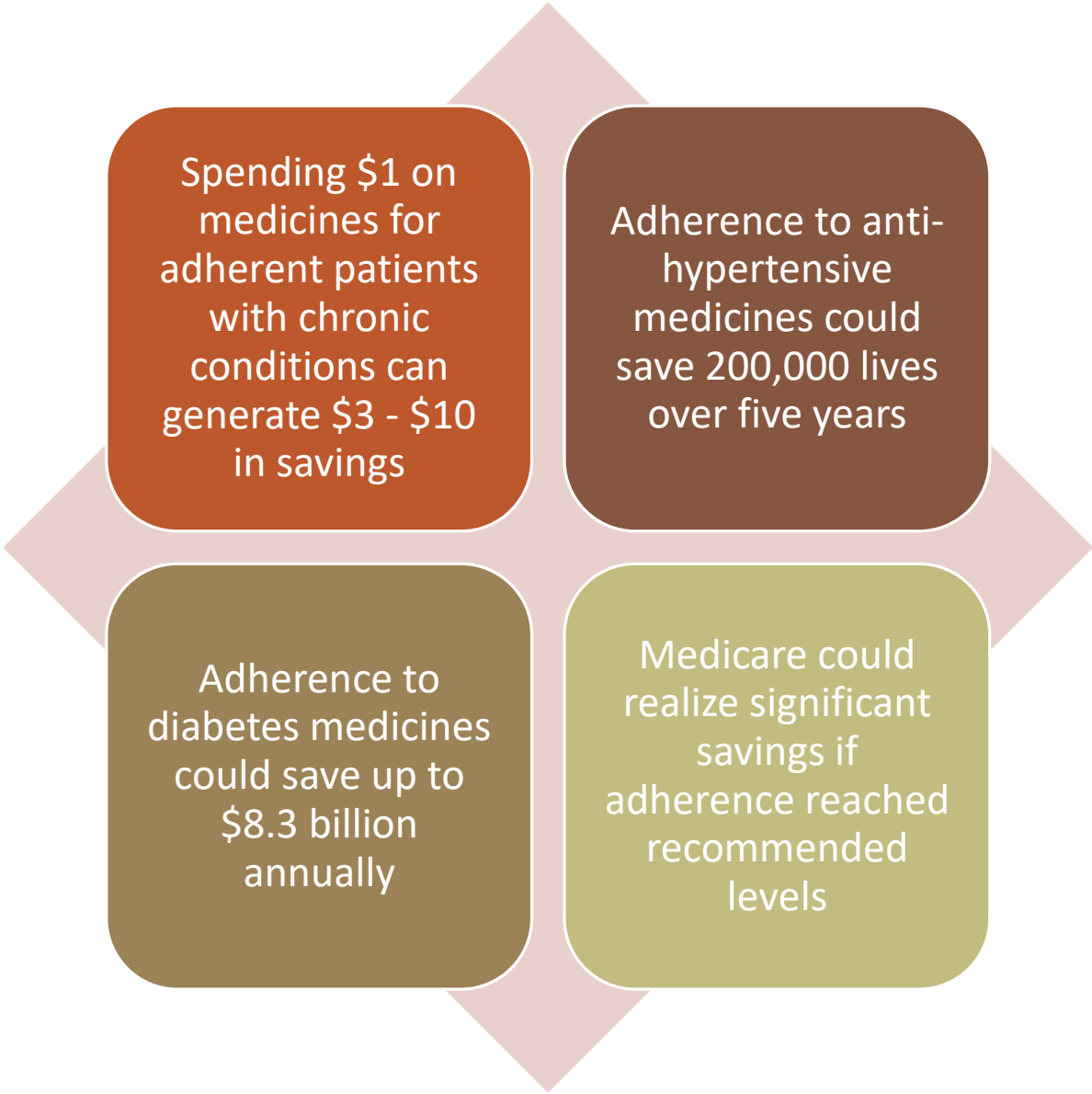
Medication Adherence: Industry Perspective

Despite innovations and advancements in treatments, over 75% of national health spending is on patients with chronic conditions

Medicines still represent one of the most effective approaches to prevention and management of diseases

Patients are not able to experience the full benefits of these treatments if they are not optimally used as intended

Benefits of Adherence



Patient-Focused Drug Development

Researchers collect patient perspective data on disease measures and treatment outcomes and integrate these findings

FDA considers patient perspectives during regulatory review

Approvals of new medicines and new uses reflect information that is meaningful to patients, their families, and health care providers and can therefore improve adherence

Innovation Can Improve Use of Medicines

Industry continues to develop innovative approaches to improve medication use, such as:

- New formulations (e.g., long-acting or extended-release preparations)
- Routes of administration that make taking medicines easier or more convenient
- Fixed-dose combinations (two or more medicines in a single dosage form)

Support for policies that also promote better use of medicines:

- Patient education
- Shared decision-making tools
- Medication therapy management
- Refill synchronization
- Technology aids
- Value-based payment arrangements

Digital Tools Can Aid in Medication Adherence

Delivery mechanisms for medicines for chronic diseases with sensors, digital displays, and memory functions with the ability to transmit the timing and amount of dose to a mobile app

Companion apps for patients with serious chronic conditions to help them track disease episodes, treatments, and drug supply, and share that data with their healthcare team

Ingestible sensors embedded in drugs for patients with serious mental illnesses to help them track whether their medicine has been taken

Interventions to Track and/or Improve Medication Adherence

Interventions to Track and/or Improve Medication Adherence

Lunch

Measuring and Evaluating Medication Adherence

Measuring and Evaluating Medication Adherence

Prof. Bernard Vrijens, PhD

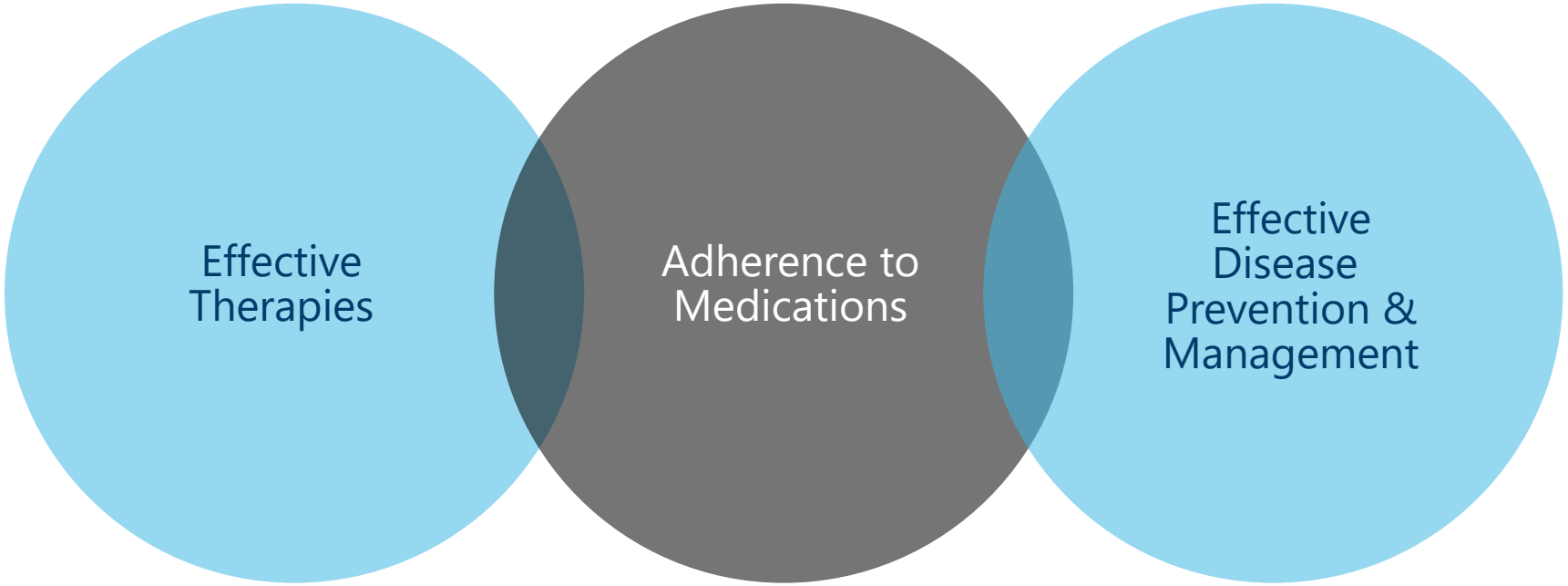
CEO & Scientific Lead, AARDEX Group

Invited Professor of Biostatistics, Liège University, Belgium

Honorary Member, ESPACOMP

bernard.vrijens@aardexgroup.com

Adherence is Key to Therapeutic Success

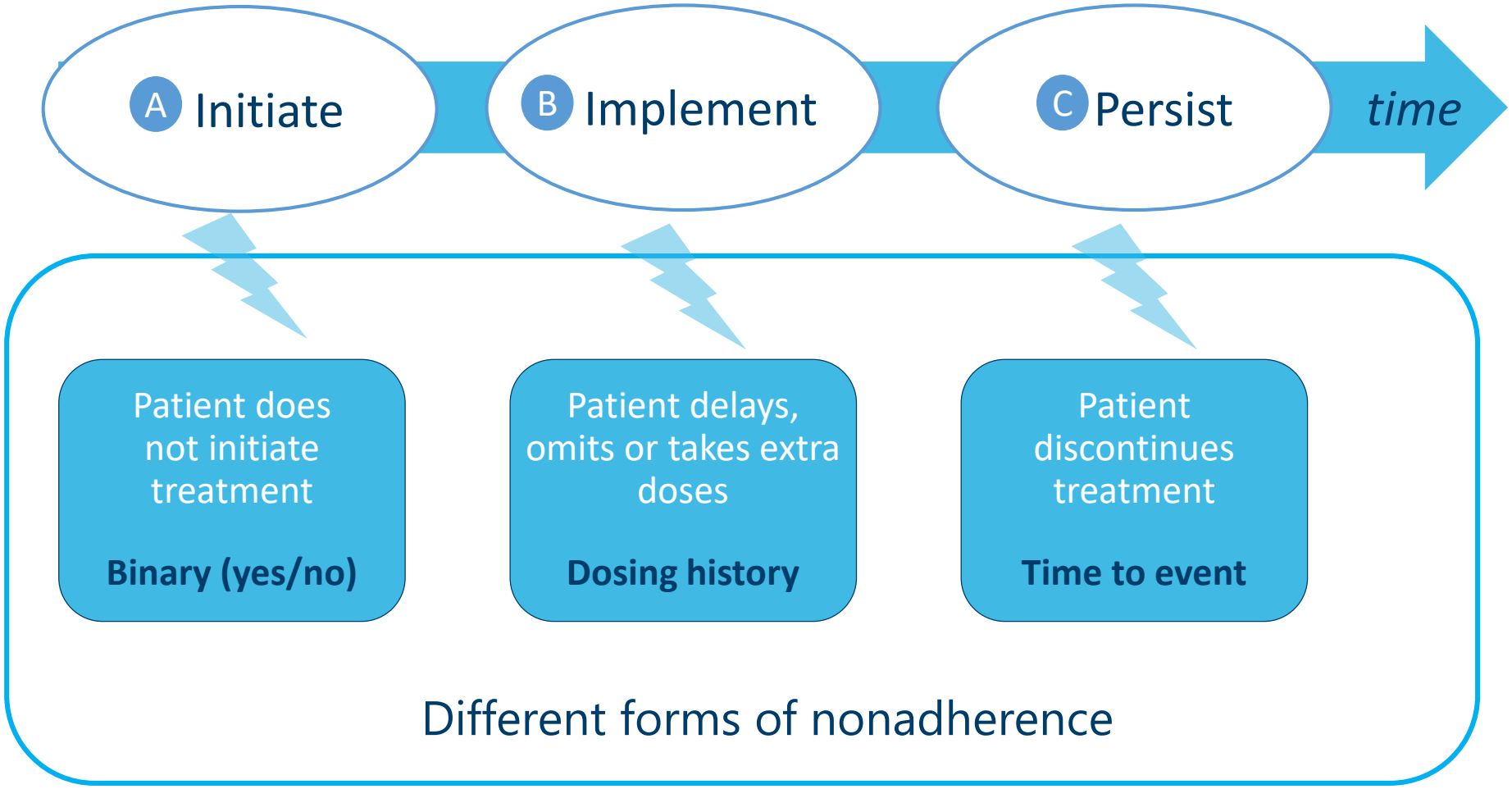


"Drugs don't work in patients who don't take them."

– C. Everett Koop, former US Surgeon General

ABC Taxonomy: Medication Adherence

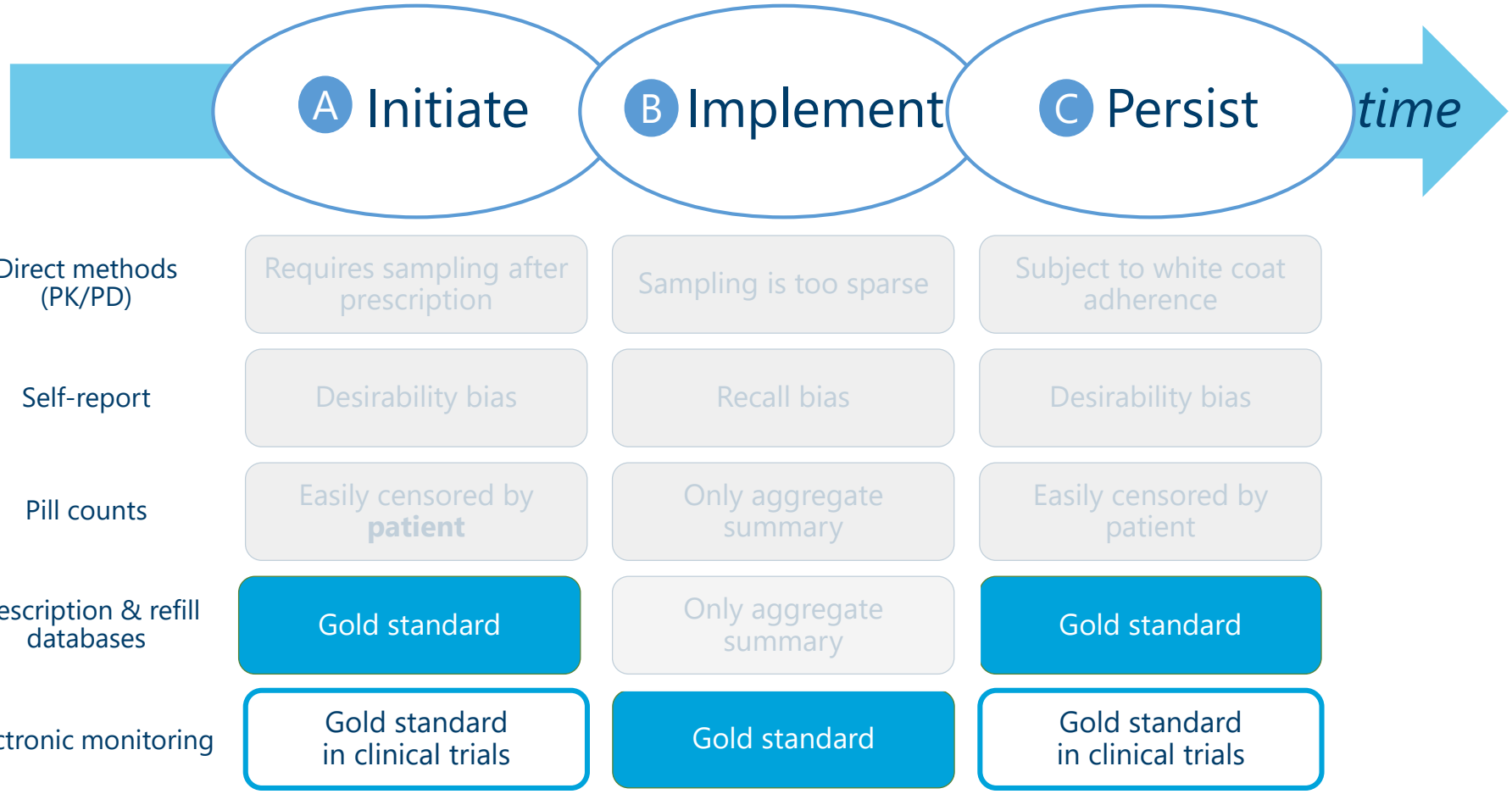
The process by which patients take their medications as prescribed



EU-sponsored research

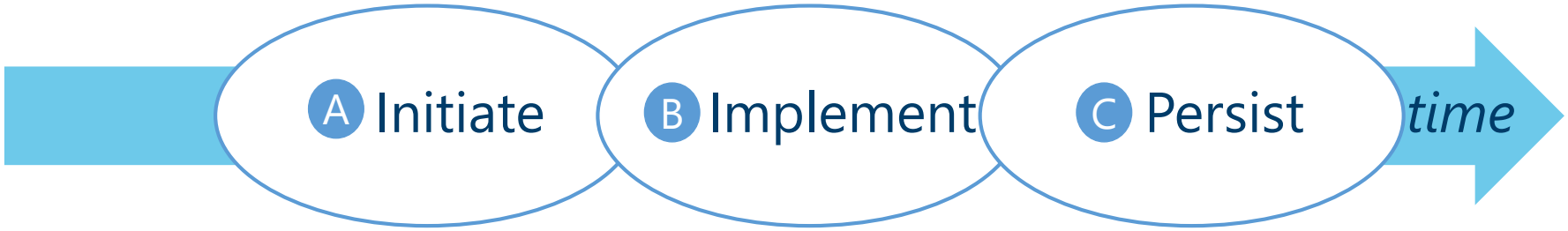
Vrijens et al., Br J Clin Pharmacol 2012;73:691-705.

Overview of assessment methods of adherence in ambulatory patients



Adapted from Vrijens & Heidbuchel, Europace 2015.

Gold Standard Measure of Adherence



In clinical trial (Drug Development)

Electronic monitoring

In medical practice

Prescription & refill databases

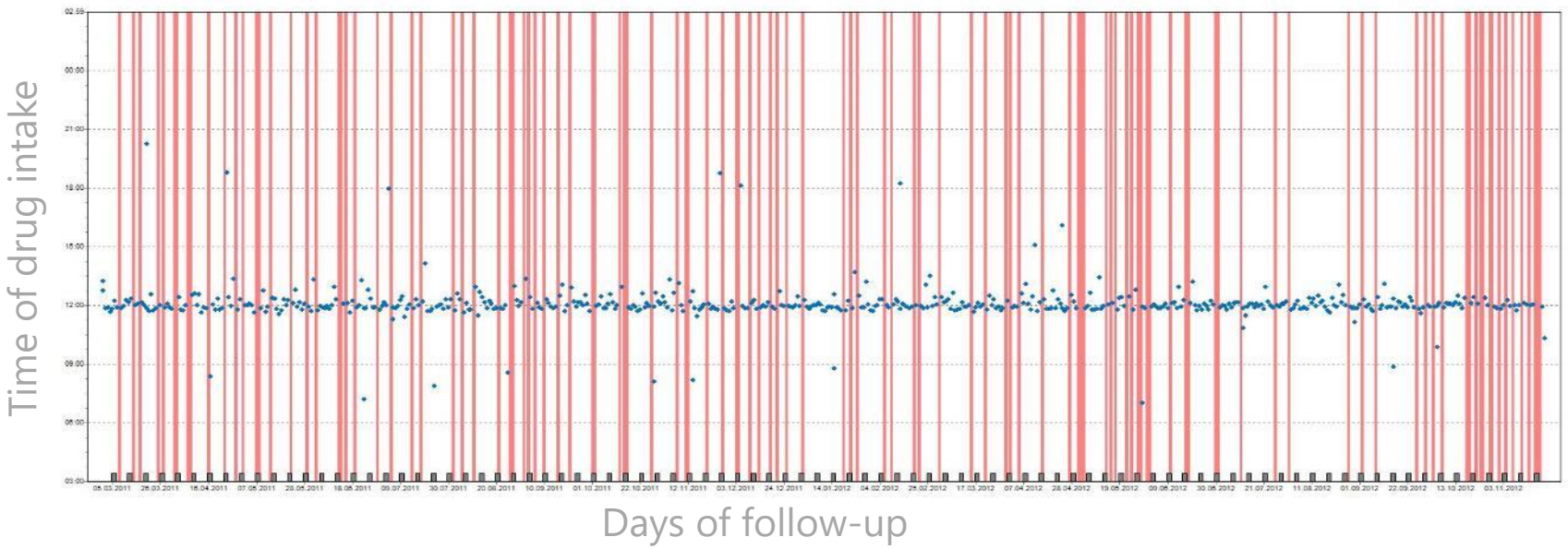
Electronic monitoring

Prescription & refill databases

Example of Electronic Monitoring

B Implement

Case Study: Dosing History Data over 2 years (2011-2012)



Follow-up: 632 days – 14 days (2%) with double dose & 115 days (18%) no doses

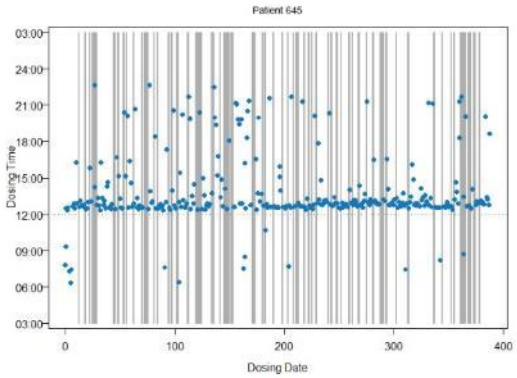
➔ 84% of prescribed doses taken

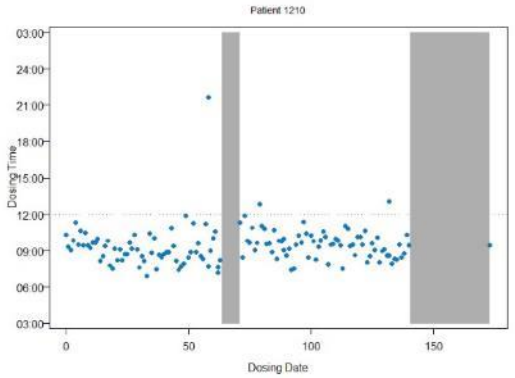
How much implementation is enough? **DRUG'S FORGIVENESS**

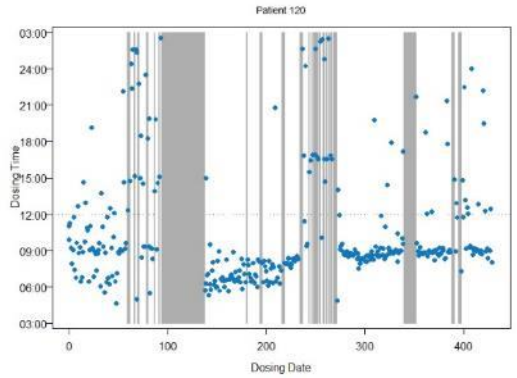
The Unfortunate 80% rule!

Each of these 6 patients took the same percentage (81%) of prescribed doses

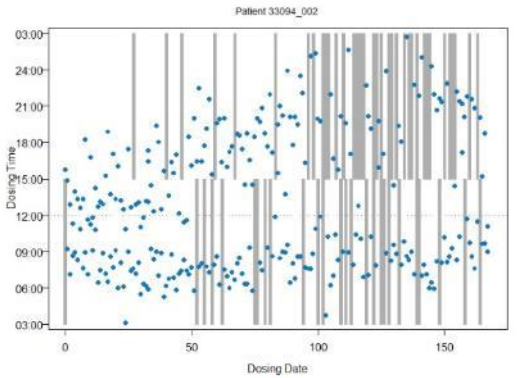
Once daily dosing

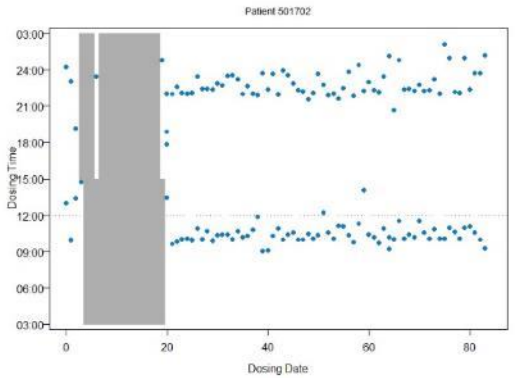


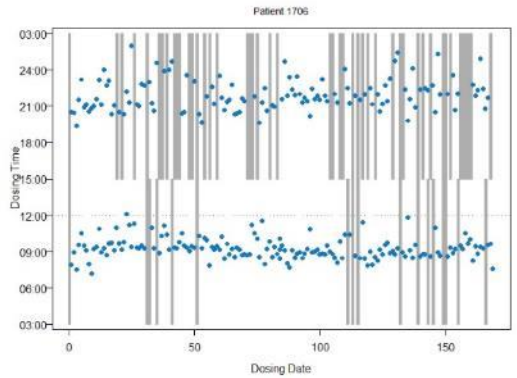




Twice daily dosing



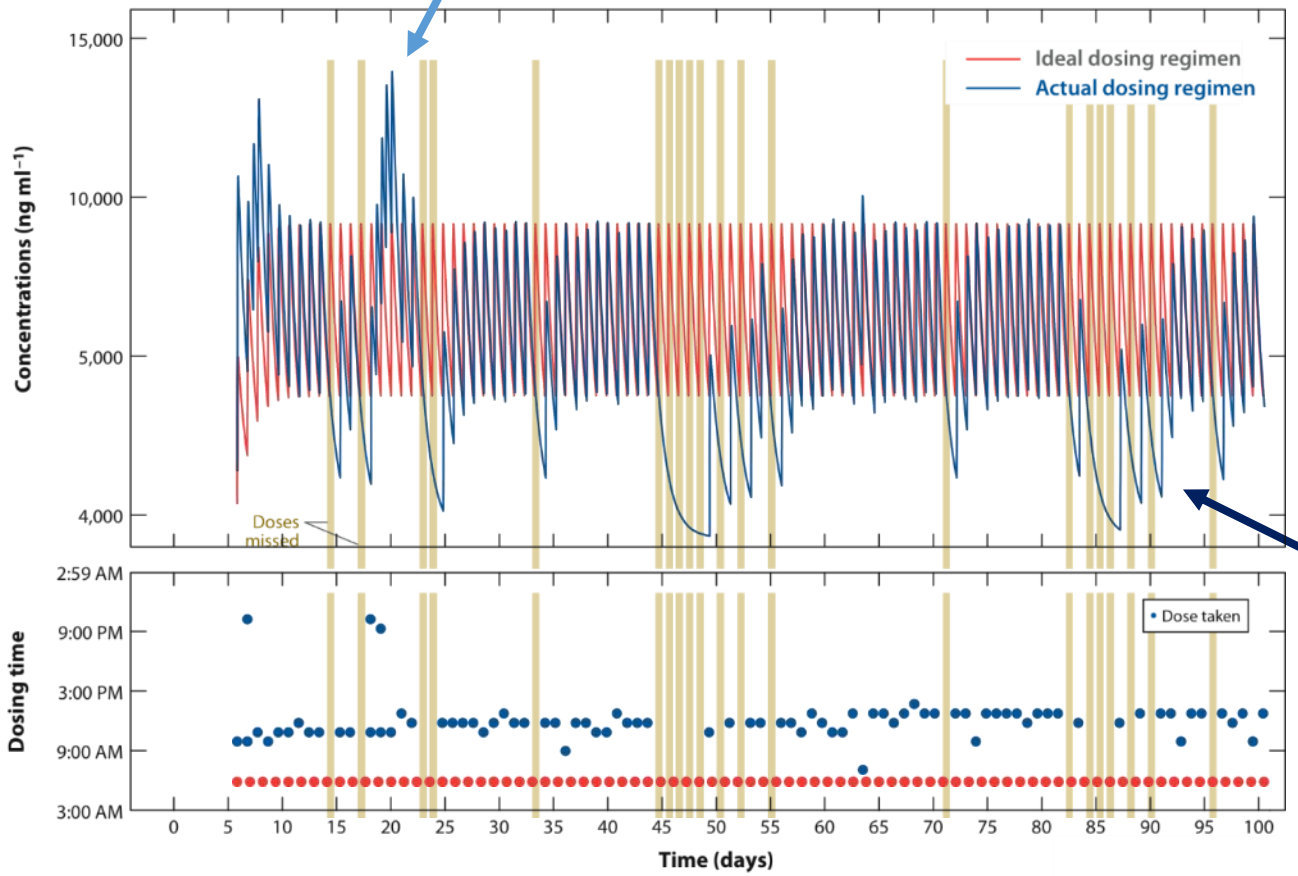




Vrijens B, Drug Utilization Research: Methods and Applications, First Edition, John Wiley & Sons, Ltd., 2016

