Join the Conversation:

Twitter: #MedAdherence2019
Welcome & Introductions
Opening Remarks from FDA
Overview of Medication Adherence
Setting the Stage
Andrew M. Peterson, PharmD, PhD, FCCP
Executive Director
Professor of Clinical Pharmacy and
Professor of Health Policy
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 provider¹

• Compliance
  – the extent to which patients are obedient and follow the instructions of a health care professional²
  – Two aspects
    • Initial compliance
    • Ongoing compliance

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\(^2\)

   *BMC Public Health*. 2006;6
More Terminology

- Abandonment
- Discontinuation
- Implementation
- Initial Medication Adherence

- Initiation
- Pharmionics
- Primary Non-Adherence
- Therapeutic Alliance
ABC Taxonomy

ABC = Ascertaining Barriers for Compliance

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-t 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
    • 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!
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

Health system/provider factors
- Insurance status
- Provider-patient communication
- Cultural competence
- Provider workload

Sociodemographic factors
- Race/ethnicity
- Gender
- Age
- Marital status
- Socioeconomic status
- Nationality
- Immigration status

Condition-related factors/comorbidities
- Time since transplant
- Transplant from living vs deceased donor
- Physical limitations

Patient psychosocial factors
- Low health literacy
- Psychological distress
- Low self-efficacy
- Poor social support
- Forgetfulness
- Drug use

Treatment factors
- Greater number of medications
- Side effects/concerns about medications
- Appointment-keeping
Adherence ‘Phenotypes’: Mapping Problems to Appropriate Interventions

Adherence Concern?

- **No**: re-assess at next opportunity
- **YES**:
  - Cognitive: memory, health literacy
  - Psychological: mental health, motivation
  - Medical: acute changes in health status
  - Regimen: complexity, side effects
  - Social: social support, access issues
  - Economic: costs, trade-offs

Interventions:
- Cognitive: education, counseling
- Psychological: nudges, de-prescribing
- Medical: evaluation, UMS, Rx change
- Regimen: prescribing, Rx assistance
- Social: community referral, mail order
- Economic: Rx assistance, generic options
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
Forgetfulness

NONADHERENCE CAUSES

Other Causes
- Intentional
- Emotional
- Educational
- Other

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
* 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.
<table>
<thead>
<tr>
<th>OBSTACLES</th>
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<tbody>
<tr>
<td>UNINTENTIONAL</td>
</tr>
<tr>
<td>• FORGETTING</td>
</tr>
<tr>
<td>• SHIFT WORK</td>
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<tr>
<td>• COST/ACCESS</td>
</tr>
<tr>
<td>• CONFUSION</td>
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<td>• WORK RESTRICTIONS</td>
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Competence and caring in relation to building trust

Counseling with a trusted clinician needs to be complemented by out-reach interventions and removal of structural and organizational barriers.
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%\(^3\)

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.
Reminders just become a nuisance over time

Patients already know they should take their meds.

Devices measure adherence but do not improve it.

Previous solutions don’t provide the instant gratification necessary to overcome Present Bias.
Paying patients to adhere to their care plan does overcome Present Bias
(Well-structured) Incentives produce lasting behavior change

Improvement to med adherence lasts after incentives end

Without incentives, remote monitoring is largely useless

- **Incentives improve adherence for other care plan elements, too**

<table>
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<th>Month</th>
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<th>$1.40/Day Incentive</th>
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<tr>
<td>1</td>
<td>72%</td>
<td>89%</td>
</tr>
<tr>
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<td>62%</td>
<td>75%</td>
</tr>
<tr>
<td>3</td>
<td>46%</td>
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<td>4</td>
<td>27%</td>
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<tr>
<td>6</td>
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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

Average Daily Adherence

89%

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

 ✓ 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
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.

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0198173
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)

Proportion of patient prescriptions that are adherent (PDC>80%)

- Synchronized Medications: 89.15%
- Non-Synchronized Medications: 56.65%

Source: Assessing the Impact of a Community Pharmacy-Based Medication Synchronization Program on Adherence Rates, NCPA, December 10, 2013
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
Adherence Rates among Medicare Advantage Members (2010 - 2018)

Source: RxAnte analysis of publicly available CMS data
Effects on adherence of some health plan direct-to-member outreach

**Pharmacist adherence**

- **7.4% lift**

  - Baseline prediction: 57.3%
  - Year-end: 54.2%

  - Operational performance:
    - 41,600 recommendations
    - 91% deployed, 42% reached

**Proactive IVR**

- **3.4% lift**

  - Baseline prediction: 83.2%
  - Year-end: 81.9%

  - 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).
Effects on adherence of provider and pharmacy incentive programs

**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**

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Patient-reported barriers and adherence trajectory over time

Barriers with increasing adherence likelihood

- Transportation
- Cost
- Hospital/nursing home admission
- Need refill/med on hold
- Forgetfulness
- Complexity/lack of understanding