Variable adherence creates drug-specific issues of efficacy, safety, & drug resistance

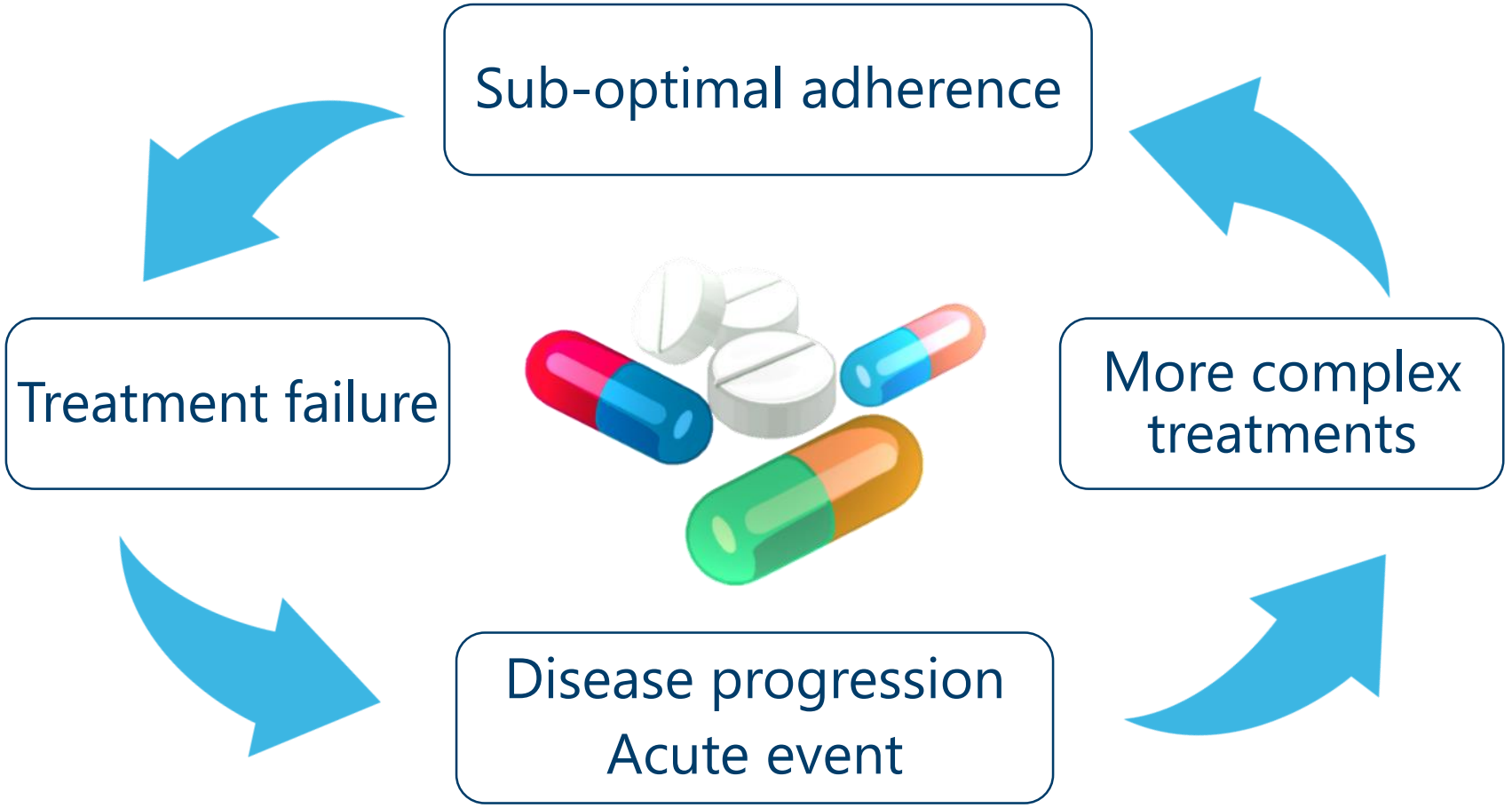
Occasional toxicity



Periodic loss of effectiveness & emergence of drug resistance

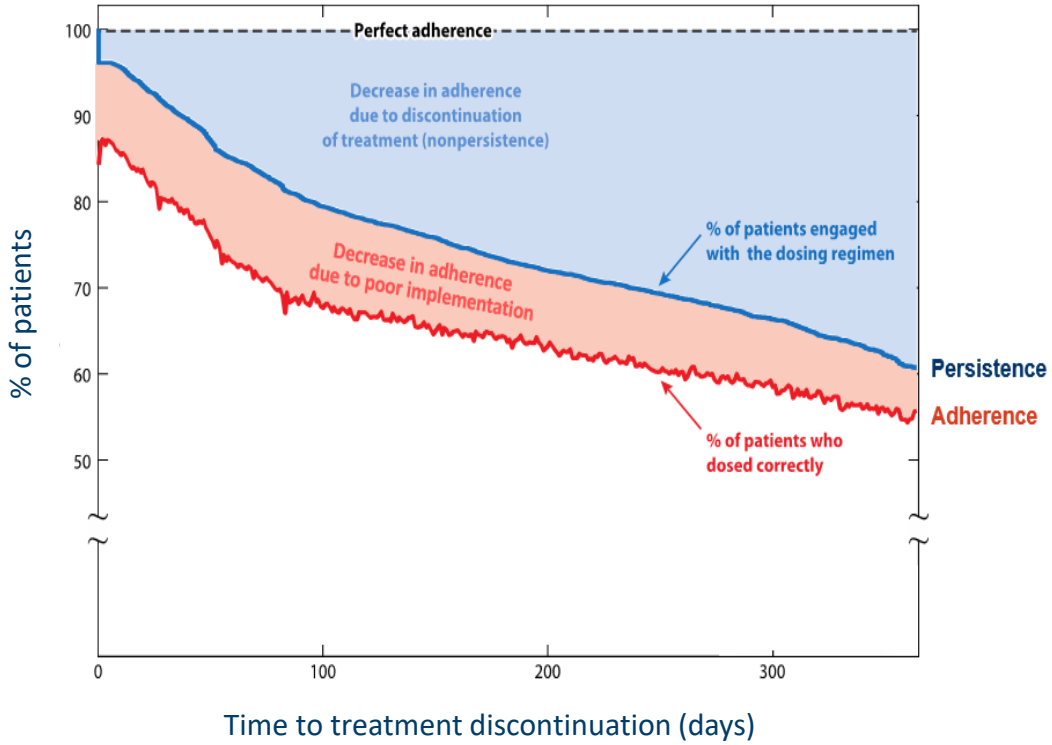
Blaschke, Osterberg, Vrijens, Urquhart, 2012, Ann Rev Pharmacol Toxicol, 52:275-301

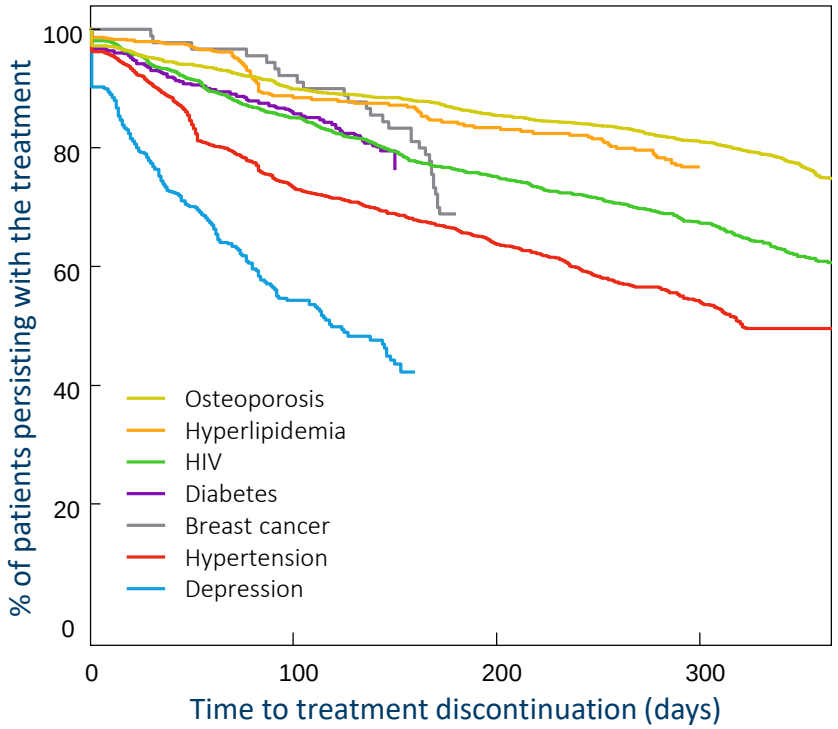
Addressing adherence is key to avoid treatment escalation & needless combination therapies



Addressing adherence is key to optimize drug development

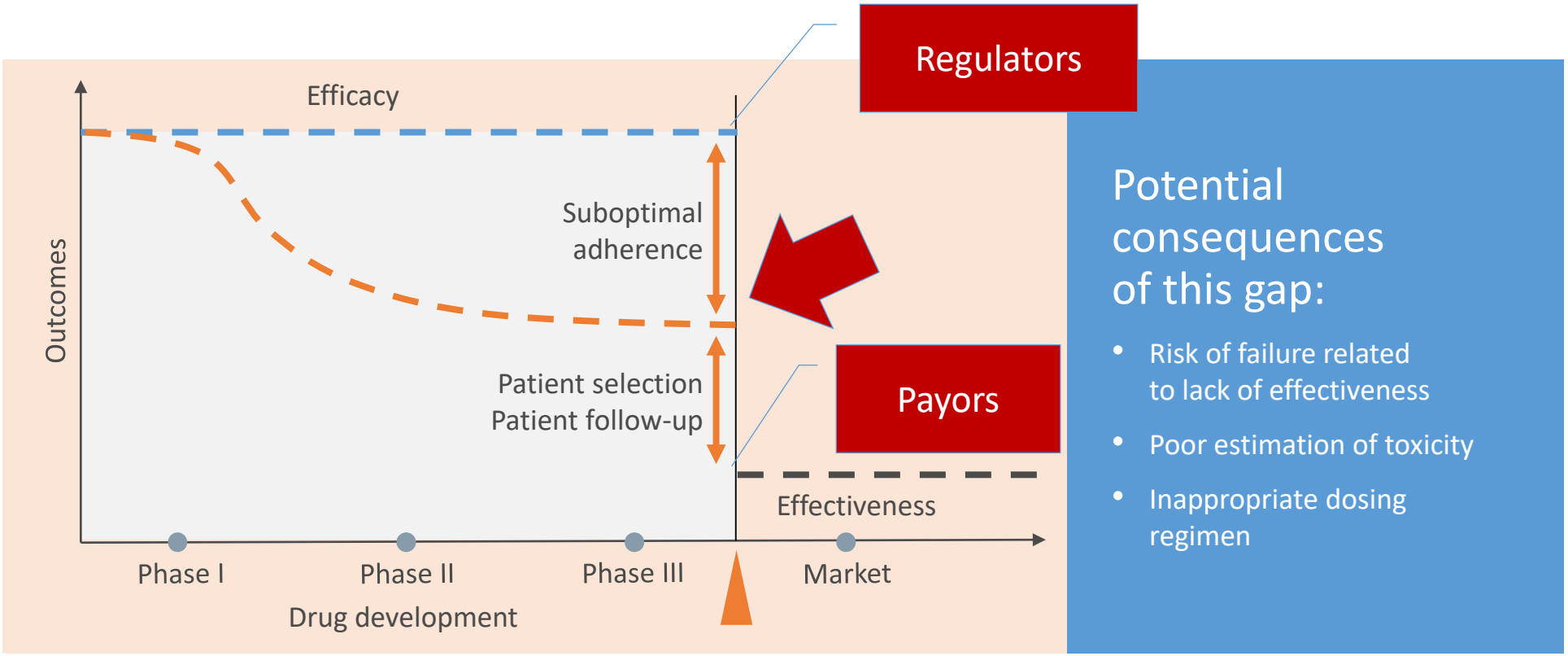
N=16,907 participants from 95 clinical studies





Blaschke, Osterberg, Vrijens, Urquhart, 2012, Ann Rev Pharmacol Toxicol, 52:275-301

The Adherence Gap

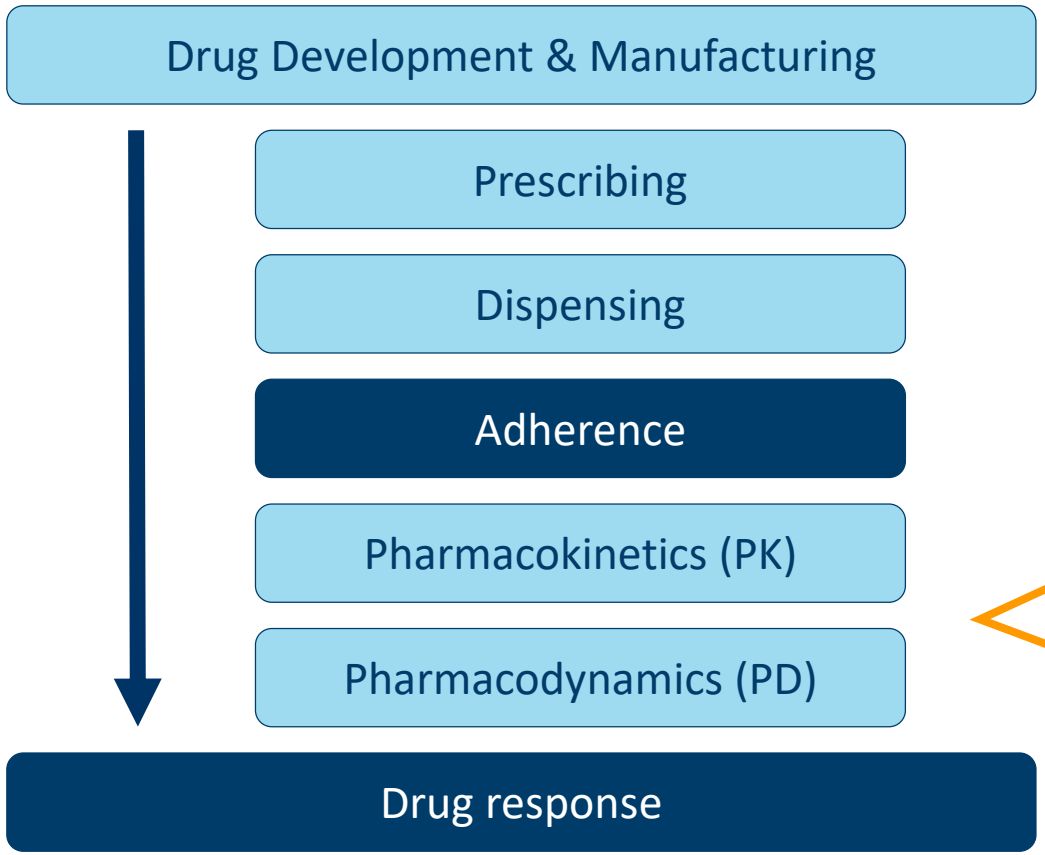


Adherence is Becoming a Regulatory Priority

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. *Mar 2019*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/08/WC500233916.pdf. *Aug 2017*

Blaschke, Osterberg, Vrijens, Urquhart, 2012, Ann Rev Pharmacol Toxicol, 52:275-301

High-fidelity measurement of patients' medication adherence: A missing link in precision medicine

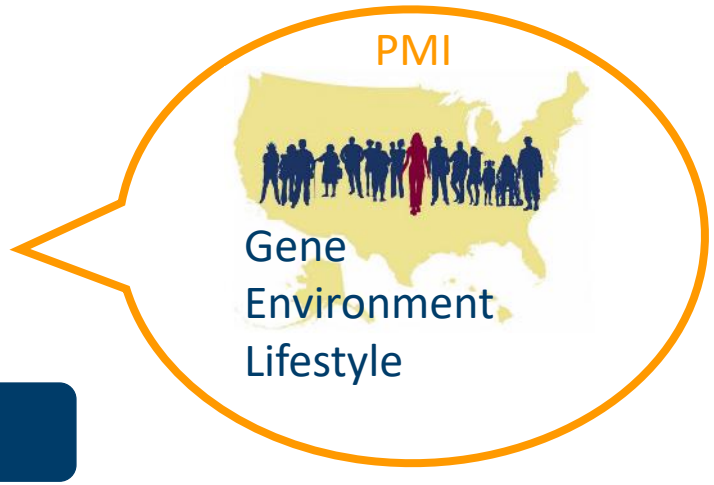


Poor medication adherence in clinical trials: consequences and solutions

Alasdair Breckenridge[1], Jeffrey K. Aronson[2], Terrence F. Blaschke[3], Dan Hartman[4], Carl C. Peck[5] and Bernard Vrijens[6]

Poor adherence to medicines in clinical trials can undermine the value of the trials; for example, by compromising estimates of the benefits and risks of a medicine. In this article, we highlight such consequences and also discuss approaches to tackle this problem.

NATURE REVIEWS | DRUG DISCOVERY
Feb 2017



www.nih.gov/precision-medicine-initiative-cohort-program

Advanced **A**nalytical **R**esearch on **D**rug **EX**posure

AARDEX GROUP

35

Medication **E** vent **M**onitoring **S**ystem **(MEMS®)**

MEMS Bibiometry

814	75k	146
peer-reviewed publications	journal citations	h-index

Nov 2019, Google Scholar.

Measuring and Evaluating Medication Adherence

Medication Adherence: Using pharmacy refill data

P. Michael Ho, MD, PhD
Co-Director, Denver-Seattle Center of Innovation (COIN) for Veteran-Centered and Value Driven Care
Co-Director, Data Science to Patient Value (D2V) Program
Professor and Vice Chair for Quality, Department of Medicine, University of Colorado School of Medicine

VA | U.S. Department of Veterans Affairs

University of Colorado Denver | Anschutz Medical Campus

WHAT DOES REFILL DATA LOOK LIKE?

Patient_ID	Drug_ID	Drug_Name_W_Dose	Issue_Date	Cancel_Date	Release_Date	Days_Supply	Prescribing_Site
123	abc	ATORVASTATIN CALCIUM 80MG TAB	3/27/19	11/14/19	4/9/19	90	554
123	abc	ATORVASTATIN CALCIUM 80MG TAB	3/27/19	11/14/19	8/6/19	90	554
123	abc	ATORVASTATIN CALCIUM 80MG TAB	3/27/19	11/14/19	10/29/19	90	554
123	abc	ATORVASTATIN CALCIUM 80MG TAB	11/13/19			90	554
123	def	HCTZ 12.5/LISINOPRIL 20MG TAB	3/27/19	11/14/19	4/2/19	90	554
123	def	HCTZ 12.5/LISINOPRIL 20MG TAB	3/27/19	11/14/19	7/7/19	90	554
123	def	HCTZ 12.5/LISINOPRIL 20MG TAB	3/27/19	11/14/19	9/25/19	90	554
123	def	HCTZ 12.5/LISINOPRIL 20MG TAB	11/13/19			90	554
456	ghi	AMLODIPINE BESYLATE 10MG TAB	1/2/19	10/10/19	2/24/19	90	554
456	ghi	AMLODIPINE BESYLATE 10MG TAB	1/2/19	10/10/19	8/12/19	90	554
456	ghi	AMLODIPINE BESYLATE 10MG TAB	10/10/19		10/10/19	90	554
456	jkl	LABETALOL HCL 100MG TAB	1/2/19	10/10/19	1/6/19	30	554
456	jkl	LABETALOL HCL 100MG TAB	1/2/19	10/10/19	7/8/19	30	554
456	jkl	LABETALOL HCL 100MG TAB	1/2/19	10/10/19	10/7/19	30	554
456	jkl	LABETALOL HCL 100MG TAB	10/10/19		10/17/19	30	554
456	mno	ROSUVASTATIN CA 20MG TAB	1/2/19	10/10/19	1/6/19	90	554
456	mno	ROSUVASTATIN CA 20MG TAB	1/2/19	10/10/19	6/12/19	90	554
456	mno	ROSUVASTATIN CA 20MG TAB	1/2/19	10/10/19	10/2/19	90	554
456	mno	ROSUVASTATIN CA 20MG TAB	10/10/19				554

ADHERENCE TERMINOLOGIES

- Initiation (initial medication adherence; primary non-adherence)
- Implementation (execution; secondary non-adherence or non-adherence)
- Persistence (discontinuation)

Patient_ID	Drug_ID	Drug_Name_W_Dose	Issue_Date	Release_Date	Days_Supply	Prescribing_Site
123	abc	ATORVASTATIN CALCIUM 80MG TAB	3/27/19	4/9/19	90	554
123	abc	ATORVASTATIN CALCIUM 80MG TAB	3/27/19	8/6/19	90	554
123	abc	ATORVASTATIN CALCIUM 80MG TAB	3/27/19	10/29/19	90	554
123	abc	ATORVASTATIN CALCIUM 80MG TAB	11/13/19		90	554

Hutchins DS Value Health 2015

ADHERENCE TO MULTIPLE MEDICATIONS

- Challenge is defining what is the goal of adherence measurement
  - Class of medication versus individual medication (e.g., HMG CoA reductase)
  - Treatment of specific condition

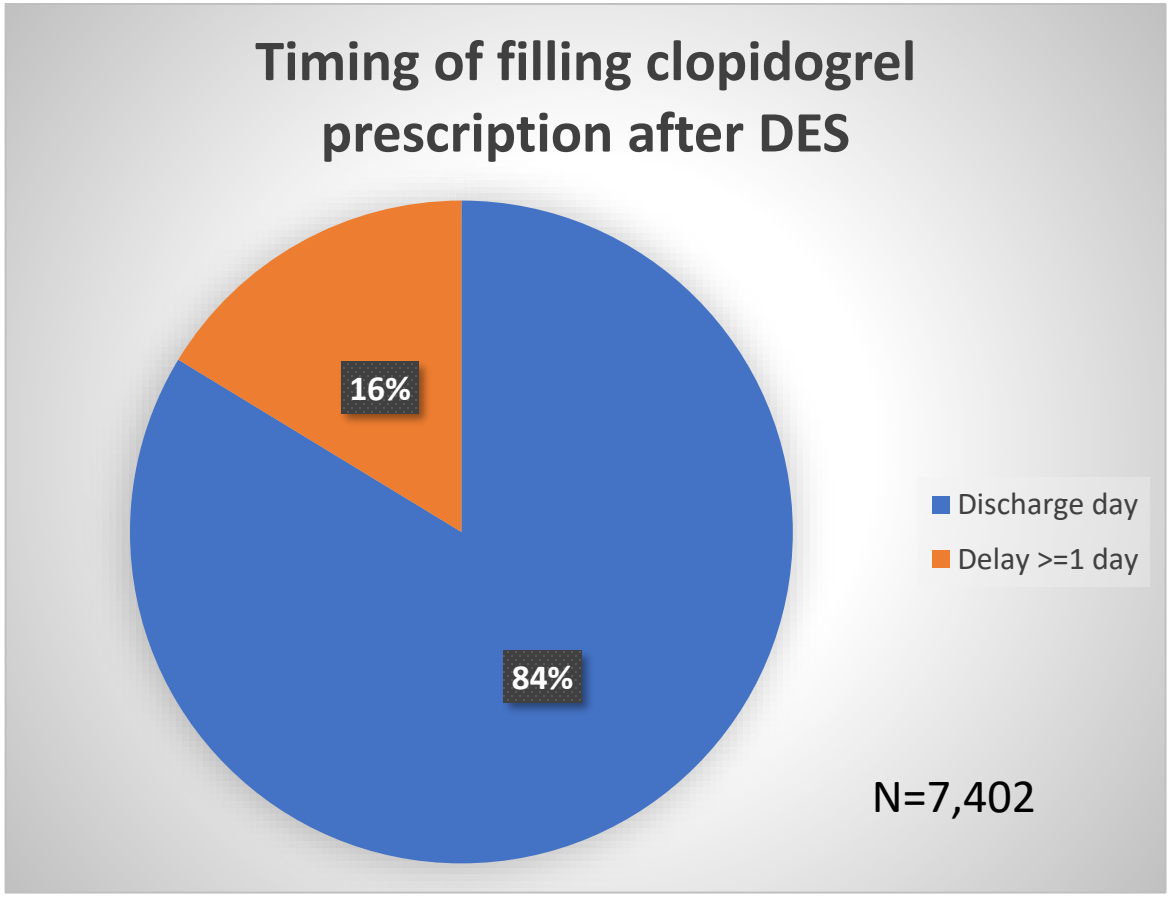
Calculation methods for adherence to multiple medications*	No. of studies, n (%)
MPR for multiple medications: In general, the numerator is the sum of days supplied for a medication (or combination of medications for MMA) and the denominator is the length of the study period. Most studies have at least one variant for either or both the numerator and the denominator	23 (15.6)
Average of ∑days of supply per medication/study period	4 (2.7)
∑days of supply for all medications/study period	4 (2.7)
∑days of supply for any medication/study period	2 (1.4)
Average of (∑days of supply/days between last prescription and first prescription) per medication; supply obtained in the last fill was excluded	2 (1.4)
Average of (∑days of supply/days between last prescription and first prescription) per medication	1 (0.7)
∑days of supply for multiple medications/(days between last prescription and first prescription + days of supply for last fill)	1 (0.7)
∑days of supply for all medications/(days between last prescription and first prescription + days of supply for last fill)	1 (0.7)
∑tablets dispensed/∑tablets recommended or prescribed	1 (0.7)
Weighted average of (∑days for supply/(days for which medication was needed − days spent in hospital)) per medication	1 (0.7)
Unclear how MPR to multiple medications was calculated	6 (4.1)

e Health 2019

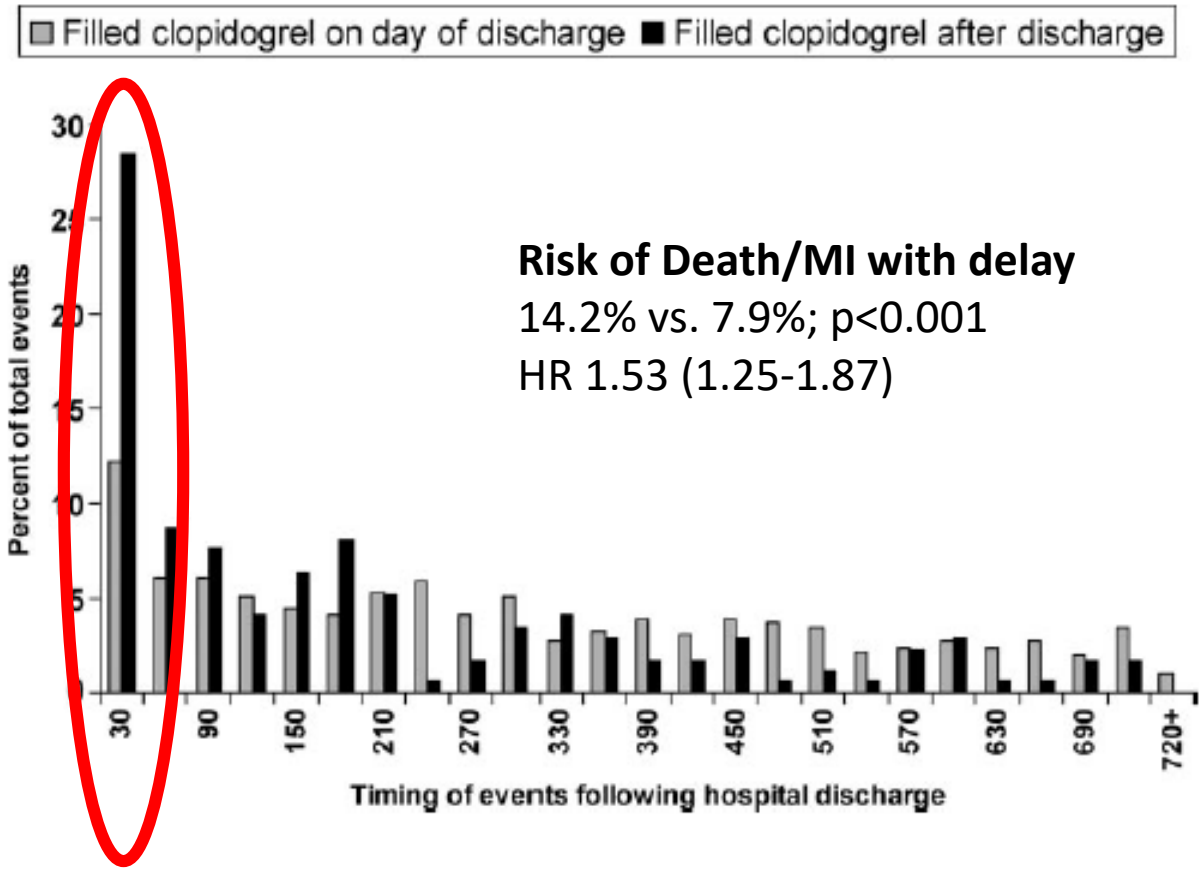
WHAT DOES REFILL DATA MEASURE?

- Patient's medication taking behavior over a period of time (i.e., months)
- Some assumptions:
  - prescription-refilling patterns correspond to the patient medication-taking behavior
  - medication is taken exactly as prescribed

Association of adherence and outcomes: Primary non-adherence and outcomes



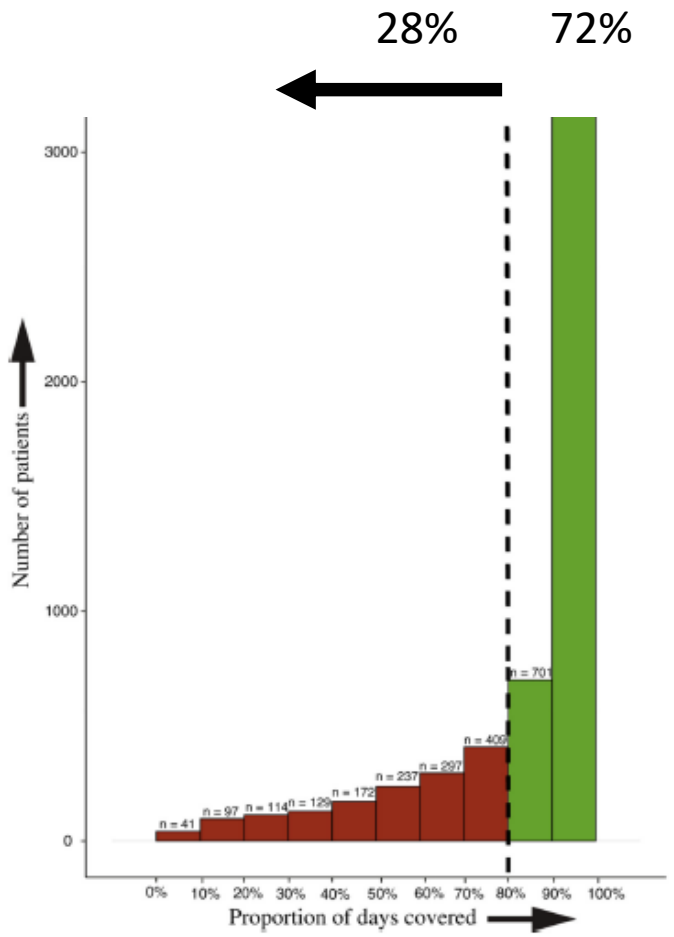
Median delay was 3 days



Risk of Death/MI with delay
14.2% vs. 7.9%; p<0.001
HR 1.53 (1.25-1.87)

Ho PM, Cir Cardiovasc Qual Outcomes 2010

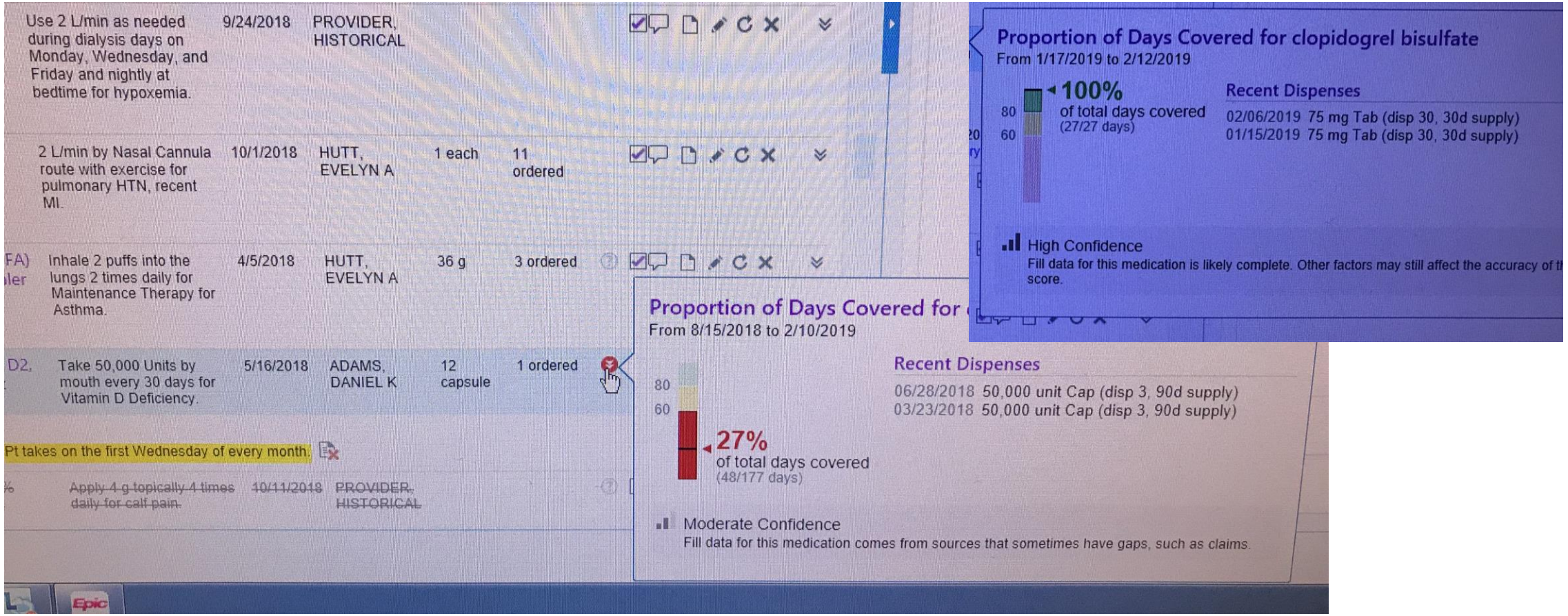
Secondary non-adherence and outcomes



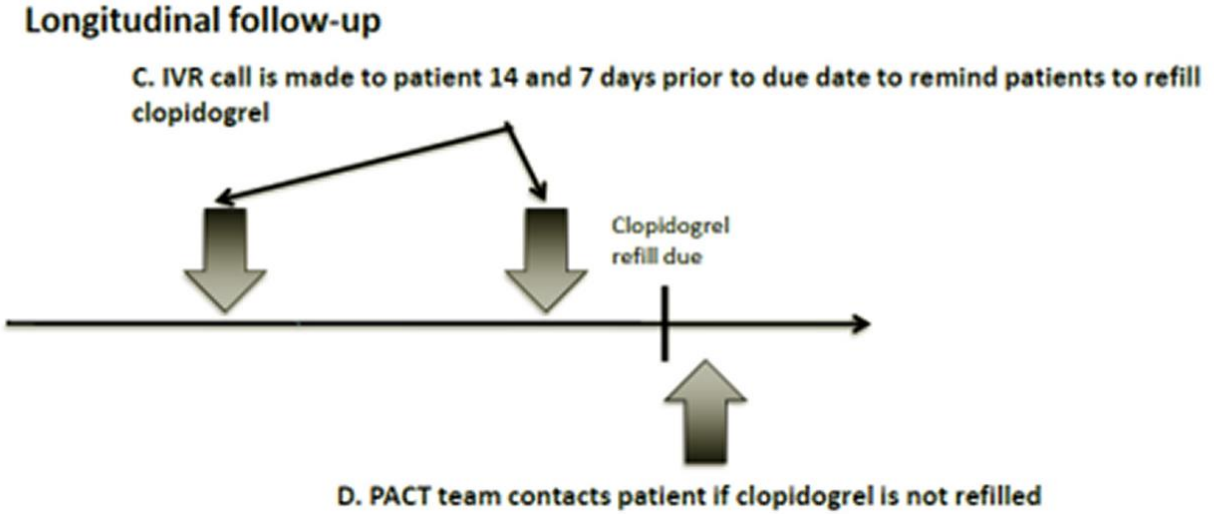
Shore S, et al. Am Heart J 2014.

Lower adherence was associated with increased risk for combined all-cause mortality and stroke (HR 1.13, 95% CI 1.07-1.19 per 10% decrease in PDC)

REFILL DATA IN THE EHR: EXAMPLE FROM EPIC



Using refill data for interventions



Contents lists available at ScienceDirect
Contemporary Clinical Trials
journal homepage: www.elsevier.com/locate/conclintrial

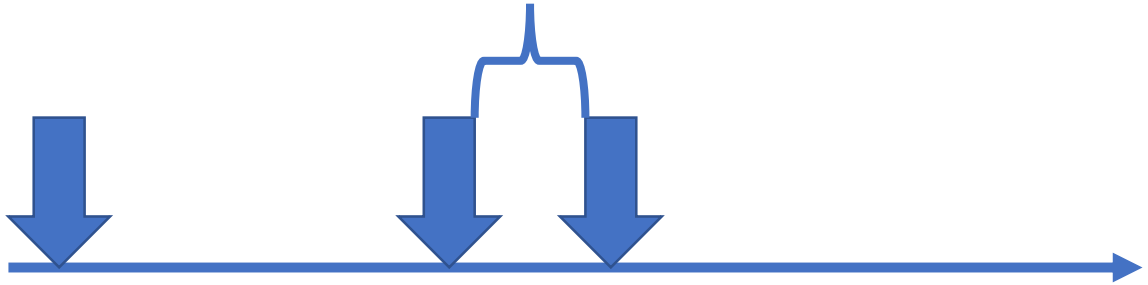
Improving anti-platelet therapy adherence in the Veterans Health Administration: A randomized multi-site hybrid effectiveness-implementation study protocol

Nudge

Personalized patient data and behavioral nudges to improve adherence to chronic cardiovascular medications

University of Colorado Denver | UCHealth | Denver VA | Denver Health

Wait for 7 days and if no refill
Patients are eligible for intervention



Date of last fill
For 90 days

Date of expected refill (D+90)

Concluding thoughts about pharmacy refills

- Measures longer term medication taking behavior
- Poor adherence as measured by refill data is associated with adverse outcomes
- Mostly used for retrospective assessment of adherence
- Emerging opportunities to use refill data prospectively in clinic and for adherence interventions

Measuring and Evaluating Medication Adherence

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Session III:
Measuring and Evaluating Medication Adherence

Neha Sheth Pandit, PharmD, AAHIVP, BCPS
Associate Professor, HIV/Infectious Diseases Pharmacotherapy
Vice Chair for Research and Scholarship
Department of Pharmacy Practice and Science
University of Maryland Baltimore School of Pharmacy

Objectives

- Discuss current practices in clinic settings to measure/evaluate adherence
- Discuss the role of medication reconciliation and its impact on adherence evaluation
- Describe the use of pharmacy claims data in clinical practice

Patient LP

- Mrs. P presents to clinic for 3 month follow-up appointment.
  - On an HIV single-tablet regimen x 3 years
  - Virologically suppressed; Last viral load 3 months ago.
- Patient Recall:
  - Are you taking your HIV regimen: YES
  - Last Dose: This morning
  - Any side effects or concerns: No
- Viral load repeated today; 6 month follow-up appt

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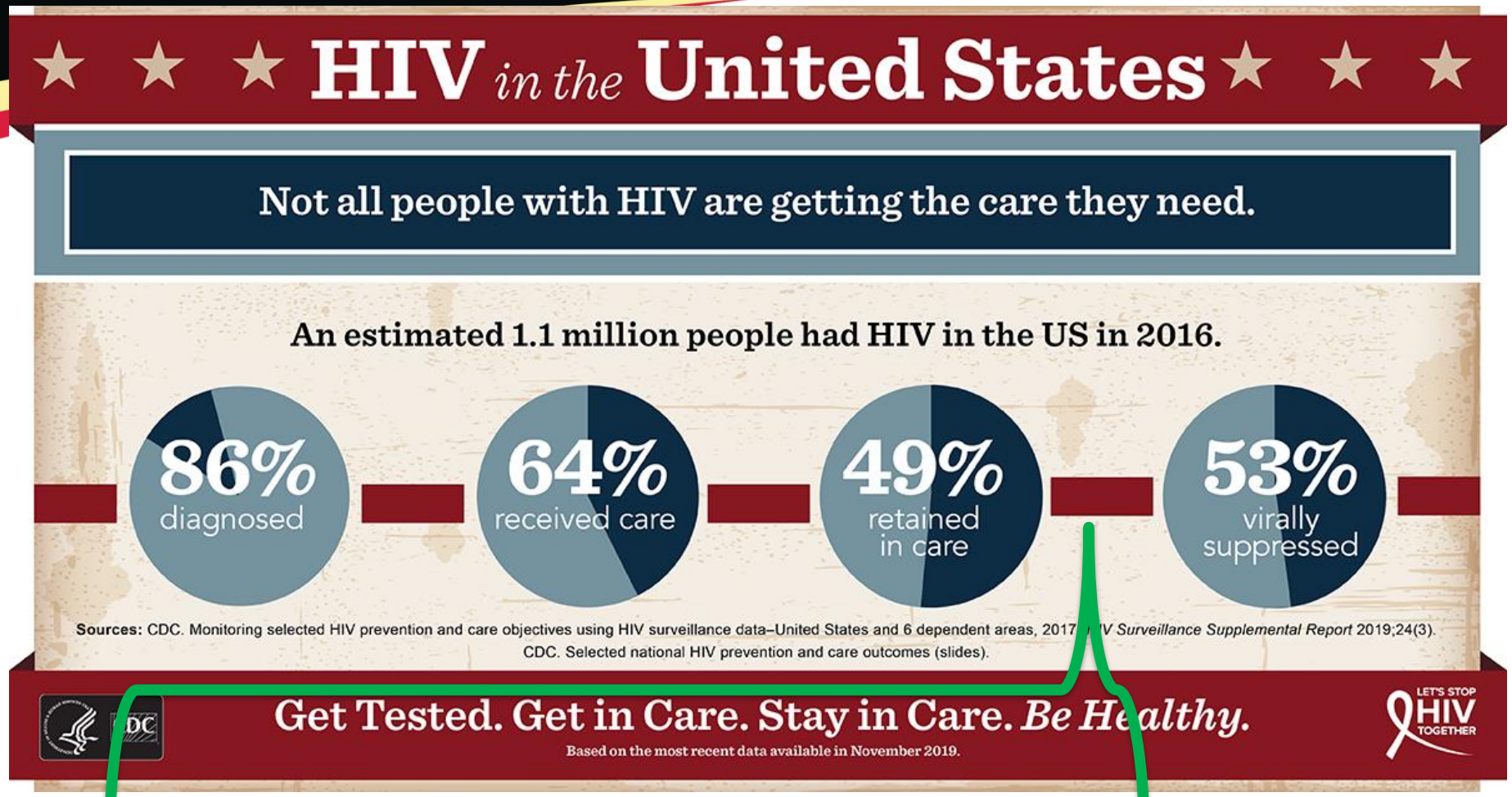
Patient LP

- HIV Viral Load: 54,000 copies/ml
- Housing:
  - 1 month ago partner died suddenly and now had to move in with son (wife and 3 kids)
- Transportation:
  - The partner was her transportation
  - Now relies on son
  - Previous pharmacy was closer to her home and currently has no way to get to pharmacy for refills
- Insurance:
  - Unemployed
  - Her partner use to handle the finances/insurance
  - Unclear if she has insurance
- Today's focus:
  - Her need to discuss her partners death
  - Son was not very supportive of their relationship
  - Son uninvolved with LP's health care



Prescribed ART → First Fill ART → Adherence

Assessing Adherence

Common:

- Subjective
  - Self-report
- Objective
  - Pharmacy refill data

Rare:

- Subjective
  - Health-care professional assessment
- Objective
  - Pill counts
  - Electronic monitoring
  - Biochemical measures
    - Drug concentration

Lam WY, et al. Biomed Res Int 2015;2015L217047.

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Real-life Medication Adherence

- Clinical Trials
  - ≥ 80% medication compliance = adherent
    - Most chronic disease states
  - True adherence in clinical trials
    - 43-78%
- Real-life Adherence
  - 50% of do not take as prescribed
- HIV Medication Adherence
  - Historically ≥ 95% adherence needed
  - Now closer to ≥ 80% due to more potent antiretroviral therapy
- It takes on average 66 days to make something habitual
  - 18 to 254 days
- Over time adherence tends to drop after 6 months

Gardner B, J Gen Pract 2012;62(605):664-666.
http://www.scriptyourfuture.org/wp-content/themes/cons/m/release.pdf
Osterberg L, et al. N Engl J Med 2005;353:487-97.
Brown MT, et al. Mayo Clin Proc 2011;86:304-14.
Kobin AB, et al. Ann Pharmacother 2011;45:372-9.

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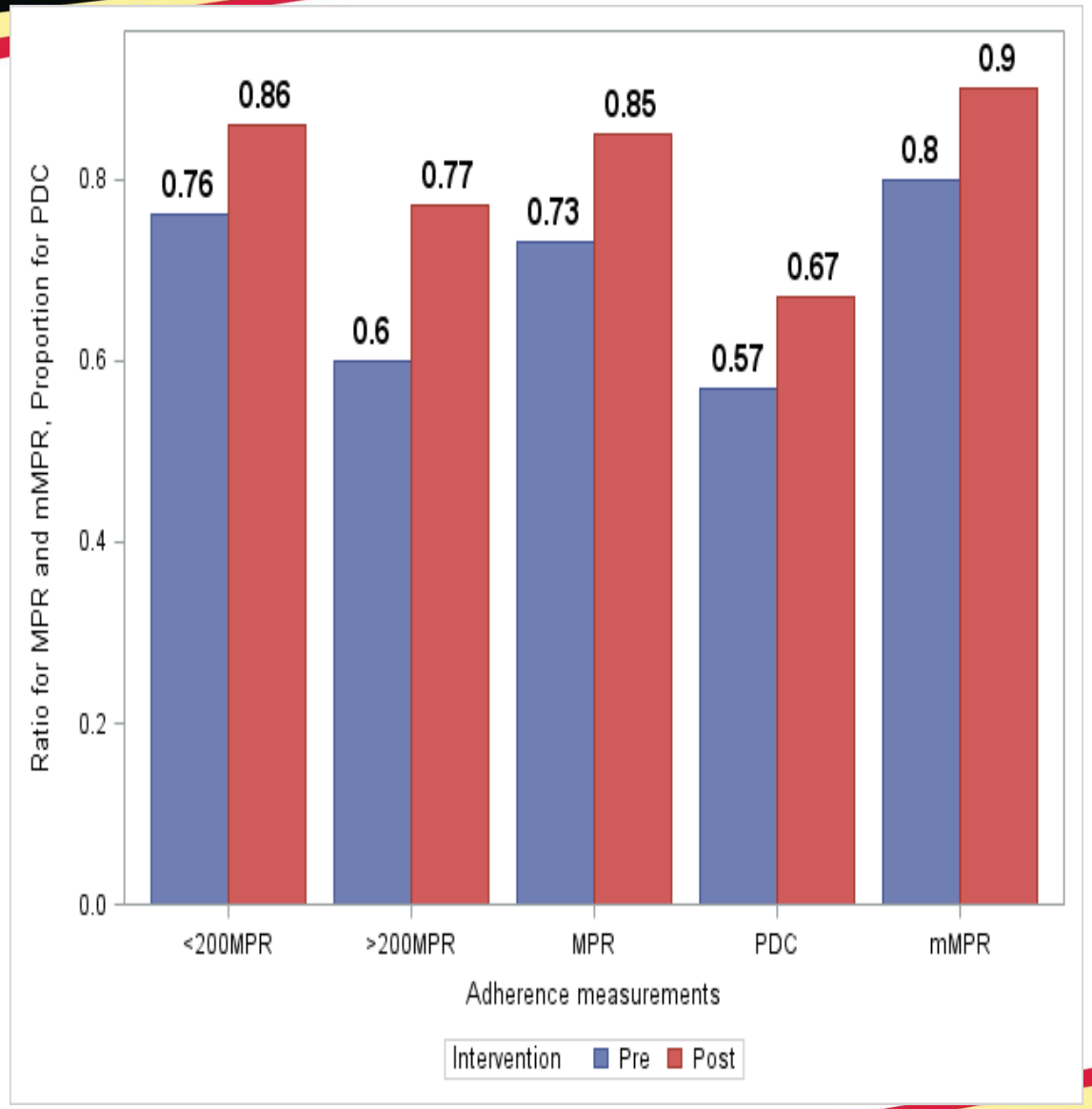
Medication Reconciliation

- Best Possible Medication History
  - Patient interview
  - Community Pharmacy
  - Prescribers
  - Self-prepared medication list
  - Pill bottles
  - Medical Records (Hospital/clinics)
- Discrepancies found in ~50% of medications reviewed
- Adherence increased from 51 to 67% after medication reconciliation
  - UP to 80% after counseling

Leguelinel-Blanche G, Eur J Intern Med 2014: 25(9):808-14.
Leguelinel-Blanche G, Medicine (Baltimore) 2015: 94(41):e1805.

LATE Study

- Hypothesis:
  - Informing prescribers about medication adherence, early detection of nonadherence can be made to improve overall adherence.
- A prospective, observational study
  - Medicaid patients prescribed antiretrovirals (ARV) at an HIV clinic who filled it >16% past the last refill's day's supply
    - 85% adherence
  - Maryland Medicaid 'soft stops'
  - Pharmacy provided the clinic with a list of these patients.
  - Adherence calculated for 6 months prior and after communication to clinic
- 130 patients includes
  - 78.5% had HIV RNA < 200 copies/ml


Ratio for MPR and mMPR, Proportion for PDC
0.0
0.2
0.4
0.6
0.8
0.76
0.86
0.6
0.77
0.73
0.85
0.57
0.67
0.8
0.9
<200MPR
>200MPR
MPR
PDC
mMPR
Adherence measurements
Intervention
Pre
Post

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AdhereP4

- Focusing on medication adherence by ensuring collaboration between **P**rescribers, **P**harmacists, **P**ayers, and health department **P**rograms (AdhereP4)

- Pharmacy claims data from Medicaid and AIDS Drug Assistance Program

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Interventions

- AIMS
- LINK LA
- Project nGage
- Rewarding Adherence Program (RAP)
- Short Term Cash and Food Assistance Program

https://www.cdc.gov/hiv/research/interventionresearch/compendium/ma/index.html

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Session III:
Measuring and Evaluating Medication Adherence

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Measuring and Evaluating Medication Adherence

Measuring Adherence to Oral Medication

Janet S. de Moor, PhD, MPH

Deputy Associate Director, Healthcare Delivery Research Program
Division of Cancer Control and Population Sciences
National Cancer Institute

NIH NATIONAL CANCER INSTITUTE

12/10/2019

Objectives

1. *Review measures of adherence used in health research.*
2. *Discuss the challenges of measuring adherence to oral cancer therapies.*
3. *Broach issues for the field to consider when designing research to improve adherence to new therapies.*

What is adherence and how is it measured?

- Adherence is a constellation of behaviors.
  - Initiation: taking the first dose.
  - Implementation: taking medication as prescribed.
  - Discontinuation: stopping medication.

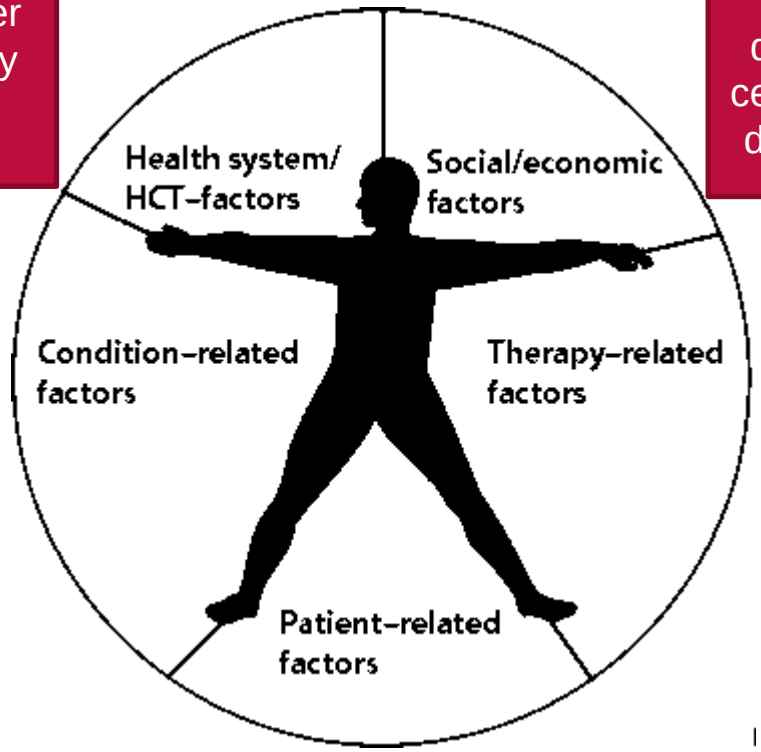
- The optimal measure of adherence depends on the adherence behavior and the research question.

Vrijens B., et al. Br J Clin Pharmacol. 2012 May; 73(5): 691-705.

The Drivers and Barriers of Medication Adherence are Complex

Patient-provider communication, provider awareness and capacity to address adherence issues

Financial constraints, distance from treatment center, literacy, competing demands, social support



Severity of disease and disability (physical, psychological, social, vocational)

Complexity of the intervention, duration of treatment, immediacy of benefits, side effects and availability of support.

Knowledge and beliefs about one's condition, motivation and self-efficacy to engage in illness-management behavior, and expectations regarding outcome of treatment/intervention.

Adherence to Long-Term Therapies Evidence for Action, World Health Organization, 2003.