Barriers with decreasing adherence likelihood

- Side effects
- MD changed dose
- Outside program/receiving samples
- Member changed dose on own
- MD discontinued
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...
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
University of Maryland
College Park, MD
301-405-8859
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
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)
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

THANK YOU CIGNA !!!
“... 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)
“… 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)
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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Overview

Introduction
  Behavioral Economics
  Potential Interventions

Example
  Shared Incentives

Discussion
Overview

Introduction

Behavioral Economics
Potential Interventions

Example

Shared Incentives

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

Introduction
Behavioral Economics
Potential Interventions

Example
Shared Incentives

Discussion
# Shared Incentives

## 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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---

**Trokel**

**Adherence**

**NYU**
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- **Side study**: compare different consent approaches in diabetics

---

**Troxel**

**Adherence**
Shared incentives trial

Shared incentives participants

- 238 primary care physicians at 3 sites
- 1,503 patients
  - age 18 – 80
  - $\text{FRS} \geq 20\%$ or CAD with $\text{LDL} \geq 120$
  - $\text{FRS} 10 – 20\%$ with $\text{LDL} \geq 140$
**SI: LDL reduction at 12 months**

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<th>Physician Incentives</th>
<th>Shared Patient and Physician Incentives</th>
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<tr>
<td>CI</td>
<td>22.7 – 30.6</td>
<td>22.5 – 30.3</td>
<td>26.6 – 33.4</td>
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<tr>
<td>$p$</td>
<td>–</td>
<td>0.87</td>
<td>0.20</td>
<td>&lt; 0.001</td>
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**SI: Average LDL over time**

![Graph showing average LDL levels over time for different groups: Control, Patient, Physician, and Shared.](image)
SI: Average adherence over time
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?

prescription  [physician]  adherence  [patient]
Overview

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**Introduction**

Behavioral Economics

Potential Interventions

**Example**

Shared Incentives

**Discussion**
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

- Spending $1 on medicines for adherent patients with chronic conditions can generate $3 - $10 in savings.
- Adherence to anti-hypertensive medicines could save 200,000 lives over five years.
- Adherence to diabetes medicines could save up to $8.3 billion annually.
- Medicare could realize significant savings if adherence reached recommended levels.
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

A. Initiate
- Patient does not initiate treatment
  - Binary (yes/no)

B. Implement
- Patient delays, omits or takes extra doses
  - Dosing history

C. Persist
- Patient discontinues treatment
  - Time to event

Different forms of nonadherence


EU-sponsored research
Overview of assessment methods of adherence in ambulatory patients

- **Initiate**: Requires sampling after prescription
- **Implement**: Sampling is too sparse
- **Persist**: Subject to white coat adherence

**Direct methods (PK/PD)**
- **Self-report**: Desirability bias
- **Pill counts**: Easily censored by patient

**Prescription & refill databases**
- **Gold standard**

**Electronic monitoring**
- **Gold standard in clinical trials**
Gold Standard Measure of Adherence

A Initiate  B Implement  C Persist

In clinical trial (Drug Development)
- Electronic monitoring

In medical practice
- Prescription & refill databases
- Electronic monitoring
- Prescription & refill databases
Example of Electronic Monitoring

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

Occasional toxicity

Periodic loss of effectiveness & emergence of drug resistance
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

The Adherence Gap

Potential consequences of this gap:
- Risk of failure related to lack of effectiveness
- Poor estimation of toxicity
- Inappropriate dosing regimen

Regulators
Payors

Outcomes
Efficacy
Suboptimal adherence
Patient selection
Patient follow-up
Effectiveness

Phase I
Phase II
Phase III
Drug development
Market

Adherence is Becoming a Regulatory Priority


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

Drug Development & Manufacturing

- Prescribing
- Dispensing
- Adherence
- Pharmacokinetics (PK)
- Pharmacodynamics (PD)

Drug response

Poor medication adherence in clinical trials: consequences and solutions


www.nih.gov/precision-medicine-initiative-cohort-program
**Advanced Analytical Research on Drug Exposure**

**Medication Event Monitoring System (MEMS®)**

<table>
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<th>MEMS Bibliometry</th>
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*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
## WHAT DOES REFILL DATA LOOK LIKE?

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</tr>
</tbody>
</table>
ADHERENCE TERMINOLOGIES

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

<table>
<thead>
<tr>
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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

<table>
<thead>
<tr>
<th>Calculation methods for adherence to multiple medications*</th>
<th>No. of studies, n (%)</th>
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<tbody>
<tr>
<td>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. Average of ∑days of supply per medication/study period</td>
<td>23 (15.6)</td>
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<tr>
<td>∑days of supply for all medications/study period</td>
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<td>∑days of supply for any medication/study period</td>
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<td>Average of (∑days of supply/days between last prescription and first prescription) per medication; supply obtained in the last fill was excluded</td>
<td>2 (1.4)</td>
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<tr>
<td>Average of (∑days of supply/days between last prescription and first prescription) per medication</td>
<td>1 (0.7)</td>
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<tr>
<td>∑days of supply for multiple medications/(days between last prescription and first prescription + days of supply for last fill)</td>
<td>1 (0.7)</td>
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<tr>
<td>∑days of supply for all medications/(days between last prescription and first prescription + days of supply for last fill)</td>
<td>1 (0.7)</td>
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<tr>
<td>∑tablets dispensed/∑tablets recommended or prescribed</td>
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<td>Weighted average of (∑days for supply/(days for which medication was needed – days spent in hospital)) per medication</td>
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<tr>
<td>Unclear how MPR to multiple medications was calculated</td>
<td>6 (4.1)</td>
</tr>
</tbody>
</table>