Adherence Measurement Approaches

- Self-report
- Proxy-report
- Prescription fill data
- Dose or pill count
- Direct Observation

- Electronic drug monitoring (e.g., MEMS caps)
- Drug or drug metabolite level
- Biomarkers
- Smart technology (ingestible sensors)

Kronish IM, et al. Transl Behav Med. 2019 Oct 3. [Epub ahead of print]

The utility of different measurement approaches differs among adherence behaviors

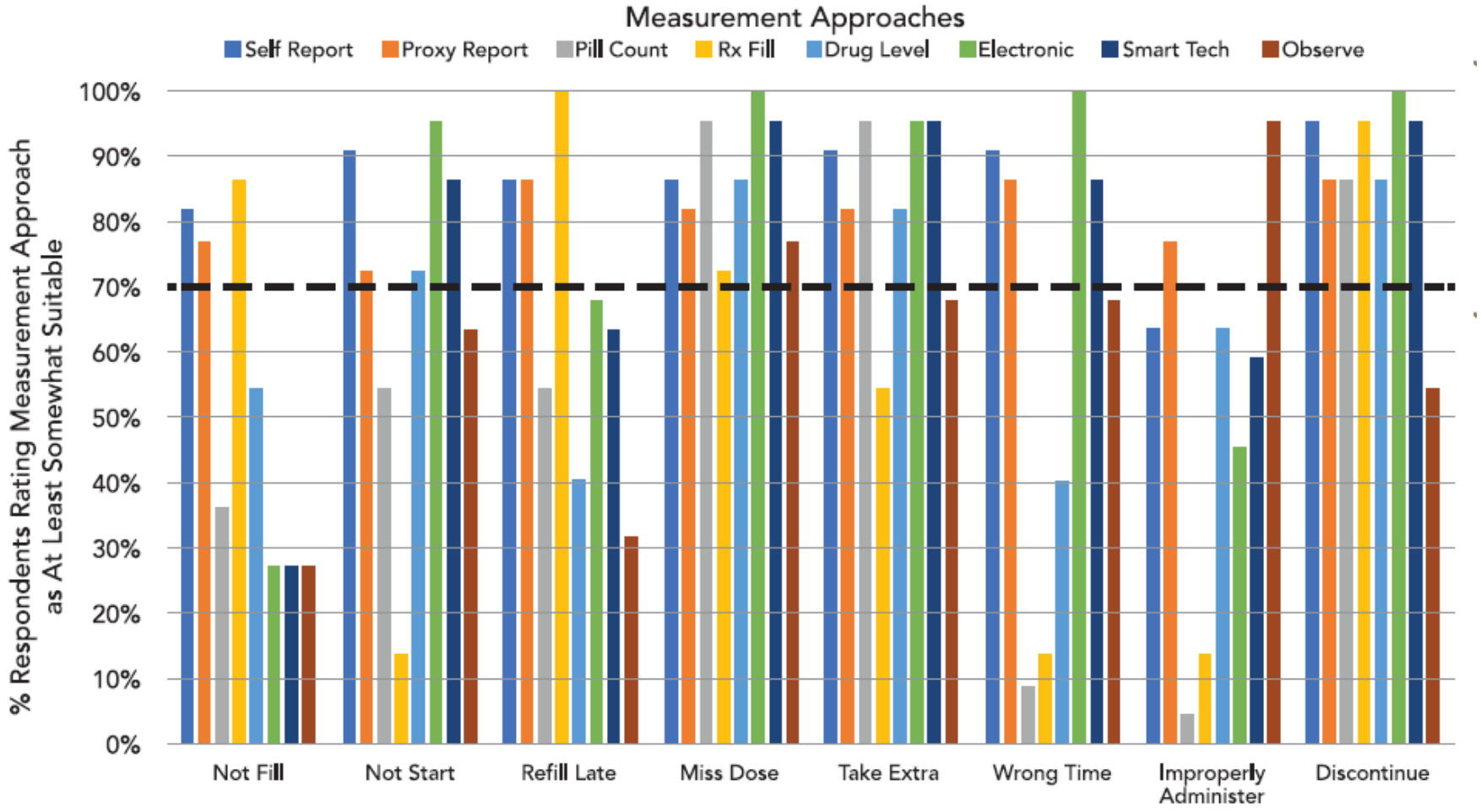


Fig. 1 | Percentage of respondents who rated each measurement approach "At Least Somewhat Suitable" for measuring each nonadherence behavior. Rx Fill = prescription refill data; Electronic = electronic drug monitoring; Smart Tech = smart technology such as digital pills or wearables; Observe = direct observation.

Kronish IM, et al. Transl Behav Med. 2019 Oct 3. [Epub ahead of print]

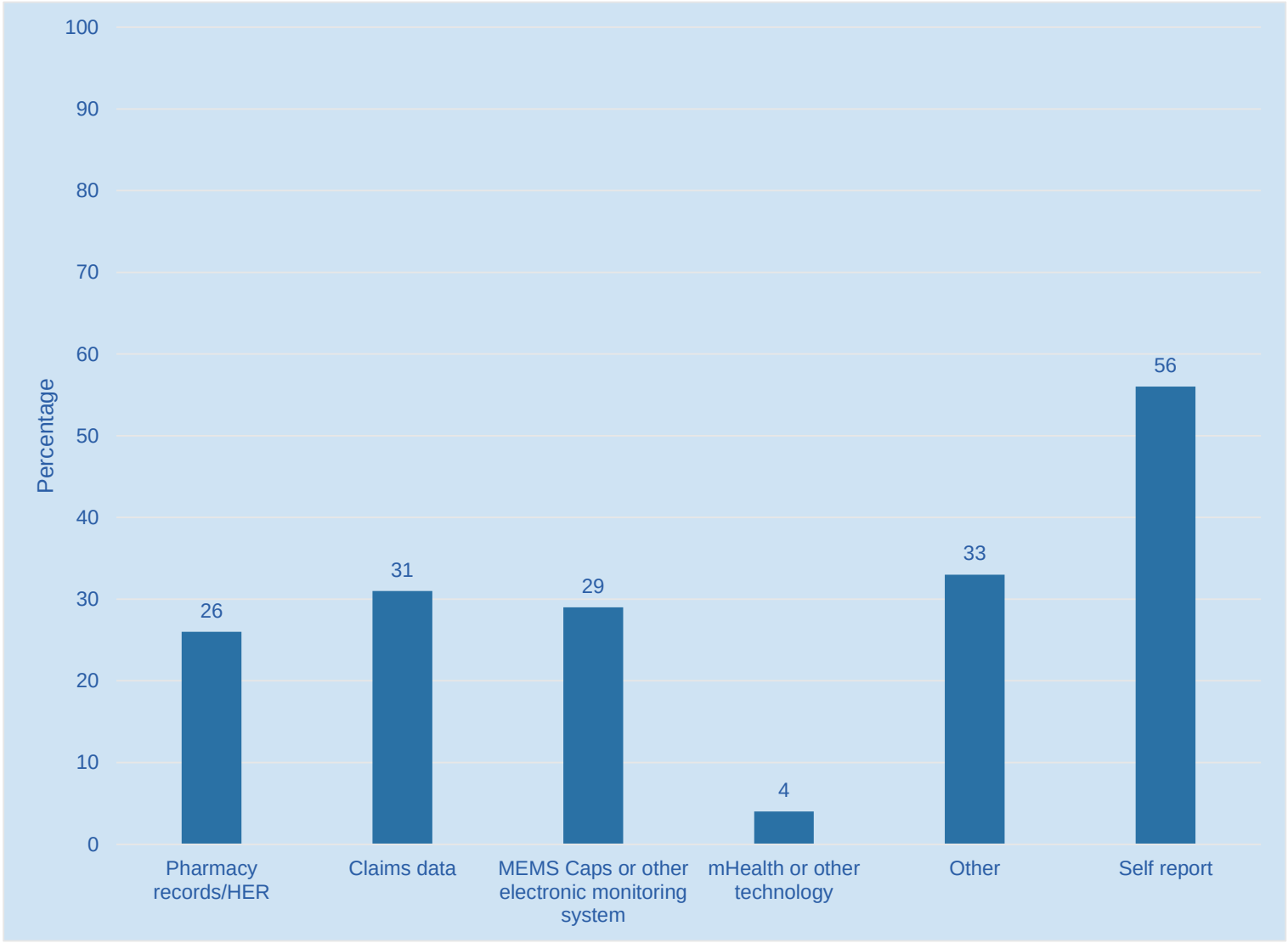
NIH Portfolio of Adherence Research: Behavioral and Health Services Studies.

- Conducted a portfolio analysis of NIH grants funded from FY17 (10/1/2016) to FY19 (5/30/2019)
- *Eligibility*: adherence related grants with a focus on human behavior or interaction with the healthcare system.
- Identified grants in Query, View, Report (QVR) using Research, Condition, and Disease Categorization (RCDC) search terms. Search terms included: “treatment adherence, therapy adherence, visit adherence, patient nonadherence, patient non-adherence, patient adherence, medication adherence, guideline adherence, exercise adherence, drug adherence, dietary adherence, diet adherence, behavioral adherence, behavior adherence, combined with 'Or’.”
- Included grants in which adherence was the primary or secondary aim of the study.

150 Grants examined adherence to prescribed medication including medication to manage cardiovascular disease, HIV, diabetes, mental health cancer, infectious disease, COPD, Asthma, and other chronic conditions.

Adherence measurement approaches in the NIH portfolio

Most grants included multiple measures of adherence. Self-report and MEMs Caps or other electronic monitoring system were the most common measurement approaches



Challenges of measuring adherence to oral cancer therapies

Complicated Regimens are Common in Cancer Treatment

Sun	Mon	Tues	Wed	Thurs	Fri	Sat.
Lenalidomide	Lenalidomide	Ixazomib Lenolidomide Dexamethazone	Lenalidomide	Lenalidomide	Lenalidomide	Lenalidomide
Lenalidomide	Lenalidomide	Dexamethazone	Rest	Rest	Rest	Rest
Rest	Rest	Ixazomib Lenolidomide Dexamethazone	Lenalidomide	Lenalidomide	Lenalidomide	Lenalidomide

Sun	Mon	Tues	Wed	Thurs	Fri	Sat
Capecitabine AM Capecitabine PM Lapatinib @ bed	Capecitabine AM Capecitabine PM Lapatinib @ bed	Capecitabine AM Capecitabine PM Lapatinib @ bed	Capecitabine AM Capecitabine PM Lapatinib @ bed	Capecitabine AM Capecitabine PM Lapatinib @ bed	Capecitabine AM Capecitabine PM Lapatinib @ bed	Capecitabine AM Capecitabine PM Lapatinib @ bed
Capecitabine AM	Lapatinib @ bed	Lapatinib @ bed	Lapatinib @ bed	Lapatinib @ bed	Lapatinib @ bed	Capecitabine AM

Adherence to Oral Cancer Agents

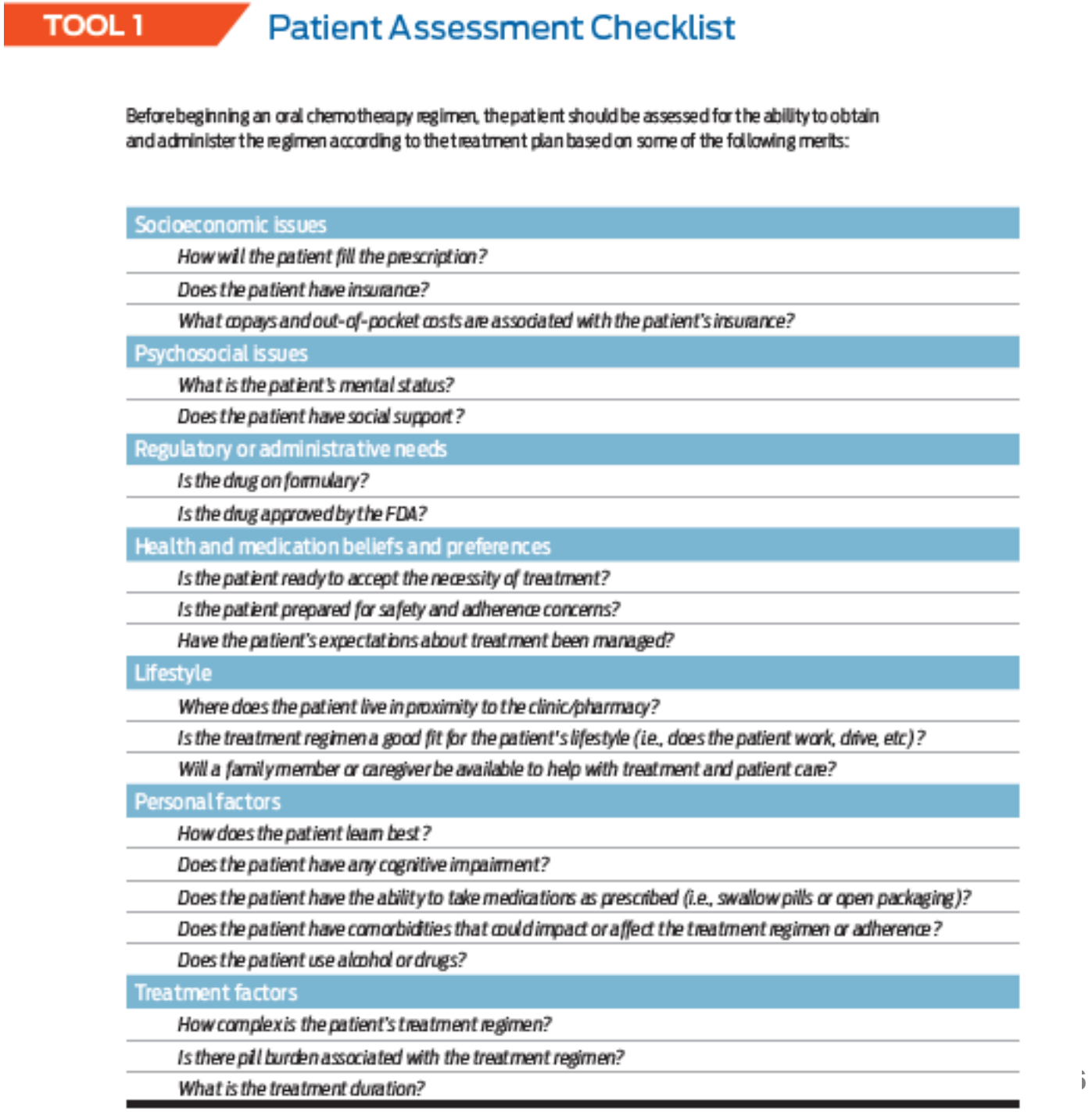
- Adherence ranges from 46-100% (other reviews have cited lower estimates).
- There is no clinically defined threshold for medication adherence to oral antineoplastic therapies, which complicates measurement and systematic reviews of the literature.
- The following measures are used to assess adherence to oral cancer agents.
  - Plasma drug level (1.6%), electronic monitoring (11.1%), pharmacy or insurance records (50.8%), pill count (7.9%), medical chart review (4.8%), self report (39.7%), physician report (11.1%), proxy report (4.8%).

Greer JA, et al. The Oncologist 2016; 21: 354-376.

Adherence to Oral Cancer Agents

- Discrepancies between studies are likely due to inconsistent methodology.
  - Disparate definitions of what constitutes adherence.
  - Failure to distinguish between different adherence behaviors.
  - Timing and frequency of data collection.
  - Differences in measurement approach.

Oncology Nursing Society Oral Adherence Toolkit: Patient Assessment Checklist



TOOL 1

Patient Assessment Checklist

Before beginning an oral chemotherapy regimen, the patient should be assessed for the ability to obtain and administer the regimen according to the treatment plan based on some of the following merits:

Socioeconomic issues
How will the patient fill the prescription?
Does the patient have insurance?
What copays and out-of-pocket costs are associated with the patient's insurance?
Psychosocial issues
What is the patient's mental status?
Does the patient have social support?
Regulatory or administrative needs
Is the drug on formulary?
Is the drug approved by the FDA?
Health and medication beliefs and preferences
Is the patient ready to accept the necessity of treatment?
Is the patient prepared for safety and adherence concerns?
Have the patient's expectations about treatment been managed?
Lifestyle
Where does the patient live in proximity to the clinic/pharmacy?
Is the treatment regimen a good fit for the patient's lifestyle (i.e., does the patient work, drive, etc)?
Will a family member or caregiver be available to help with treatment and patient care?
Personal factors
How does the patient learn best?
Does the patient have any cognitive impairment?
Does the patient have the ability to take medications as prescribed (i.e., swallow pills or open packaging)?
Does the patient have comorbidities that could impact or affect the treatment regimen or adherence?
Does the patient use alcohol or drugs?
Treatment factors
How complex is the patient's treatment regimen?
Is there pill burden associated with the treatment regimen?
What is the treatment duration?

Oncology Nursing Society Oral Adherence Toolkit: Methods to encourage patient adherence

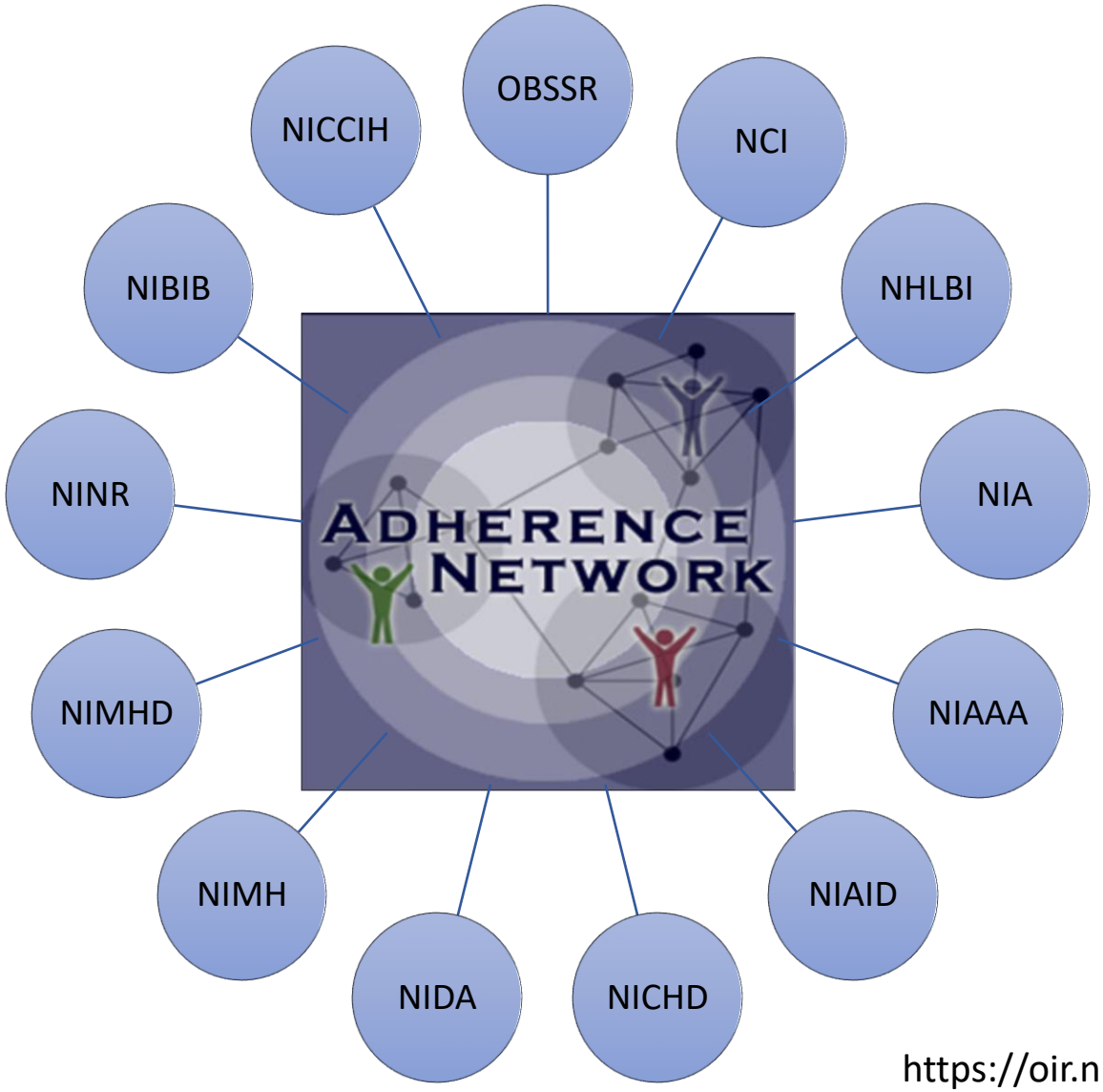
- Calendar or daily medication checklist
- Pill diaries
- Patient and family education
- Establishing routine, which includes drug administration
- Home psychological support
- Pillboxes with multiple compartments (as packaging form and storage needs permit)
- Electronic reminders
  - Alarms on clocks, timers and cell phones
  - Smartphone applications
  - Glowing or electronic pillboxes
  - Text message reminder
  - Automated voice recording (phone call) reminder
  - Medication-dispensing machines

Funding Opportunities for Adherence Research

- PA-18-004/PA-18-014 Oral Anticancer Agents: Utilization, Adherence, and Health Care Delivery
  - The purpose of this funding opportunity announcement (FOA) is to encourage research grant applications to: (1) assess and describe the current state of oral anticancer medication utilization, delivery, and adherence; (2) identify structural, systemic, and psychosocial barriers to adherence; and (3) develop models and strategies to improve safe and effective delivery of these agents so that clinical outcomes are optimized.
  - Expires January 8, 2020.

Funding Opportunities for Adherence Research

- PA-18-722/PA-18-723 Improving Patient Adherence to Treatment and Prevention Regimens to Promote Health
  - This funding opportunity announcement (FOA) calls for research grant applications that address patient adherence to treatment and prevention regimens to promote health outcomes.



National Institutes of Health Adherence Research Network

Mission:

- Provide leadership, vision, and support to strengthen adherence research funded by the NIH
- Evaluate and disseminate scientific information & funding opportunities for adherence research at NIH

https://oir.nih.gov/sigs/adherence-research-network-scientific-interest-group

Considerations for future research

Issues for the field to consider when designing research to improve adherence to new therapies.

- Adherence is a complex set of behaviors determined by a multi-level constellations of factors. Our interventions and methods should reflect that.
- Many chronic diseases (i.e., cancer) are diagnosed in older adults. The interventions and monitoring systems put in place need to be responsive to the relationship older adults have with technology.

Issues for the field to consider when designing research to improve adherence to new therapies

- Successfully integrating adherence data captured through remote monitoring into clinical practice raises logistical, legal, and economic considerations.
  - Integrating data into clinical workflow
  - Addressing increase in providers' workload
  - Managing alerts during off-duty hours
  - Reimbursement for time spent responding to alerts
  - Protecting patient's privacy and complying with the Health Insurance Portability and Accountability Act (HIPAA)

www.cancer.gov

www.cancer.gov/espanol

Measuring and Evaluating Medication Adherence

Break

Study Designs to Evaluate Tracking, Improvement in Medication Adherence, and Impact on Clinical Outcomes

STUDY DESIGNS TO EVALUATE MEDICATION ADHERENCE TRACKING AND IMPROVEMENT STRATEGIES

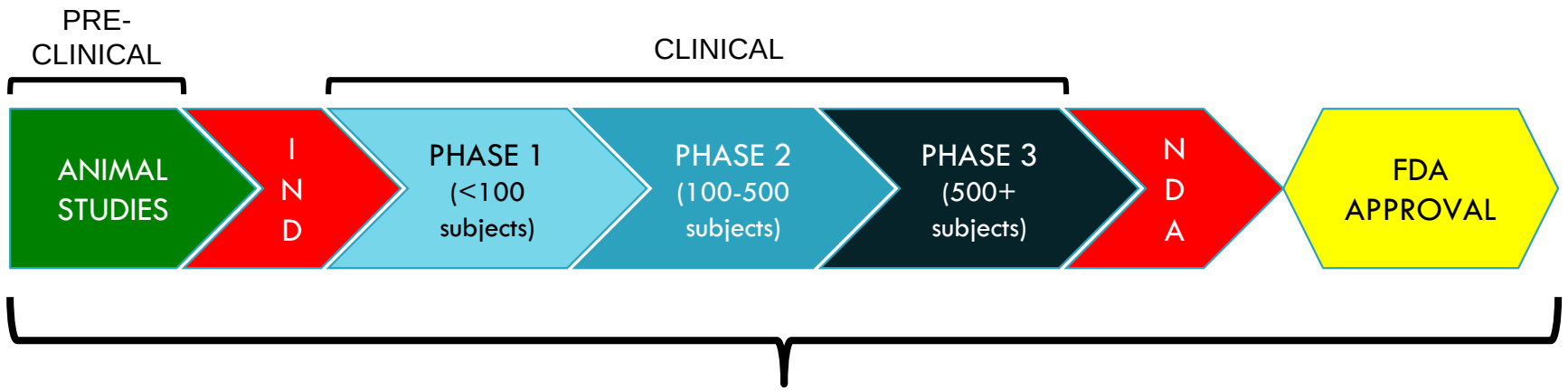
Niteesh K. Choudhry, MD, PhD

HARVARD UNIVERSITY
Professor | Harvard Medical School and Harvard T.H. Chan School of Public Health

BRIGHAM AND WOMEN'S HOSPITAL, DEPARTMENT OF MEDICINE
Executive Director | Center for Healthcare Delivery Sciences
Associate Physician | Division of Pharmacoepidemiology and Pharmacoeconomics and Hospital Medicine Unit

New diagnostics and therapeutics are subject to a strict regulatory process

IN THE CASE OF PRESCRIPTION DRUGS:

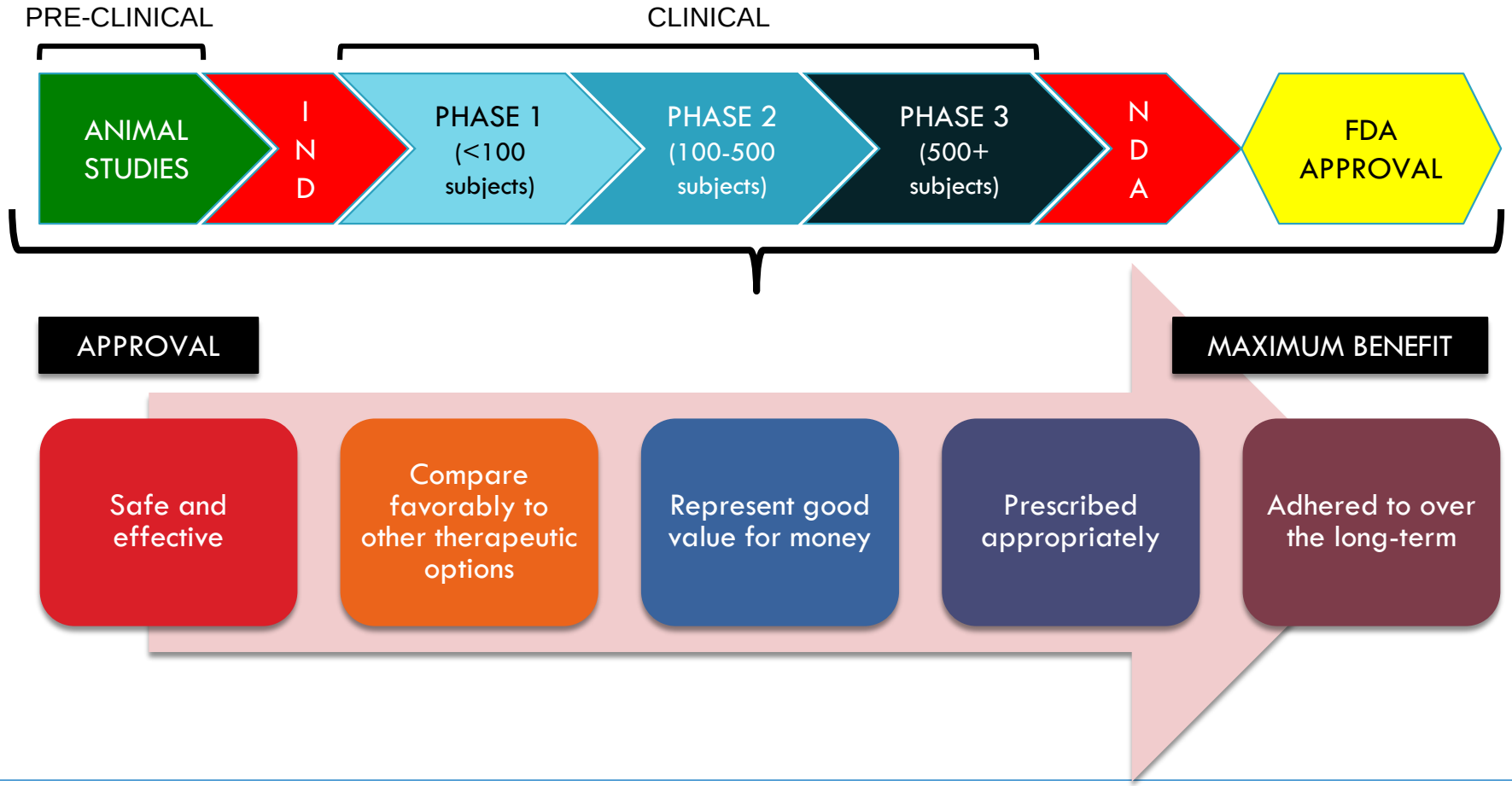


SAFE AND EFFECTIVE FOR USE

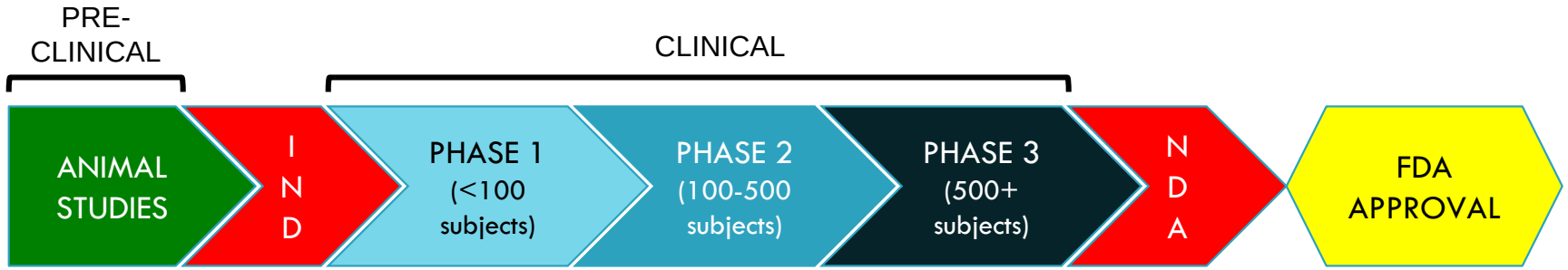
≠

MAXIMUM VALUE

Many things must happen for new technologies to improve human health



Trials to support regulatory approval should differ from those intended to evaluate adherence interventions



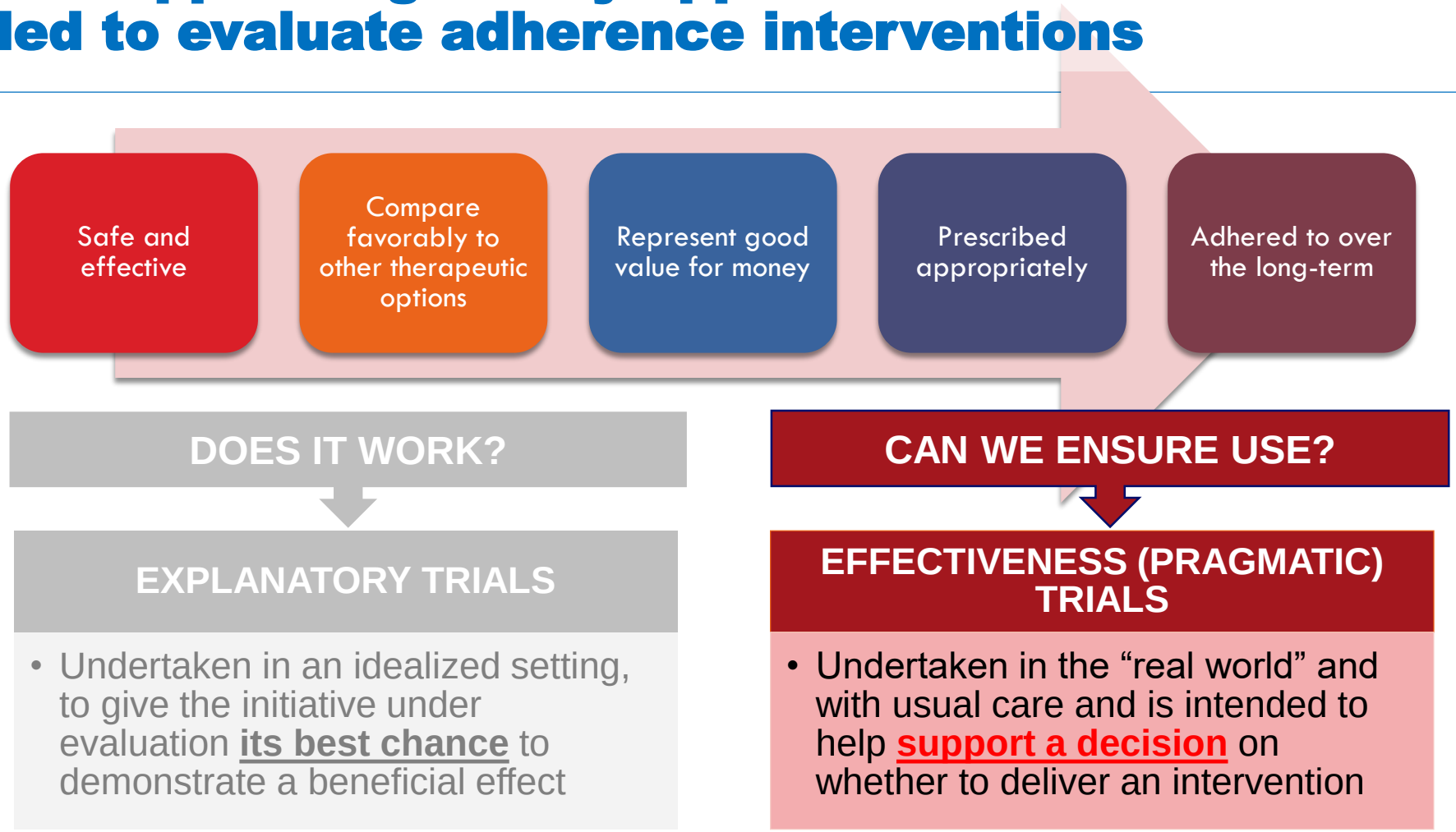
DOES IT WORK?

EXPLANATORY TRIALS

- Undertaken in an idealized setting, to give the initiative under evaluation **its best chance** to demonstrate a beneficial effect

SOURCE: BMJ 2015;350:h2147 | doi: 10.1136/bmj.h2147

Trials to support regulatory approval should differ from those intended to evaluate adherence interventions



SOURCE: BMJ 2015;350:h2147 | doi: 10.1136/bmj.h2147

Several features are more common in effectiveness (pragmatic) trial designs

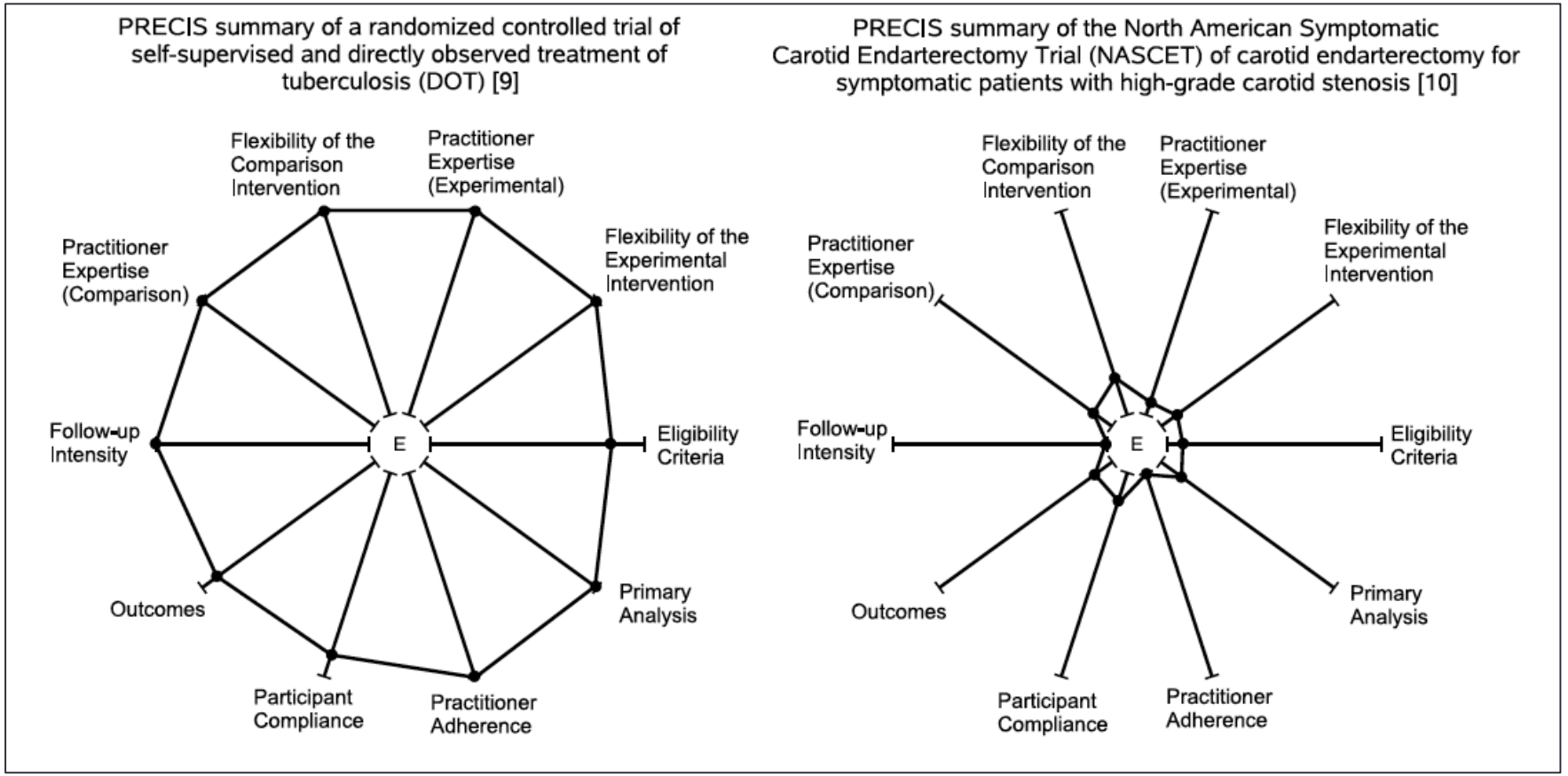
PRECIS-2

Domain	Description
Eligibility	To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?
Recruitment	How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?
Setting	How different are the settings of the trial from the usual care setting?
Organization	How different are the resources, provider expertise, and the organization of care delivery in the intervention arm of the trial from those available in usual care?
Flexibility (delivery)	How different is the flexibility in how the intervention is delivered and the flexibility anticipated in usual care?
Flexibility (adherence)	How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?
Follow-up	How different is the intensity of measurement and follow-up of participants in the trial from the typical follow-up in usual care?
Primary outcome	To what extent is the trial's primary outcome directly relevant to participants?
Primary analysis	To what extent are all data included in the analysis of the primary outcome?

SOURCE: BMJ 2015;350:h2147 | doi: 10.1136/bmj.h2147

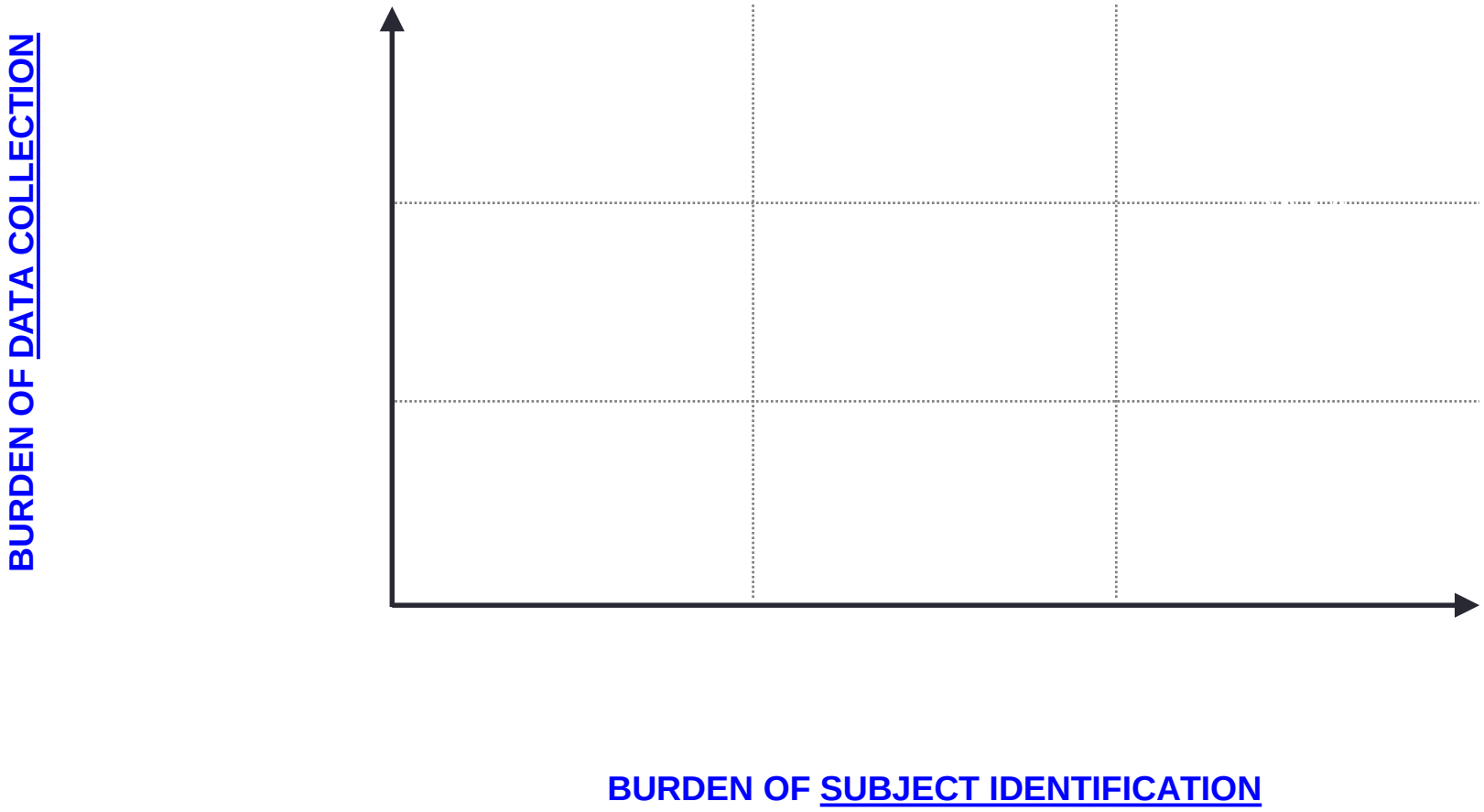
The PRECIS Tool

PRAGMATIC/EFFECTIVENESS TRIAL DESIGNS



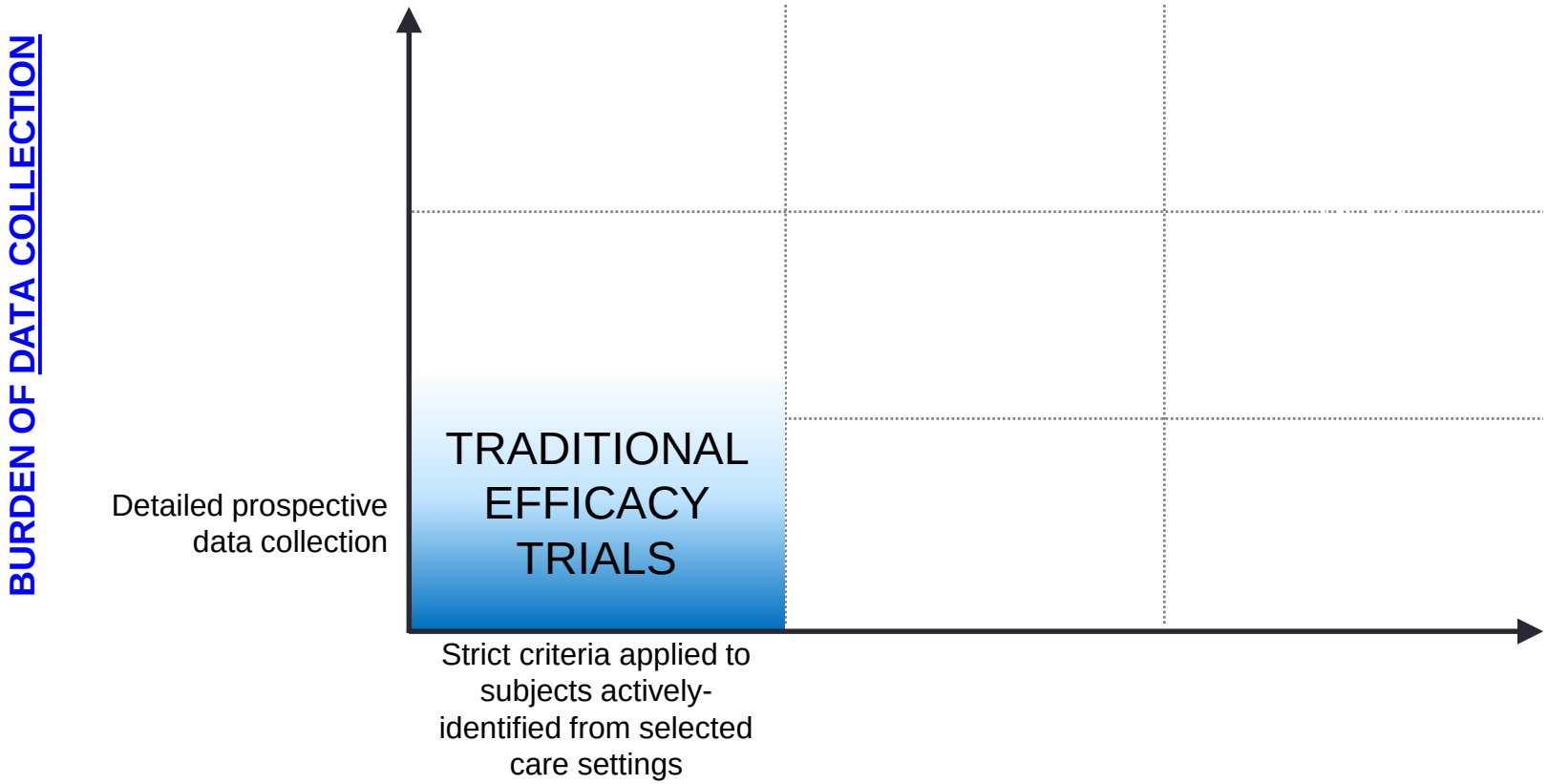
SOURCE: SOURCE: Journal of Clinical Epidemiology 2009; 62: 464-475

How can pragmatic trials be made more efficient?



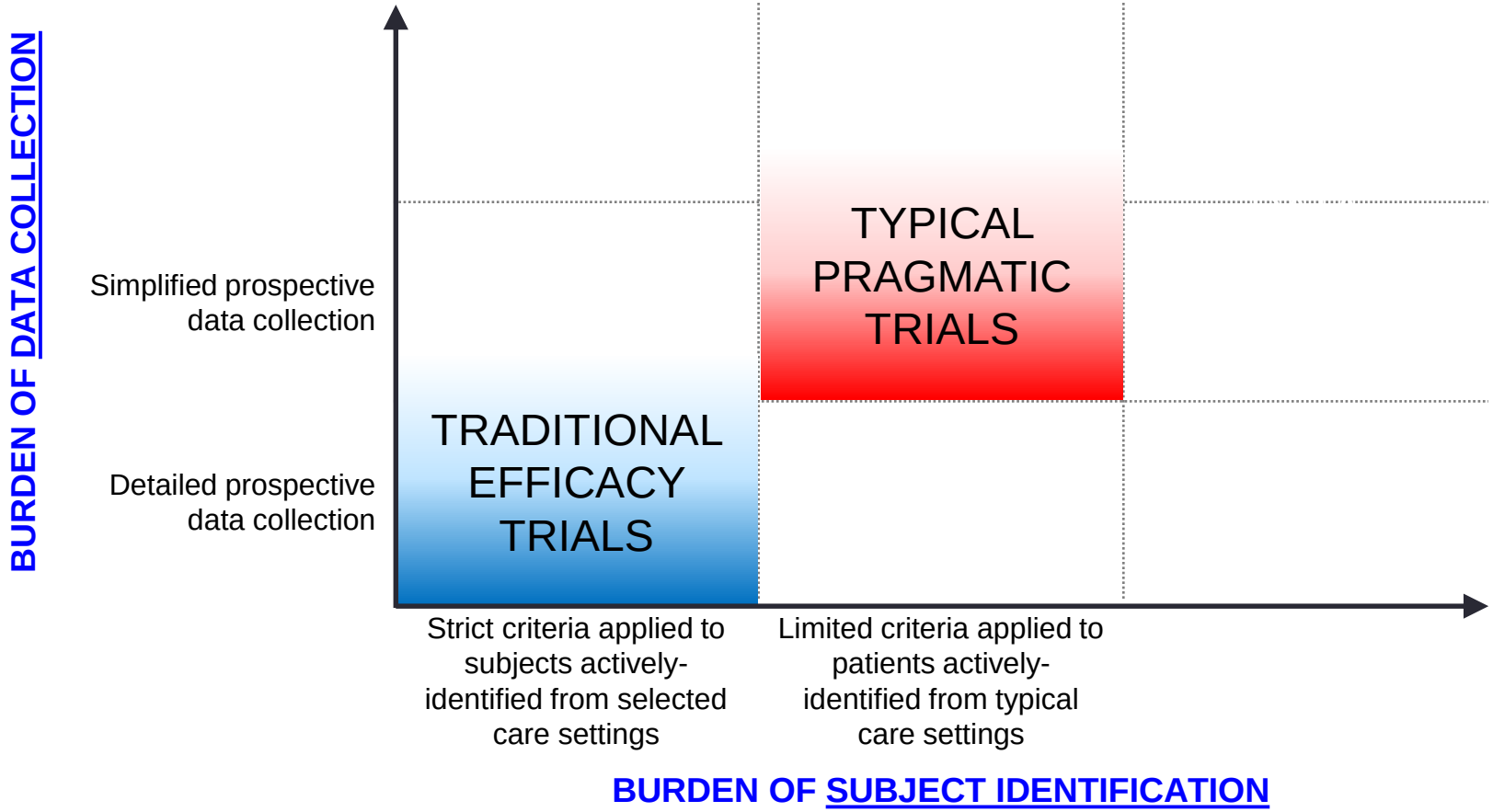
SOURCE: Choudhry NK. N Engl J Med 2017; 377: 957-964

How can pragmatic trials be made more efficient?



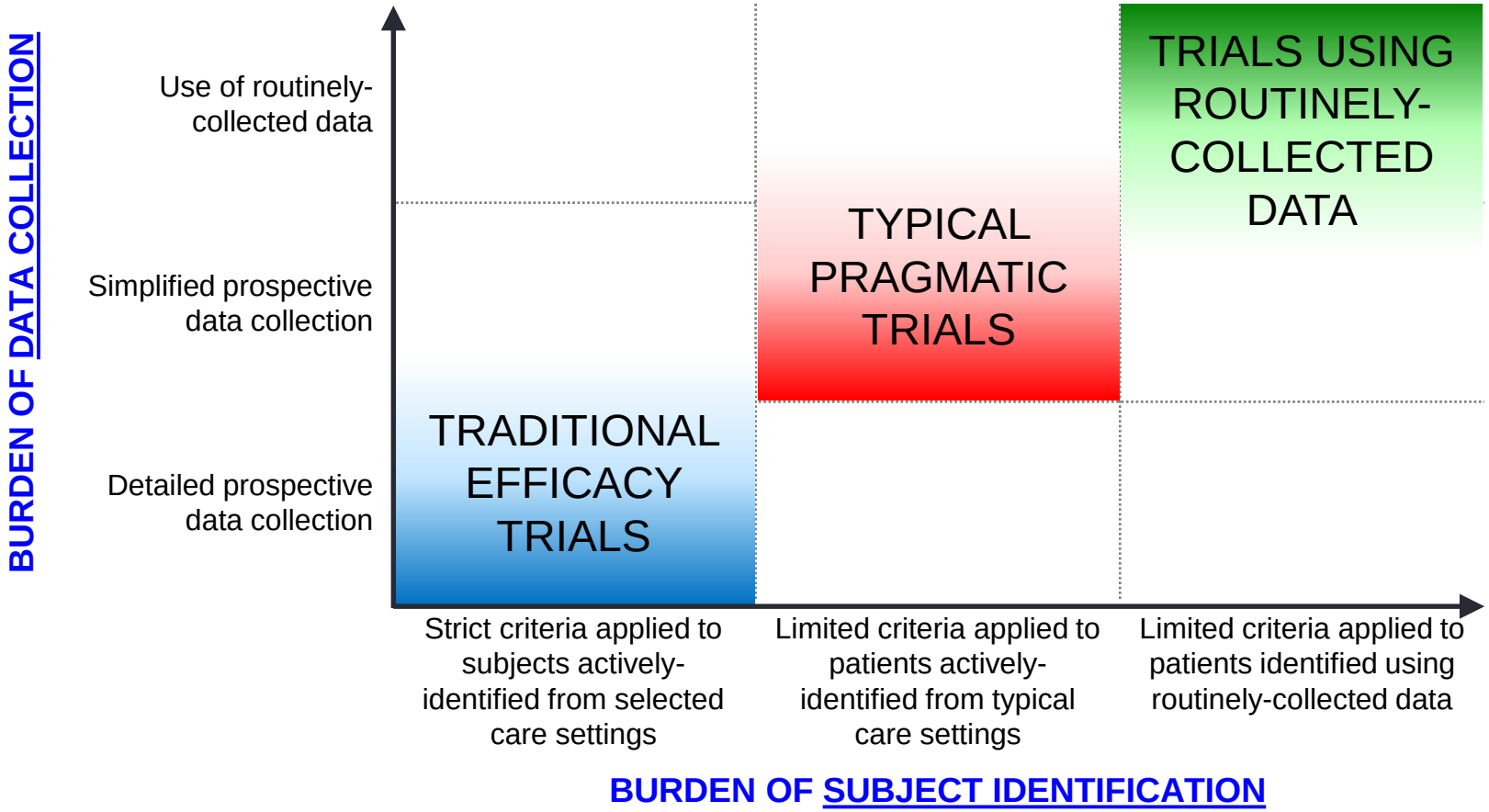
SOURCE: Choudhry NK. N Engl J Med 2017; 377: 957-964

How can pragmatic trials be made more efficient?



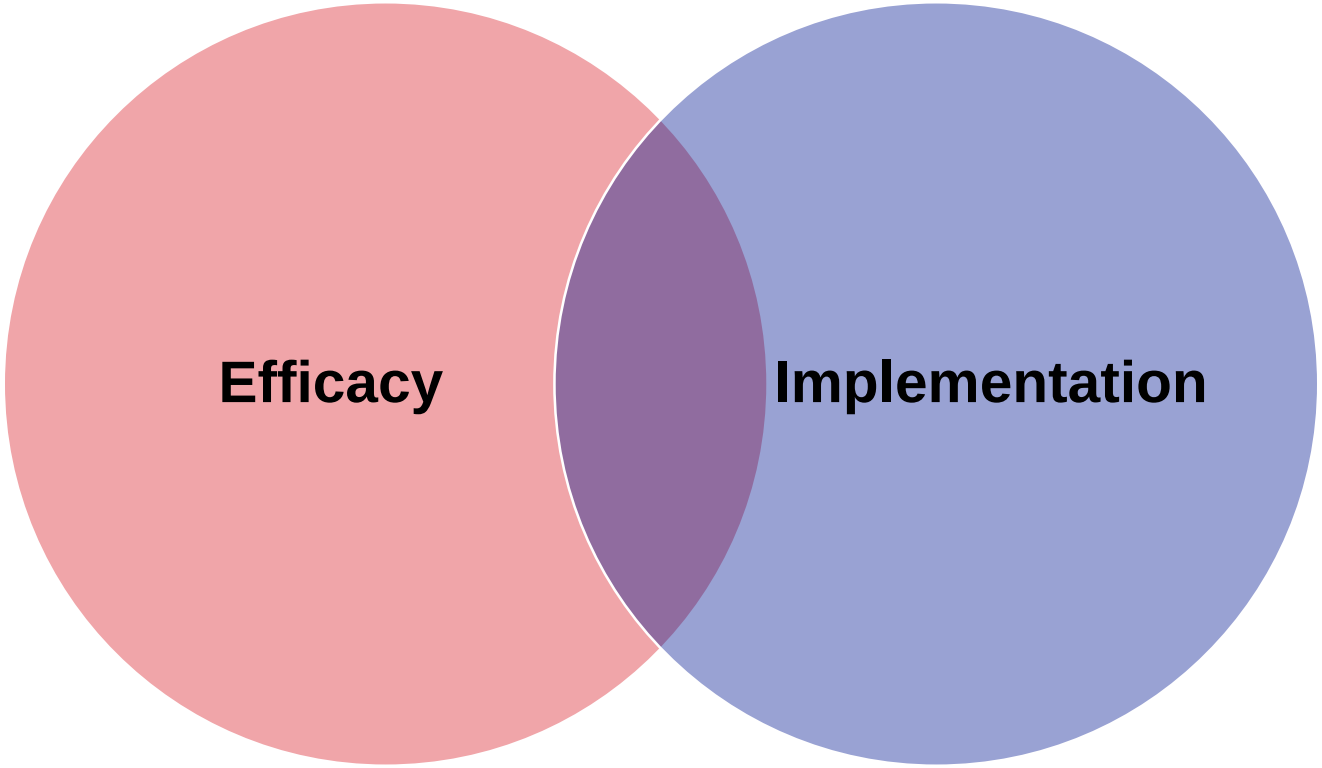
SOURCE: Choudhry NK. N Engl J Med 2017; 377: 957-964

How can pragmatic trials be made more efficient?



SOURCE: Choudhry NK. N Engl J Med 2017; 377: 957-964

Efficacy and implementation could be evaluated simultaneously



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Study Designs to Evaluate Tracking, Improvement in Medication Adherence, and Impact on Clinical Outcomes

Real World Relevance Without Sacrificing Rigor

Trial Design Considerations for Adherence Interventions

Michael Stirratt, Ph.D.
NIMH Division of AIDS Research + NIH Adherence Network

Medication Adherence: Landscape, Strategies, and Evaluation Methods
December 10, 2019

National Institute of Mental Health

Better Intervention Science Needed

- Cochrane review of 182 adherence intervention RCTs (randomized clinical trials)
- **Many compromised by biases or inadequate power**
- **Among 18 "low-bias" RCTs, only 5 impacted behavior and clinical outcomes**
- "Current methods of improving medication adherence for chronic health problems are mostly complex and not very effective, so that the full benefits of treatment cannot be realized."

Nieuwlaat et al, Cochrane Report, 2014

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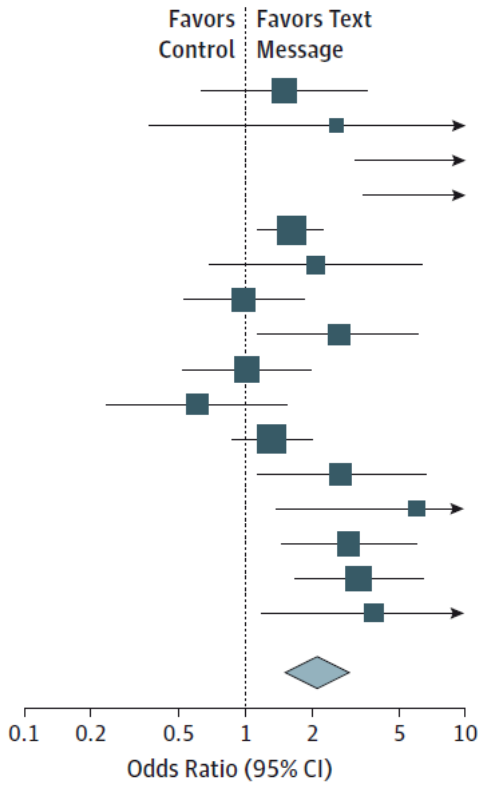
Better Intervention Science Needed

Figure 2. Meta-analysis of the Effect of a Mobile Telephone Text Message Intervention on Medication Adherence

Source	Statistics for Each Study		
	Odds Ratio	(95% CI)	*P* Value
Márquez Contreras et al,[43] 2004	1.508	(0.631-3.605)	.36
da Costa et al,[29] 2012	2.571	(0.371-17.831)	.34
Hardy et al,[30] 2011[a]	21.131	(3.161-141.237)	.002
Khonsari et al,[31] 2015[a]	12.273	(3.405-44.236)	<.001
Lester et al,[32] 2010	1.612	(1.144-2.271)	.006
Lv et al,[21] 2012	2.074	(0.686-6.251)	.20
Lua and Neni,[33] 2013	0.985	(0.535-1.812)	.96
Maduka and Tobin-West,[34] 2013	2.644	(1.135-6.160)	.02
Mbuagbaw et al,[35] 2012	1.026	(0.519-2.026)	.94
Park et al,[36] 2014	0.610	(0.236-1.585)	.31
Pop-Eleches et al,[37] 2011	1.330	(0.882-2.005)	.17
Quilici et al,[38] 2013	2.705	(1.109-6.596)	.03
Strandbygaard et al,[39] 2010	6.018	(1.368-26.466)	.02
Vervloet et al,[40] 2012	2.959	(1.448-6.046)	.003
Wald et al,[41] 2014	3.267	(1.686-6.331)	<.001
Wang et al,[42] 2014	3.857	(1.180-12.606)	.03
Overall	2.107	(1.517-2.926)	<.001



Meta-analysis:

Text message interventions improve medication adherence

Caveat:

"These results should be interpreted with caution given the short duration of trials and reliance on self-reported medication adherence measures."

Thakkar 2016 JAMA

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Better Intervention Science Needed

IOM 2001 Crossing the Quality Chasm

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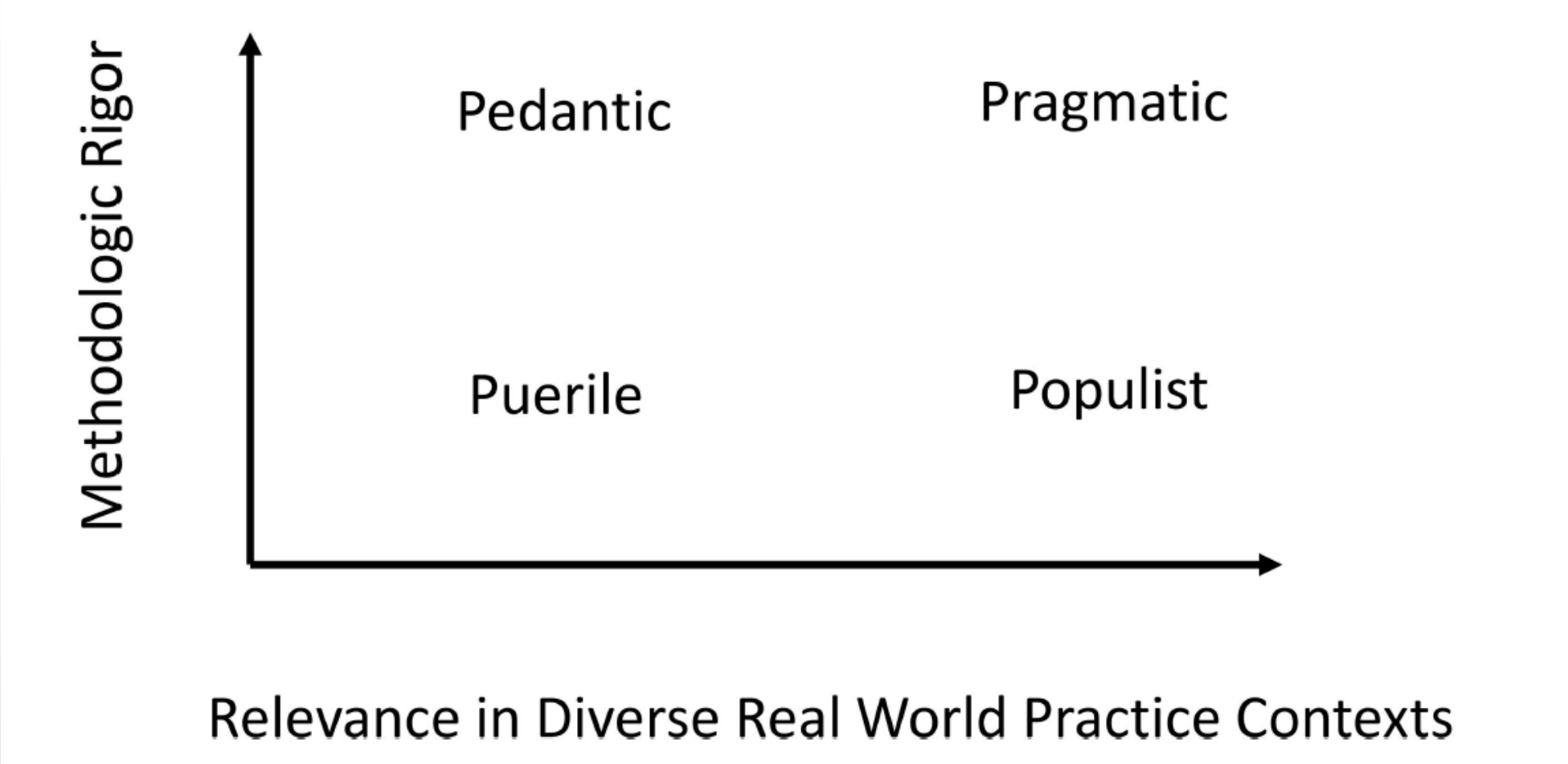
Relevance and Rigor via Pragmatic Trials



Geng, Peiris, & Kruk 2017 PLOS Medicine

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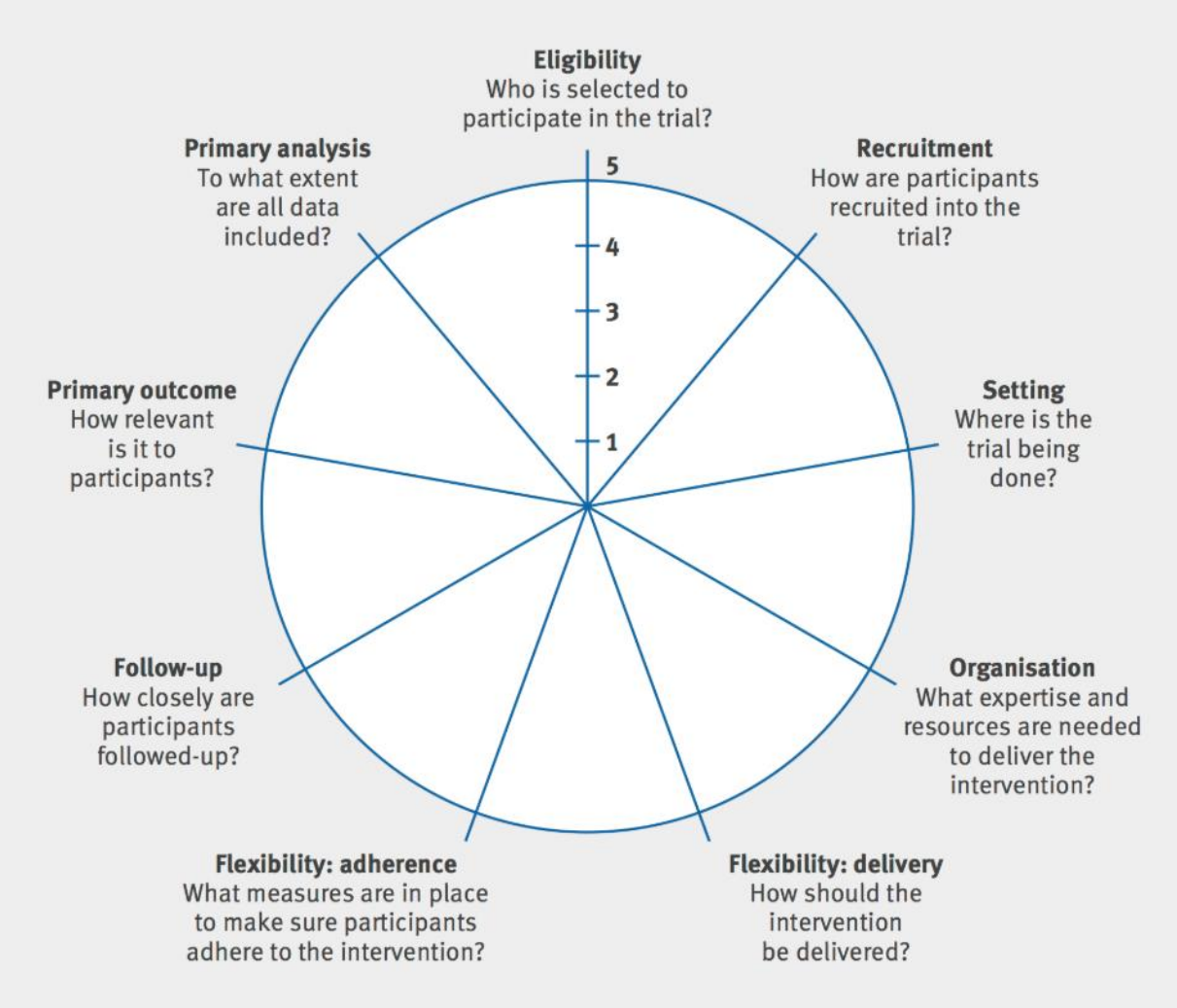
Relevance and Rigor via Pragmatic Trials



PRECIS-2 criteria

Loudon 2015 BMJ

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Striking the Balance: HIV Adherence Intervention Trials

- Medications
  - HIV antiretroviral treatment (ART)
  - HIV pre-exposure prophylaxis (PrEP)
- Populations
  - Highly marginalized
  - Heavy comorbidity burden
- Challenges
  - Non-adherence common
  - Age and racial/ethnic disparities

Striking the Balance: HIV Adherence Intervention Trials

CDC Centers for Disease Control and Prevention

Medication Adherence (MA) Chapter

The Prevention Research Synthesis (PRS) Project routinely updates the MA chapter by adding newly identified EBIs that improve HIV medication adherence or viral load suppression among persons living with HIV (PLWH). Additional details about the MA Chapter or the Prevention Research Synthesis (PRS) Project can be obtained by contacting PRS.

Updated on November 22, 2019

NEW Medication Adherence (MA) Interventions for 2019

- Adherence Improving self-Management Strategy (AIMS) [PDF – 960 KB] *ILI – Good*
- LINK LA [PDF – 271 KB] *GLI – Good*
- Project nGage [PDF – 905 KB] *ILI – Good*
- Rewarding Adherence Program (RAP) [PDF – 904 KB] *ILI – Good*
- Short-Term Cash and Food Assistance [PDF – 1 MB] *ILI – Good*

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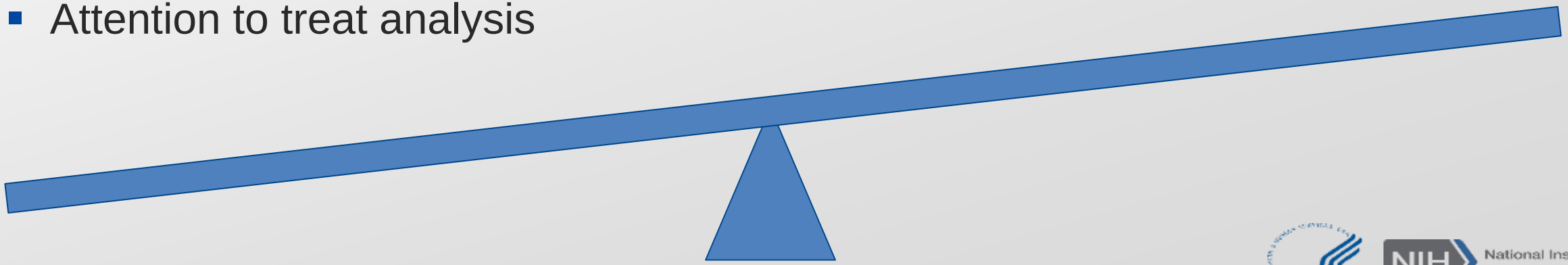
Striking the Balance: HIV Adherence Intervention Trials

- Pragmatic aspects
  - Real world care settings
  - Limited exclusion criteria* allowing participants with co-comorbidities
  - Comparator is usual care
  - Tailored intervention delivery
  - Attention to treat analysis



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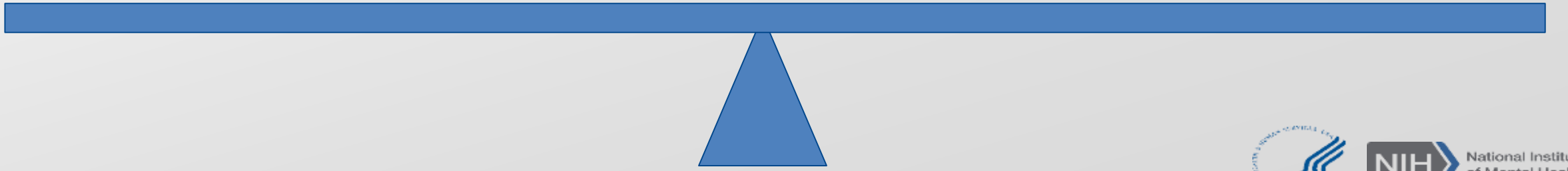
Striking the Balance: HIV Adherence Intervention Trials

- Pragmatic aspects
  - Real world care settings
  - Limited exclusion criteria* allowing participants with co-comorbidities
  - Comparator is typically usual care
  - Tailored intervention delivery
  - Attention to treat analysis

- Adding rigor (explanatory aspects)
  - *Only enroll those w/non-adherence or poor clinical outcomes (viral load)
  - Well powered on primary outcome
  - More objective/periodic assessment
  - Clinically meaningful follow-up period
  - Examine intervention “dosage” and mechanisms of behavior change



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"WelTel" HIV Treatment Adherence Trial

Weekly text message asks
"How are you?"

Patients respond *"Fine"* or *"Problem"*
& nurses call back those with problems

RCT outcomes at 12 mos. (N = 538 drug naïve ART initiators in Kenya			
	Viral suppression at 12 months	**RR (95% CI)**	**p value**
Intervention	**57%**	**0.85 (0.72-0.99)**	**0.04**
Standard care	**48%**		

Qualitative interviews with intervention arm participants:

- Felt "cared for"
- Comforted by having a communication channel regardless of any problems

Lester et al *Lancet* 2010; van der Kop *PLOS Med* 2012

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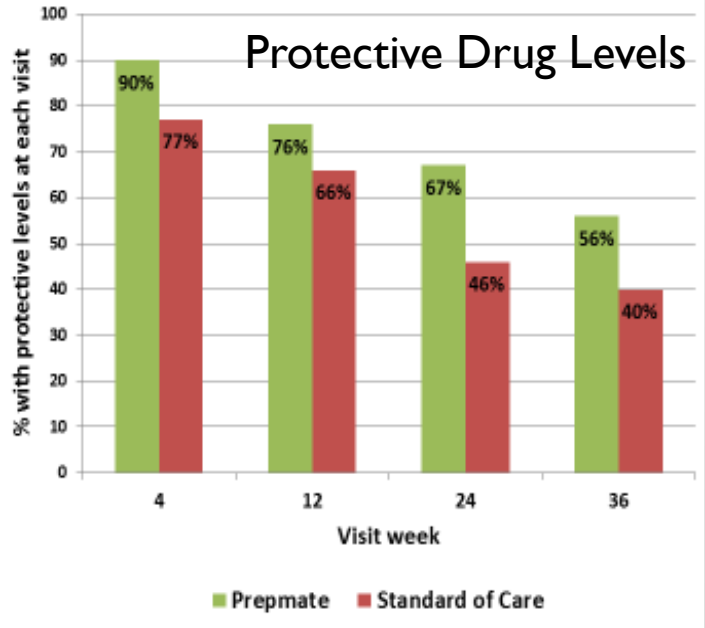
“EPIC” HIV PrEP Adherence Trial

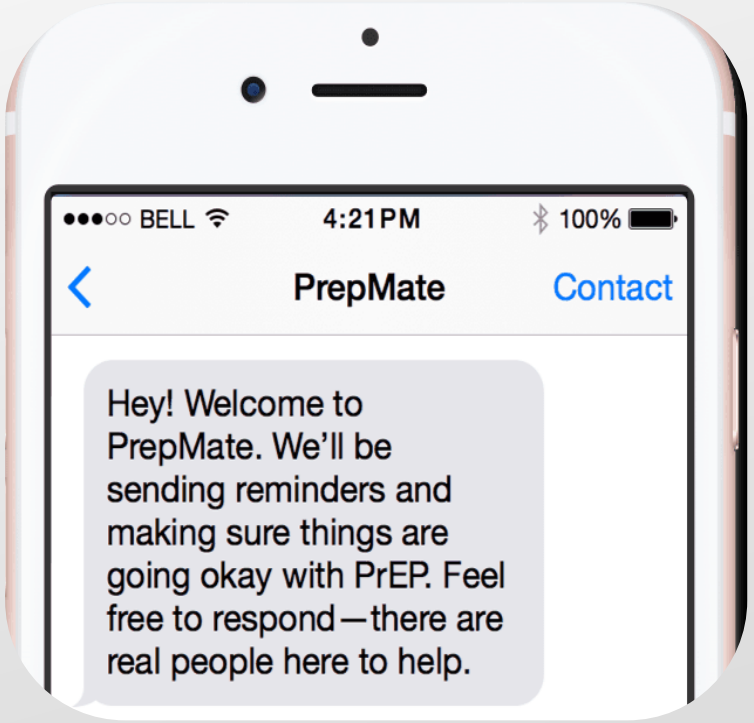
Clinical Infectious Diseases

MAJOR ARTICLE

Randomized Controlled Trial of a Mobile Health Intervention to Promote Retention and Adherence to Preexposure Prophylaxis Among Young People at Risk for Human Immunodeficiency Virus: The EPIC Study



Adjusted OR*	**2.06 (95% CI 1.07-3.99) P=0.03**



Liu et al *CID* 2018

National Institute of Mental Health

Trial Trends: Individual Level RCTs and More

- Individual-level RCTs still dominate
- Presently advancing:
  - Cluster randomized trials
  - Stepped-wedge trials – a particularly pragmatic design
- Frontier approaches:
  - Dose-finding trials for adherence interventions
  - Trial designs consonant with technologic research (e.g., BIT, CEEBIT, Micro-randomized designs, N-of-1 designs)

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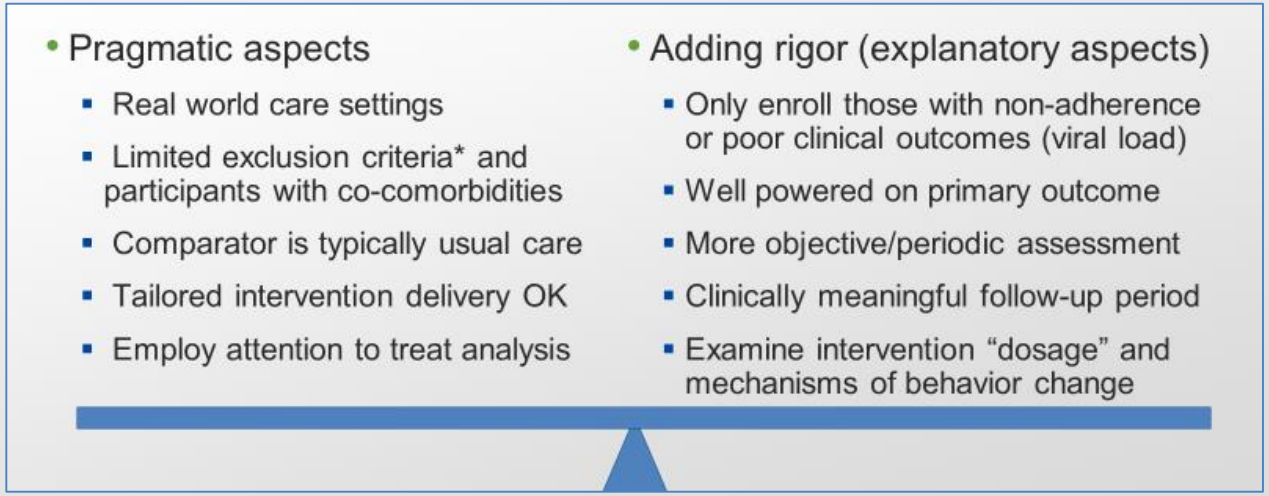
Take Away Messages

- Goal: maintain real world relevance without sacrificing rigor
- Many methodologic considerations noted here can improve the validity and impact of adherence intervention trials
- Real-world RCTs dominate -- and designs are diversifying



THANKS!

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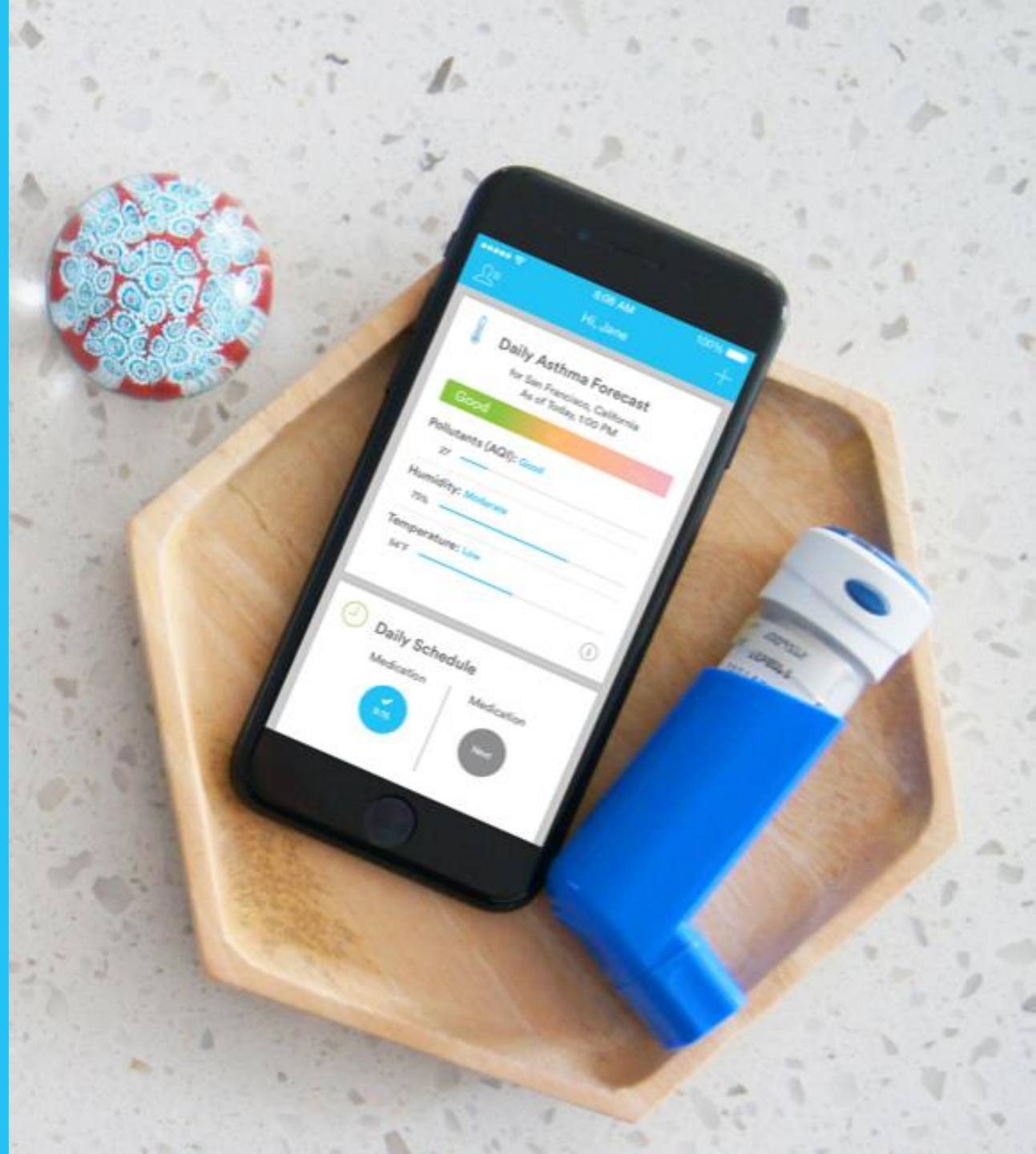
Study Designs to Evaluate Tracking, Improvement in Medication Adherence, and Impact on Clinical Outcomes

Medication adherence using electronic medication monitors

Rahul Gondalia | December 10, 2019

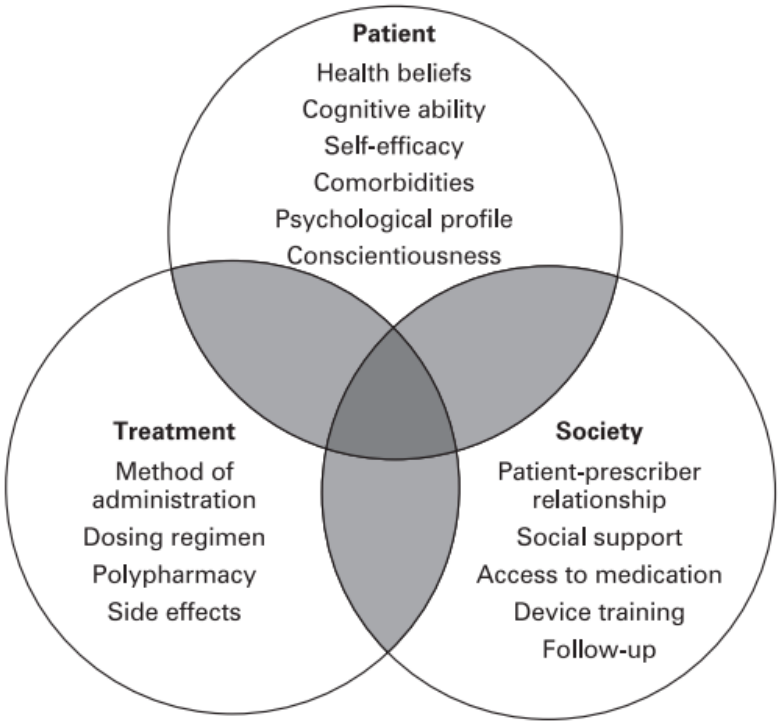
Session IV: Study Designs to Evaluate Tracking, Improvement in Medication Adherence, and Impact on Clinical Outcomes

Propeller



Medications and adherence in asthma and COPD

- COPD & asthma are leading causes of morbidity[1,2]
- Inhaled daily medications
  - Corticosteroids, long-acting beta-agonists & muscarinic antagonists
- Adherence in practice is around 10-40%[3]
- Difficulty assessing adherence
  - Prescribing, dispensing records
  - Self-report
  - Dose counter
  - Weighing canisters
- Novel methods to quantify adherence[4]



Adherence is multifactorial[3]

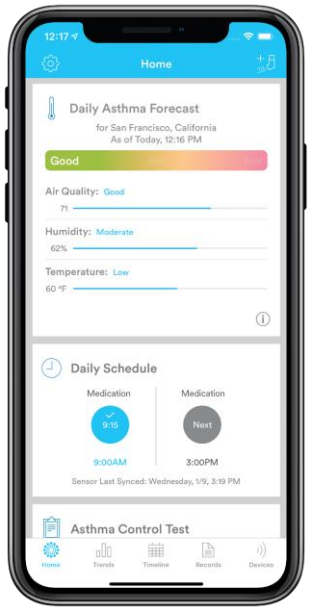
1. GOLD 2020. www.goldcopd.org
2. GINA 2019. www.ginasthma.org
3. Bourbeau & Bartlett. Thorax. 2008 Sep 1;63(9):831-8
4. Chan et al. JACI: In Practice. 2015 May 1;3(3):335-49

Inhaler use monitoring using Propeller

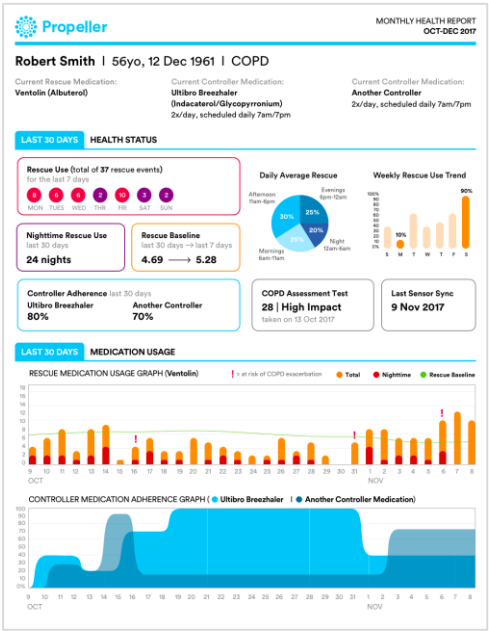
Propeller is a connected health platform.

Bluetooth enabled sensors that track rescue and controller medication adherence.

Passively syncs with a smartphone or tablet.

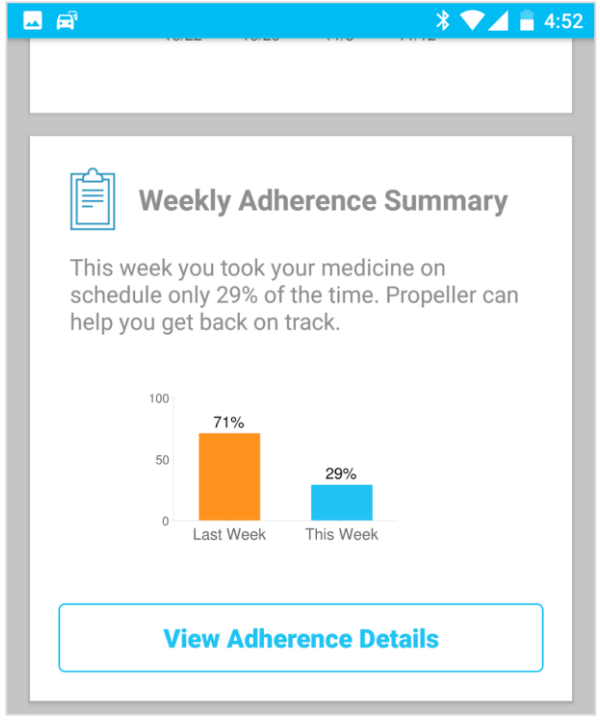


Produces objective reports of medication adherence and trends. Can alert the care team.

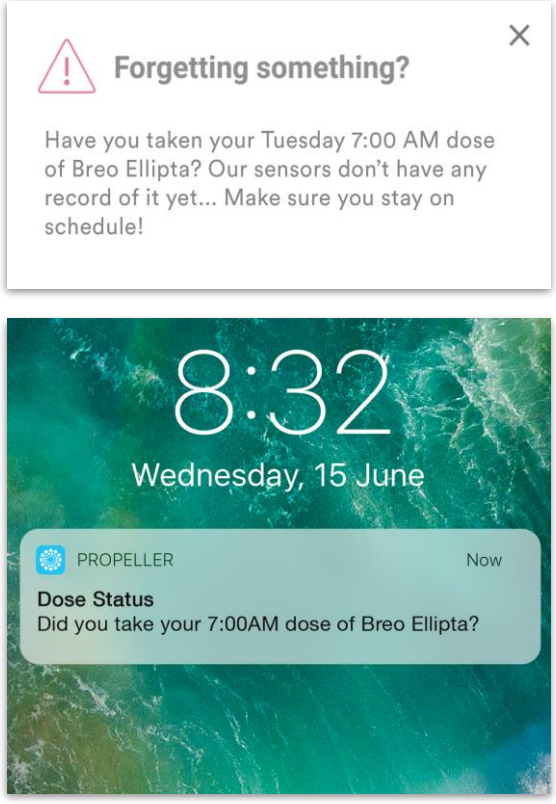


Patient-facing tools to improve adherence

Propeller takes a multi-faceted approach to remind patients to take their daily meds



Weekly goal setting and adherence summary

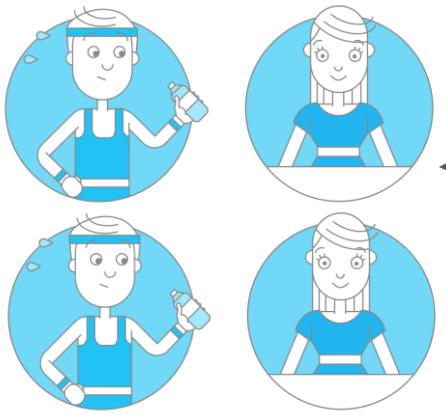


In-app reminders

Sensor reminder sounds

Study design considerations

Efficacy



E.g., younger, tech savvy

Population

General asthma / COPD

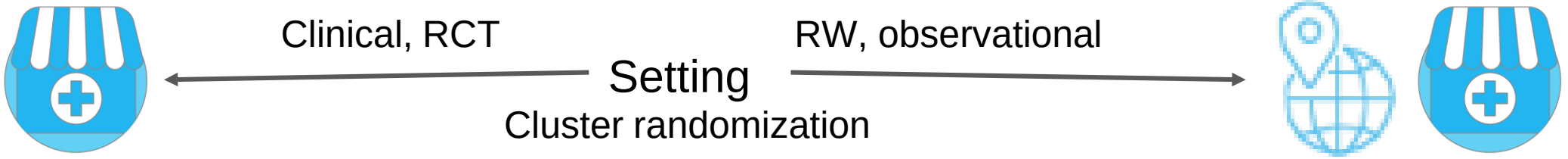
Effectiveness

Clinical, RCT

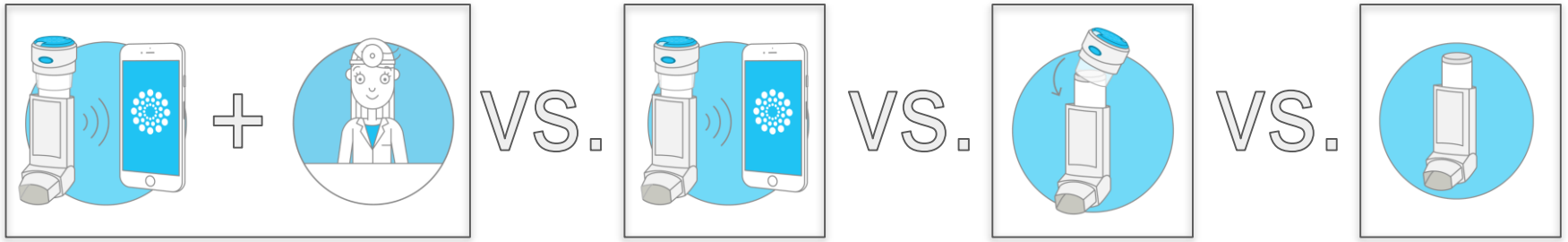
Setting

Cluster randomization

RW, observational

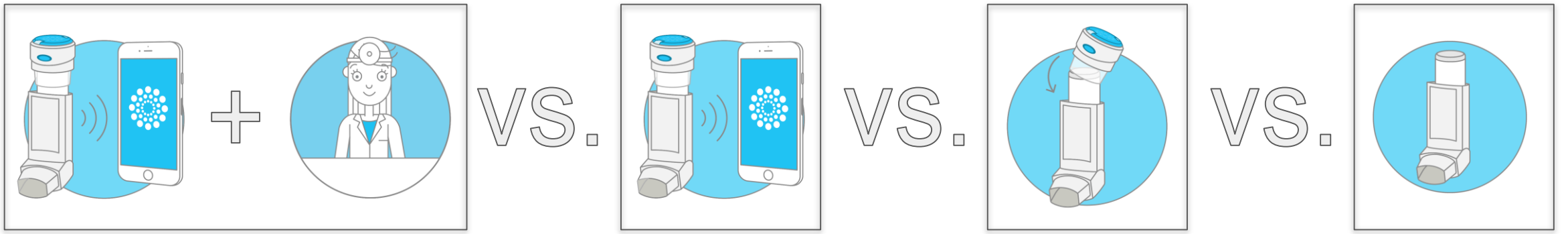


Defining the intervention



Defining adherence

How should adherence be calculated?

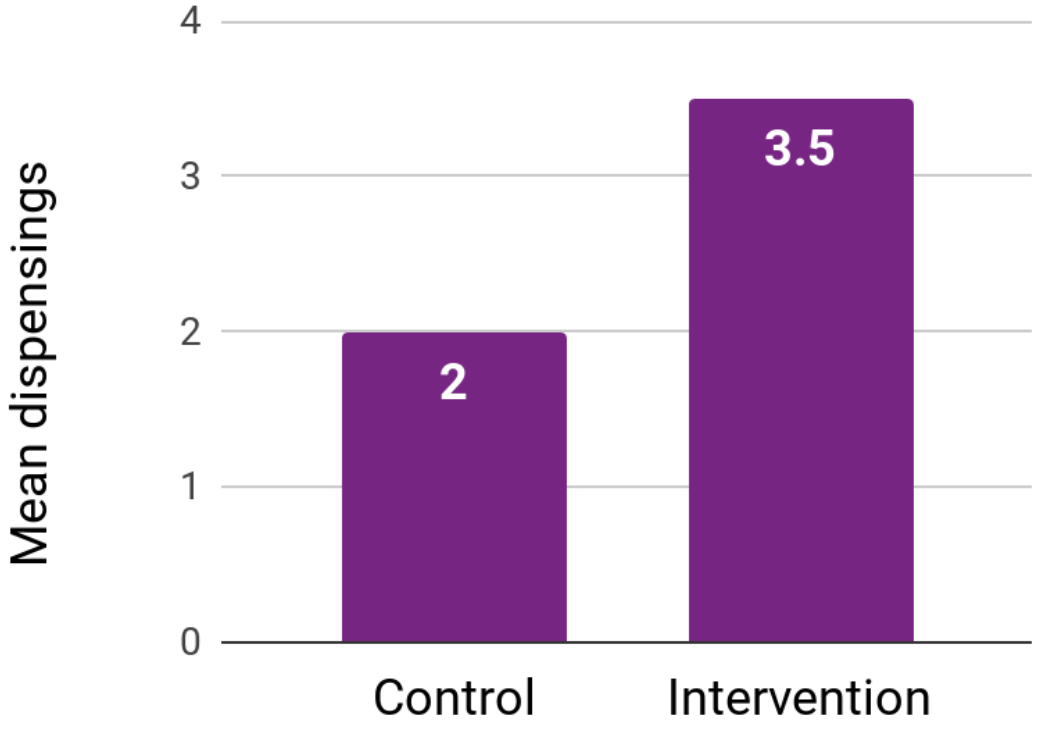


Objective monitoring: puffs taken / puffs prescribed

Rx / dispensing
Self-report
Weighing canister
Dose counter

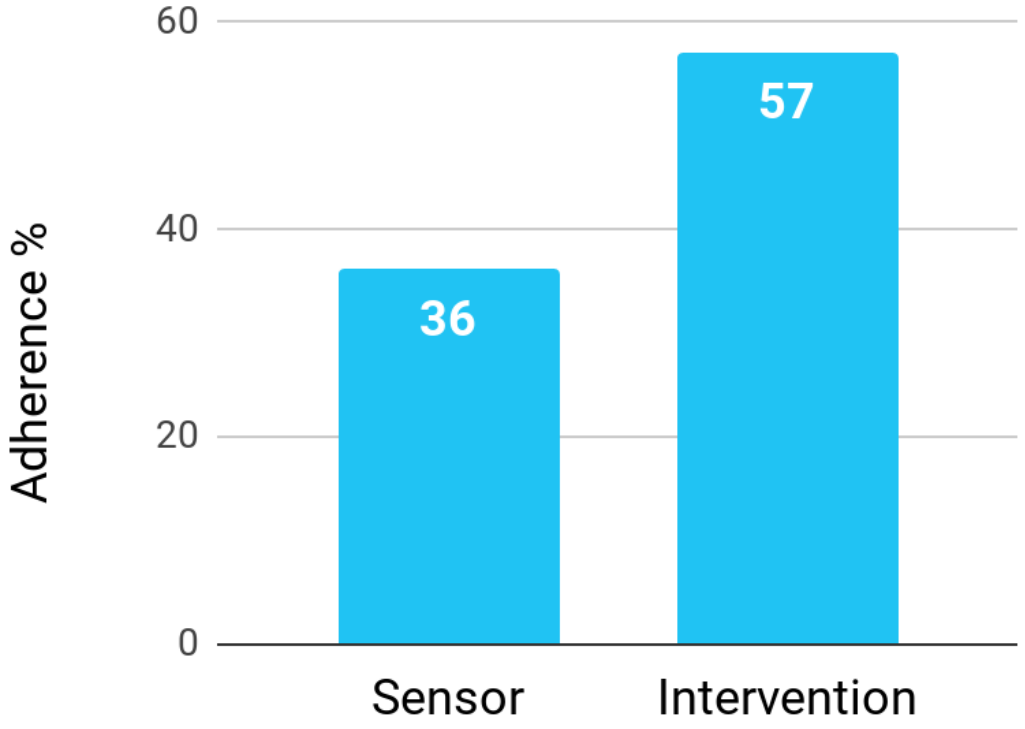
Early studies in asthma

Design: Observational, real world
Treatment: No sensor vs. sensor
Duration: 6 months
Outcome: ICS/LABA dispensings
N: 134



Stanford et al. Am J Respir Crit Care Med. 2019; A5930–A5930

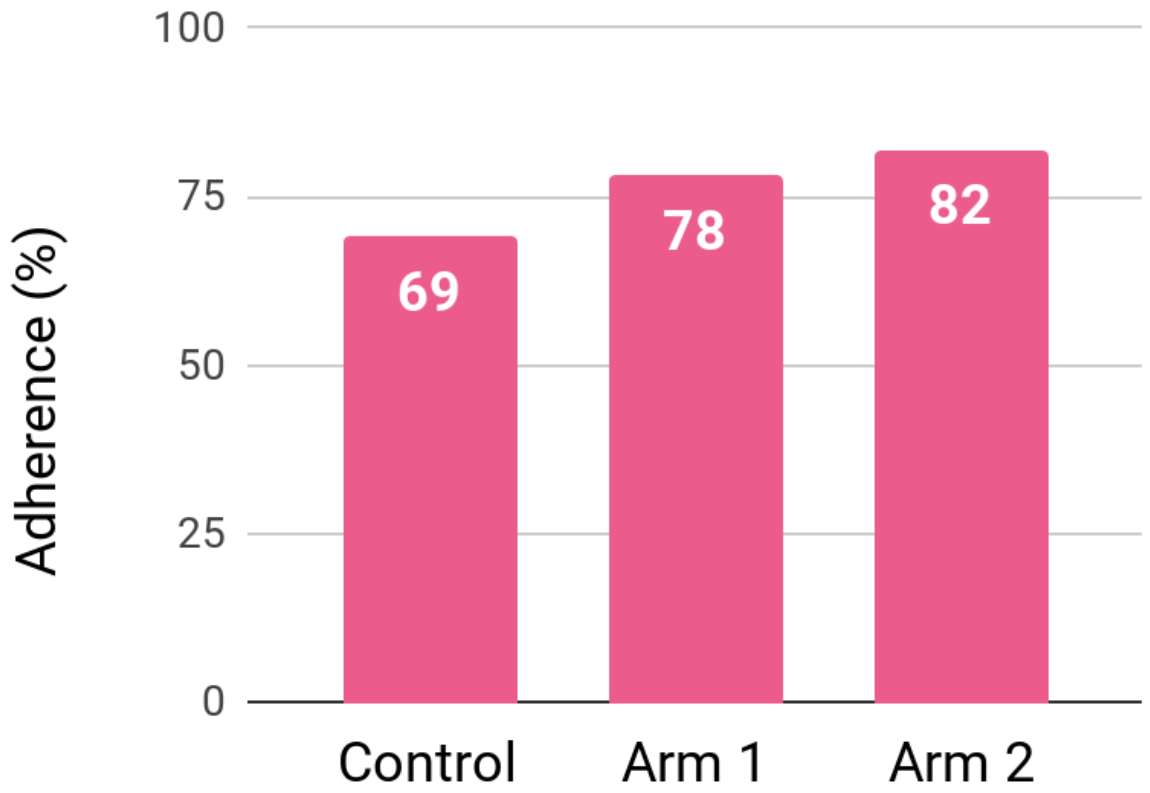
Design: RCT, real world in clinic
Treatment: Sensor vs. Sensor+App+HCP
Duration: 6 months
Outcome: Controller adherence (%)
N: 125



Van Sickle et al. Eur Respir J. 2016;48:PA1018

Efficacy study in asthma

Design: Multicenter RCT, in clinic
Treatment: Sensor vs. Sensor+app vs. Sensor+app+HCP
Duration: 6 months
Outcome: ICS/LABA adherence (%)
N: ~250



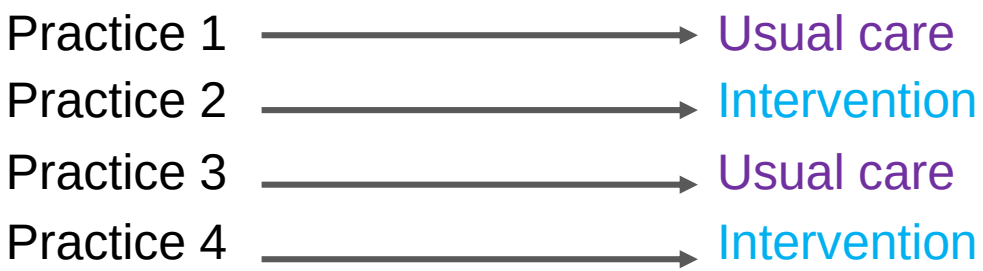
Moore et al. Eur Respir J. 2019;54:OA3561

- Common that efficacy does not translate to effectiveness[5]
- Efficacy → effectiveness
  - Define target population
  - Generalizability
  - Study duration
  - Setting
  - Comparator
  - Broader outcome

5. Woodcock et al. Eur Respir J. 2018 Feb 1;51(2):1701531

Adherence and clinical outcomes

- Many null studies of adherence and reduced exacerbations
  - Patient population (e.g. low powered, low risk, adherent)
  - Inadequate follow up time
  - Exposure measurement error
- Effectiveness needs to be considered, but cluster randomization *can* help[6]



6. Donner & Klar AJPJ. 2004 Mar;94(3):416-22.

Adherence and clinical outcomes

Planned cluster randomized trial

- Treatment: Usual care vs. offer Propeller sensors+app
- Duration: 1 year
- Outcome: treatment failure (exacerbation, escalation, mortality)
- Secondary outcome: adherence
- N: > 1,000 COPD patients from >150 clinics
    - History of exacerbations and poor adherence

Takeaways

- A clear study question and goal is necessary
- A well-defined intervention, comparator and outcome
- Population selection considerations
  - Eligibility
  - Study duration
  - Sample size
  - Generalizability and transportability
- A longer study duration is important for chronic diseases
- The level of rigor and effectiveness will defined by the study design

Acknowledgements

- Patients using Propeller who provided valuable insight
- Research partners
- Clinical research team at Propeller
    - Meredith Barrett, Leanne Kaye and David Stempel

Rahul Gondalia, PhD MPH

rahul.gondalia@propellerhealth.com

Thank you

Study Designs to Evaluate Tracking, Improvement in Medication Adherence, and Impact on Clinical Outcomes

December 2019

Improving Medication Adherence

George M. Savage, MD
Co-Founder & Chief Medical Officer

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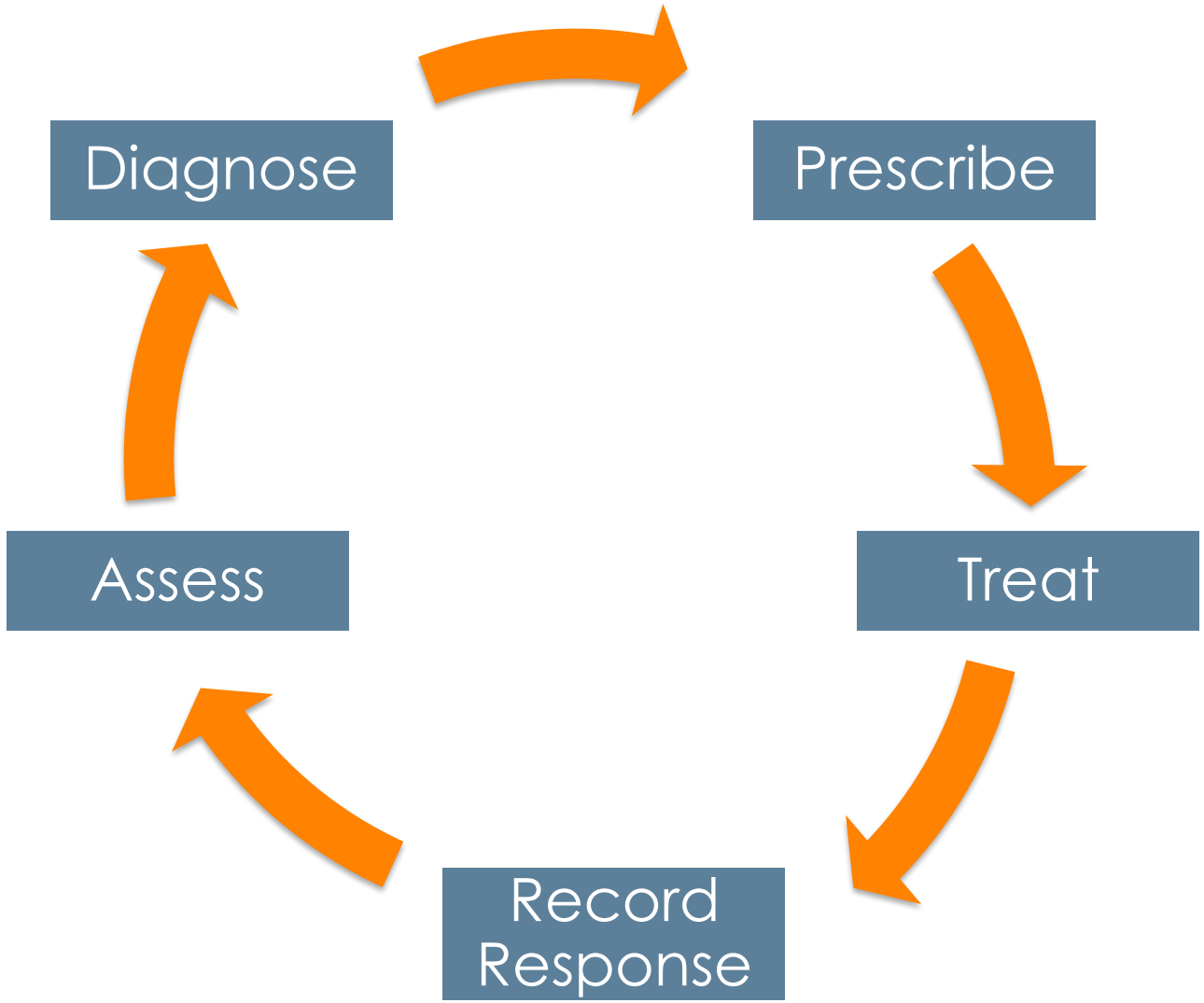
Pharmacotherapy Feedback Loop

Effective in the hospital, interrupted in the ambulatory setting



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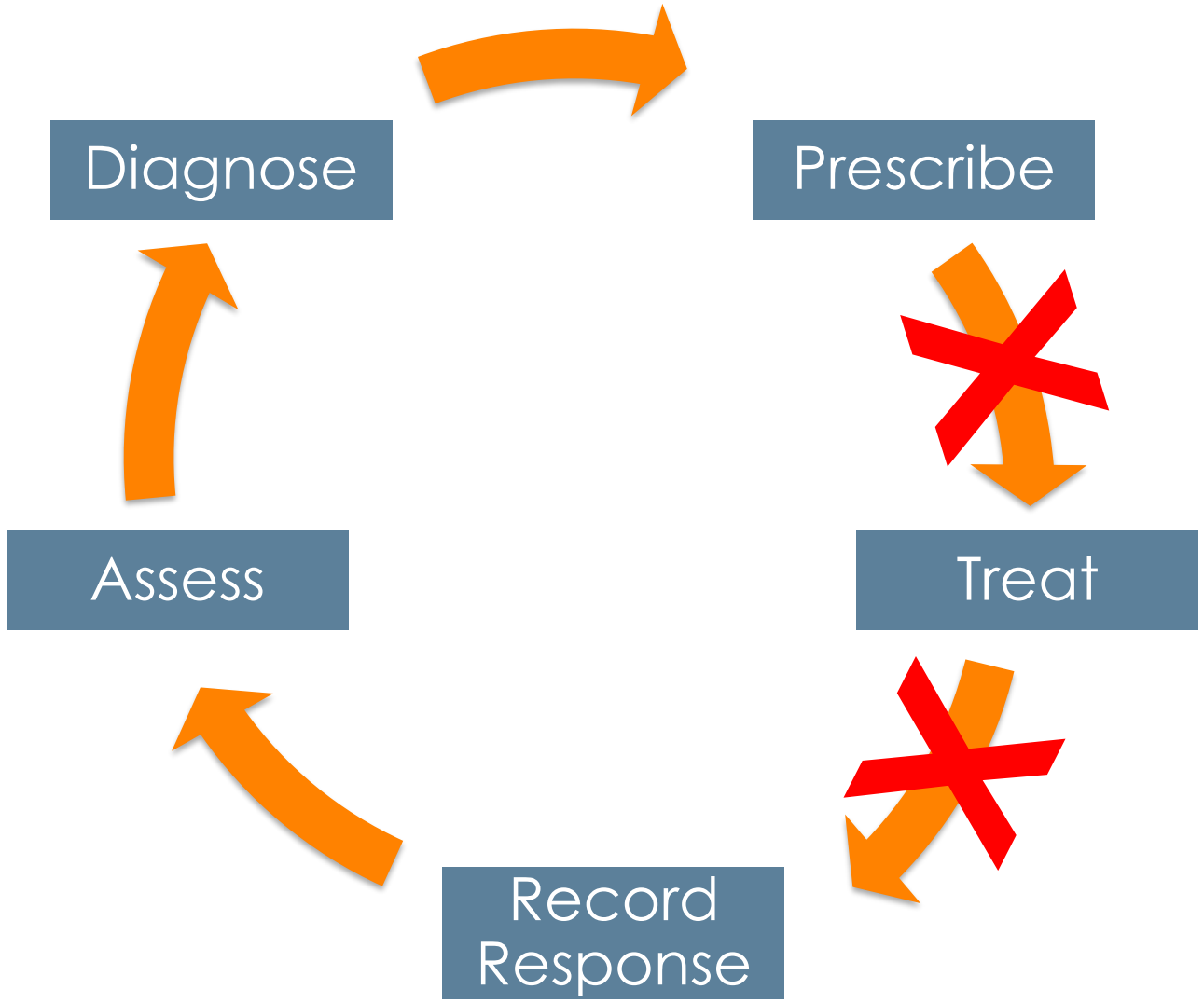
Pharmacotherapy Feedback Loop

Effective in the hospital, interrupted in the ambulatory setting



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Digital Medicines Provide Real-Time Feedback

Objective medication ingestion and physiologic data for patient, caregiver, and HCP

Edible sensor co-encapsulated with medication at pharmacy

Patch records actual medication-taking and other metrics

Bluetooth link to smartphone

Cellular/WiFi link to cloud

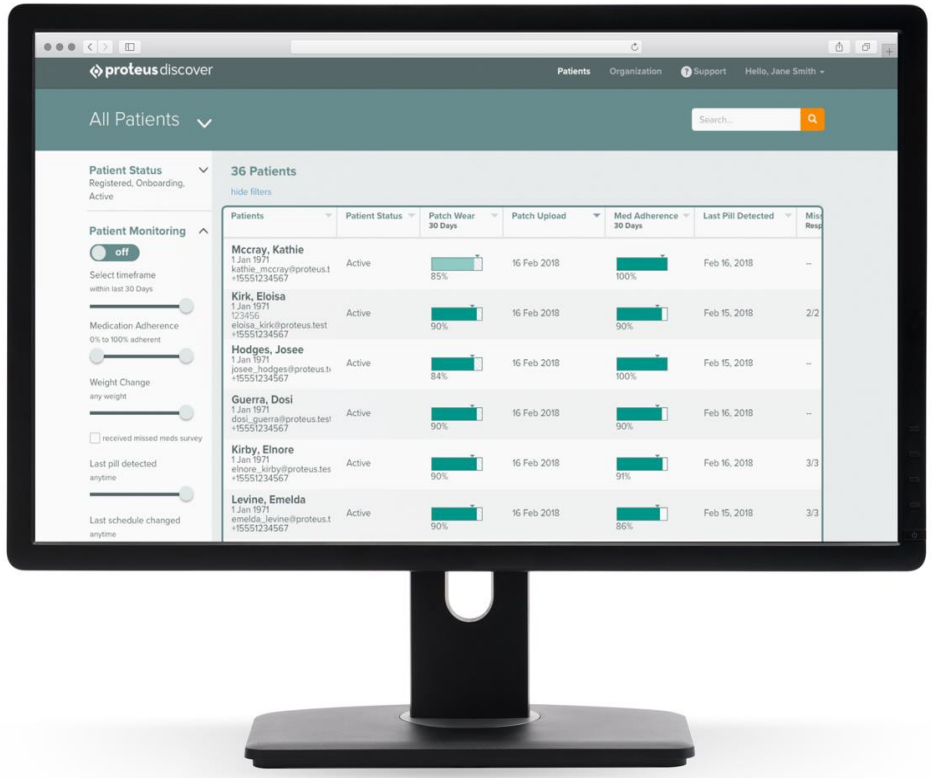
Used by Patients

Digital Medicines

Wearable Sensor

Patient Mobile App

Used by Healthcare Teams



Provider Web/EHR App

proteus DIGITAL HEALTH

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RCT Concludes Digital Medicines Superior to DOT in TB

Concordance to DOT 99.3% (CI 98.1;100); 93% of WOT doses confirmed compared to 63% for DOT

PLOS MEDICINE

RESEARCH ARTICLE

Wirelessly observed therapy compared to directly observed therapy to confirm and support tuberculosis treatment adherence: A randomized controlled trial

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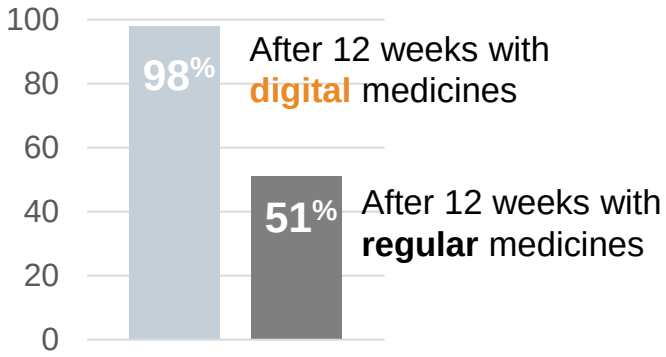
Conclusions

In terms of accuracy, WOT was equivalent to DOT. WOT was superior to DOT in supporting confirmed daily adherence to TB medications during the continuation phase of TB treatment and was overwhelmingly preferred by participants. WOT should be tested in high-burden TB settings, where it may substantially support low- and middle-income country (LMIC) TB programs.

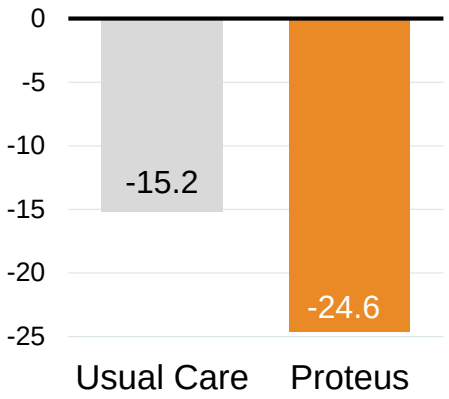
Cluster-Randomized Study in Drug Refractory HTN & T2DM

Digital feedback improved all clinical end-points compared to usual care

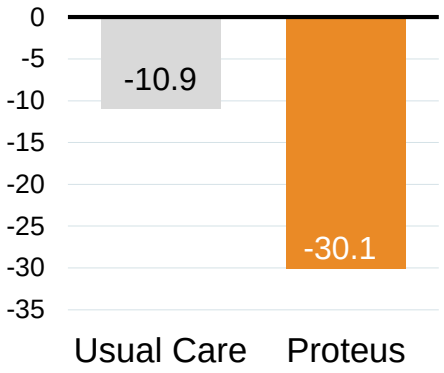
Percent of patients at BP goal after 12 weeks with digital medicines



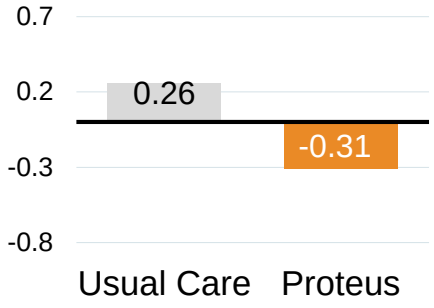
Change in SBP (mm Hg)



Change in LDL (mg/dL)

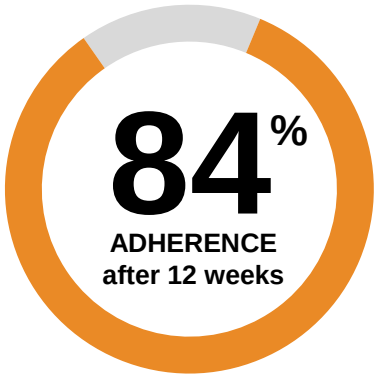


Change in A1c (%, Baseline ≥8)



Randomized Controlled Clinical Study Population

- **After 24+ weeks on regular medicines: 0% at BP goal**
- 100% of population (N = 109) failed multiple medications over at least 6 months
- SBP ≥140 mm Hg; A1c ≥7%; ± elevated lipids
- Diabetes duration = 10 years
- Mean age = 59
- 56% earn <$20k/year
- 31% <high school education
- 46% Hispanic; 16% African-American
- 22% psychiatric comorbidities



Frias J et al. Effectiveness of Digital Medicines to Improve Clinical Outcomes in Patients with Uncontrolled Hypertension and Type 2 Diabetes: Prospective, Open-Label, Cluster-Randomized Pilot Clinical Trial. J Med Internet Res 2017;19(7):e246

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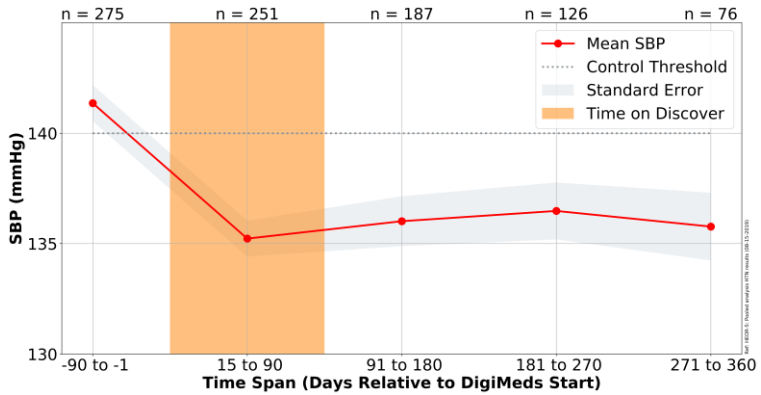
RWE Confirms RCT Findings and Demonstrates Durability

Single-arm commercial pilot implementations across health systems in HTN and T2DM

Hypertension

292 patients across 5 health systems used Proteus Discover for hypertension for 91 ± 85 days:

- Mean age: 64.2 ± 12.6 years
- Mean adherence: **86.7% ± 11.7%**
- Mean patch wear: **92.9% ± 12.5%**



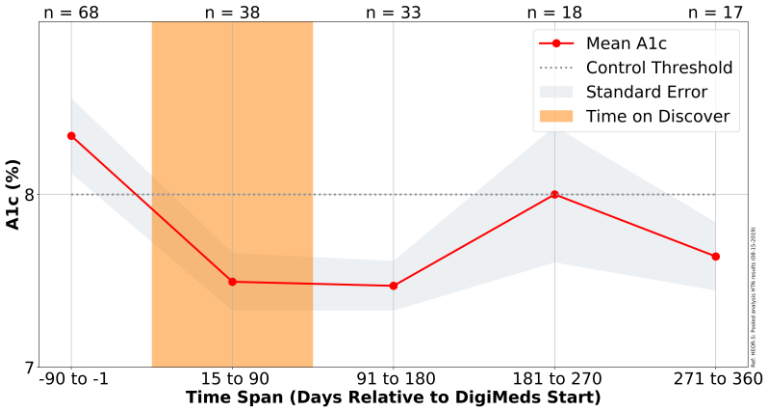
Clinical Results

- Mean change in SBP 15 to 90 days vs. -90 to -1 days: 6.4 mmHg (141.6 to 135.2, P<0.001, all patients, n = 251)
- Mean change in SBP 15 to 90 days vs. -90 to -1 days: 11.5 mmHg (149.6 to 138.1, P<0.001, uncontrolled patients, n = 149)

Diabetes (Type 2)

105 patients across 3 health systems used Proteus Discover for diabetes for 92 ± 58 days:

- Mean age: 61.6 ± 10.4 years
- Mean adherence: **86.6% ± 11.0%**
- Mean patch wear: **94.5% ± 9.3%**



Clinical Results

- Mean change in A1c 15 to 90 days vs. -90 to 0 days: -0.7 (8.2 vs 7.5, P<0.001, all patients, n = 38)
- Mean change in A1c 15 to 90 days vs. -90 to 0 days: -1.3 (9.3 vs 8.0, P<0.001, uncontrolled patients, n = 20)

- 36% of all real-world CMB patients have psychiatric comorbidities (65% of which have SMI)
- 13% of all real-world CMB patients have substance use disorders (41% of which have alcohol use)
- 32% of patients are ≥ 70 years of age

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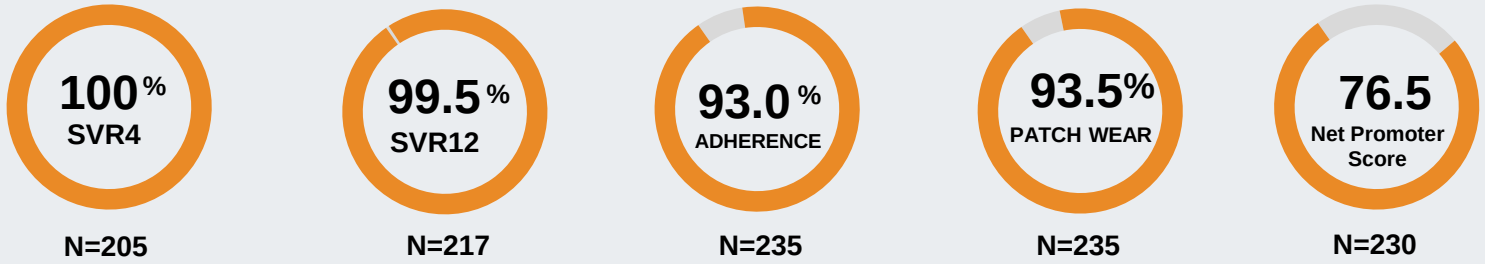
Feedback Effective in Curing HCV in High-Risk Population

Single-arm prospective multi-center study enrolling patients denied treatment due to adherence risk

Number of Sites	18 (including Johns Hopkins, Providence, UCSF, Mount Sinai, Duke and Henry Ford)
Study population	Adults newly initiating treatment for chronic HCV
Inclusion Criteria	One or more risk factors for nonadherence: • Active alcohol or substance use, OR • Hospitalization within past 2 years for a psychiatric comorbidity, OR • Evidence of nonadherence to medications, OR • History of at least one missed clinic visit for hepatitis management, OR • Patient-reported history of one or more transportation barriers
Number of Patients	288
Digital Medications	Epclusa®, Harvoni®, Mavyret™
Study Duration	8-12 weeks of treatment with up 20 weeks of follow-up
Results	

Sulkowski M, et al AASLD 2019

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Feedback Effective in Curing HCV in High-Risk Population

Single-arm prospective multi-center study enrolling patients denied treatment due to adherence risk

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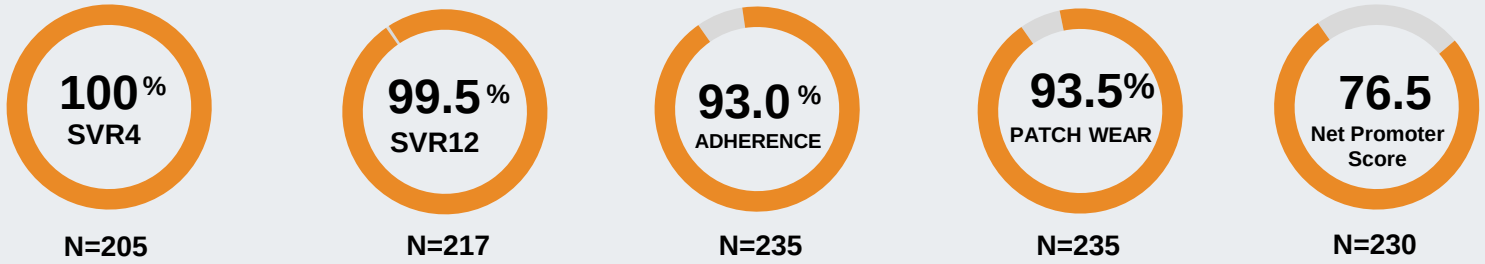
RWE as next step: State Medicaid value-based pilot contract signed with first patient expected in the first quarter of 2020	
Number of Patients	288
Digital Medications	Epclusa®, Harvoni®, Mavyret™
Study Duration	8-12 weeks of treatment with up 20 weeks of follow-up
Results	

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Real-Time Data Allows HCPs to Focus on Patients with Problems

PrEP/HIV patient mean adherence of 91.6% and patch wear of 84.3%, but lower for some individuals

Universal Filters
The following filters will apply to all graphs

Therapeutic Area
- [ ] (All)
- [ ] CMB
- [ ] Colorectal Cancer
- [ ] Hep C
- [x] HIV
- [ ] TB

Cancel Apply

Clinical Sites
- [x] (All)
- [x] Harbor UCLA Medical Center
- [x] The Ruth M Rothstein CORE Ce…
- [x] UCSD Antiviral Research Center

Cancel Apply

Start Codes
- [x] (All)
- [x] ateam
- [x] bruin
- [x] leaf
- [x] ucsd_hiv

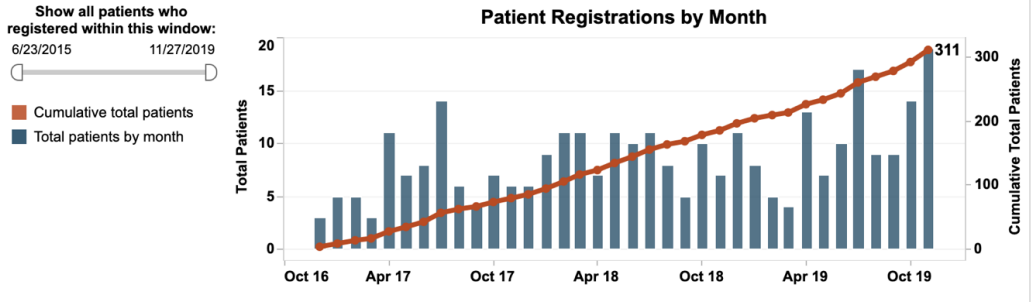
Cancel Apply

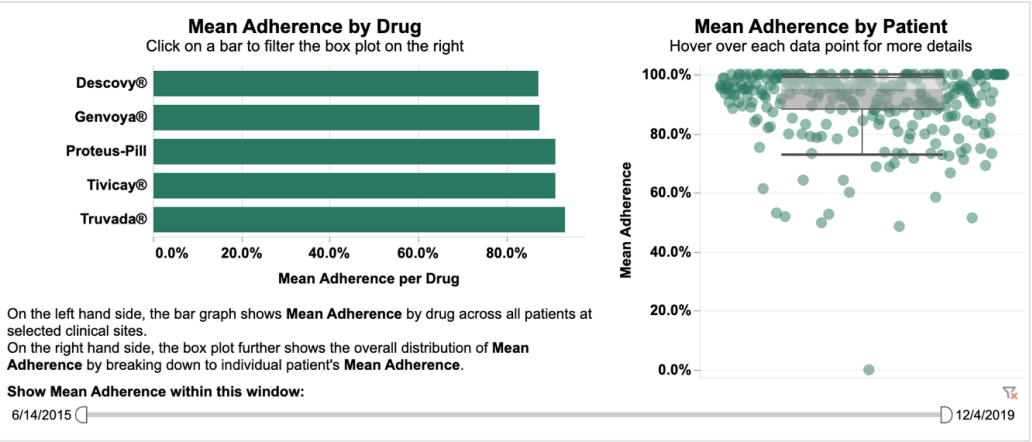
Notes: Due to incomplete information of historical patients, Freeman Hospital and Scripps Green Hospital are excluded in this dashboard.

Showing data for all patients under **HIV** studies at **All**.

Current Registered Patients	Current Onboarding Patients	Current Active Patients	Mean Adherence	Total Ingestions	Mean Patch Wear	Mean Days on Discover	In-progress Cycles	Completed Cycles
0	0	45	91.6%	16,494	84.3%	93		

Show all patients who registered within this window:
6/23/2015 11/27/2019



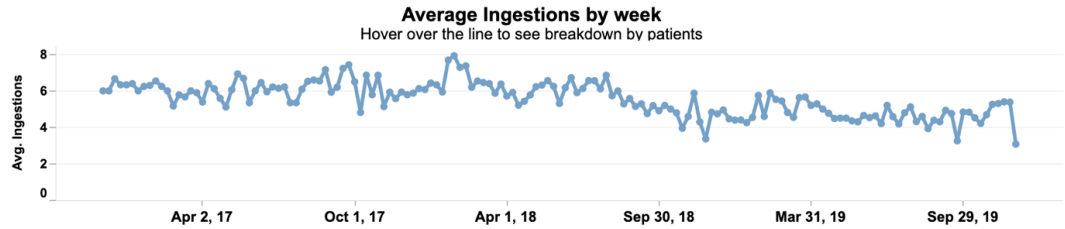


On the left hand side, the bar graph shows **Mean Adherence** by drug across all patients at selected clinical sites.
On the right hand side, the box plot further shows the overall distribution of **Mean Adherence** by breaking down to individual patient's **Mean Adherence**.

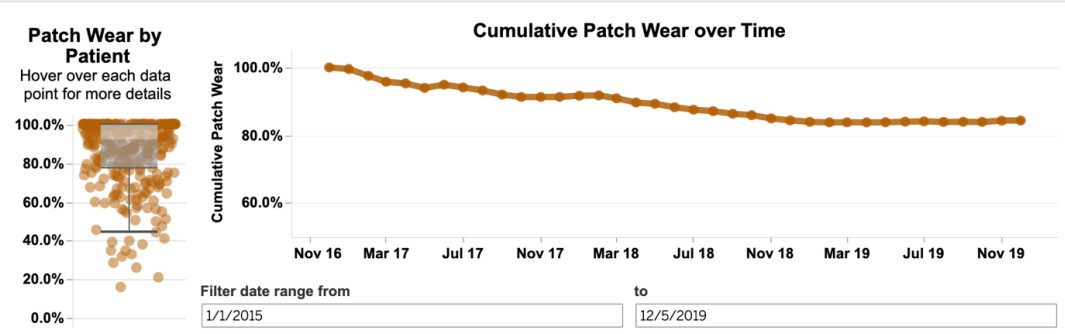
Show Mean Adherence within this window:
6/14/2015 12/4/2019

Total Ingestions by Drug

	Descovy®	Genvoya®	Proteus-Pill	Tivicay®	Truvada®	Grand Total
Total Ingestions	2,374	656	4,159	1,184	8,121	16,494
Total Patients	36	14	185	16	181	303



Show all ingestions within this window:
June 12, 2015 December 4, 2019



Filter date range from 1/1/2015 to 12/5/2019

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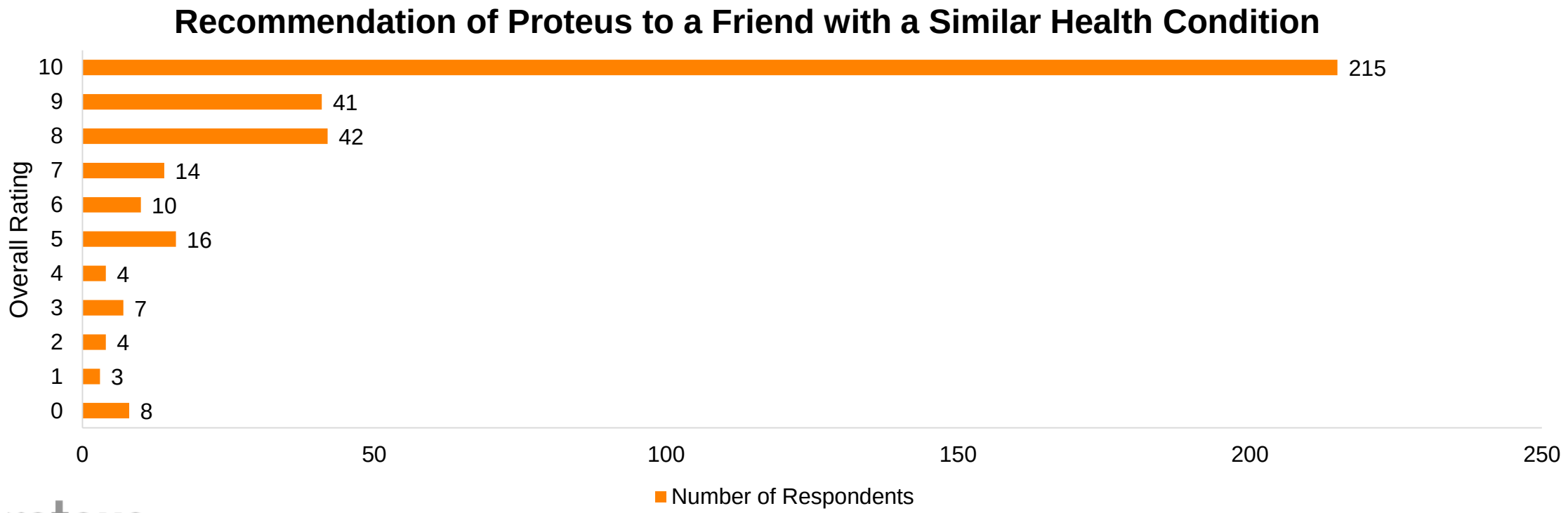
Patient Satisfaction from RWE

N = 356

- Considering your complete experience with Proteus Discover, how likely or unlikely would you be to recommend Proteus Discover to a friend with a similar health condition?
- **71.9%** of respondents are promoters (9-10) of Proteus Discover.
- Among these 256 promoters, **84.0%** chose the highest rank of 10 as their recommendation of Proteus to a friend with a similar health condition.
- Net Promoter Score is +57. (NPS is calculated as % promoters minus % detractors (0-6))



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Study Designs to Evaluate Tracking, Improvement in Medication Adherence, and Impact on Clinical Outcomes

Closing Remarks

Adjournment

Thank You!

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