Pednekar PP Value 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

Timing of filling clopidogrel prescription after DES

- 84% filled on discharge day
- 16% delayed >=1 day

N=7,402

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


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

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
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
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 used to handle the finances/insurance
  - Unclear if she has insurance
- Today’s focus:
  - Her need to discuss her partner’s death
  - Son was not very supportive of their relationship
  - Son uninvolved with LP’s health care
HIV in the United States

Not all people with HIV are getting the care they need.

An estimated 1.1 million people had HIV in the US in 2016.

- 86% diagnosed
- 64% received care
- 49% retained in care
- 53% virally suppressed


Based on the most recent data available in November 2019.

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
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% 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
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
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
AdhereP4

• Focusing on medication adherence by ensuring collaboration between Prescribers, Pharmacists, Payers, and health department Programs (AdhereP4)

• Pharmacy claims data from Medicaid and AIDS Drug Assistance Program
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
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
Measuring and Evaluating Medication Adherence

Join the conversation with #MedAdherence2019
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
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.

The Drivers and Barriers of Medication Adherence are Complex

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

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

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

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 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)

The utility of different measurement approaches differs among adherence behaviors.
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

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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%).

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

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:

<table>
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<th>Socioeconomic issues</th>
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<tr>
<td>How will the patient fill the prescription?</td>
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<tr>
<td>Does the patient have insurance?</td>
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<tr>
<td>What copays and out-of-pocket costs are associated with the patient’s insurance?</td>
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</table>

<table>
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<th>Psychosocial issues</th>
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<tbody>
<tr>
<td>What is the patient’s mental status?</td>
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<tr>
<td>Does the patient have social support?</td>
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<th>Regulatory or administrative needs</th>
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<td>Is the drug on formulary?</td>
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<td>Is the drug approved by the FDA?</td>
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<th>Health and medication beliefs and preferences</th>
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<td>Is the patient ready to accept the necessity of treatment?</td>
</tr>
<tr>
<td>Is the patient prepared for safety and adherence concerns?</td>
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<td>Have the patient’s expectations about treatment been managed?</td>
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<tbody>
<tr>
<td>Where does the patient live in proximity to the clinic/pharmacy?</td>
</tr>
<tr>
<td>Is the treatment regimen a good fit for the patient’s lifestyle (i.e., does the patient work, drive, etc.)?</td>
</tr>
<tr>
<td>Will a family member or caregiver be available to help with treatment and patient care?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Personal factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>How does the patient learn best?</td>
</tr>
<tr>
<td>Does the patient have any cognitive impairment?</td>
</tr>
<tr>
<td>Does the patient have the ability to take medications as prescribed (i.e., swallow pills or open packaging)?</td>
</tr>
<tr>
<td>Does the patient have comorbidities that could impact or affect the treatment regimen or adherence?</td>
</tr>
<tr>
<td>Does the patient use alcohol or drugs?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>How complex is the patient’s treatment regimen?</td>
</tr>
<tr>
<td>Is there pill burden associated with the treatment regimen?</td>
</tr>
<tr>
<td>What is the treatment duration?</td>
</tr>
</tbody>
</table>
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.

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)
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:**

- **Pre-Clinical**
  - Animal Studies
  - IND (IND, IND, IND, IND)

- **Clinical**
  - Phase 1 (≤100 subjects)
  - Phase 2 (100-500 subjects)
  - Phase 3 (500+ subjects)

- FDA Approval

SAFE AND EFFECTIVE FOR USE
SAFE AND EFFECTIVE FOR USE ≠ MAXIMUM VALUE
Many things must happen for new technologies to improve human health

PRE-CLINICAL

ANIMAL STUDIES

IND

PHASE 1
(<100 subjects)

PHASE 2
(100-500 subjects)

PHASE 3
(500+ subjects)

CLINICAL

FDA
APPROVAL

APPROVAL

MAXIMUM BENEFIT

Safe and effective

Compare favorably to other therapeutic options

Represent good value for money

Prescribed appropriately

Adhered to over the long-term

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

**EXPLANATORY TRIALS**

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

**EFFECTIVENESS (PRAGMATIC) TRIALS**

• Undertaken in the “real world” and with usual care and is intended to help support a decision on whether to deliver an intervention

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

Safety and effective

Compare favorably to other therapeutic options

Represent good value for money

Prescribed appropriately

Adhered to over the long-term

CAN WE ENSURE USE?

EFFECTIVENESS (PRAGMATIC) TRIALS
• Undertaken in the “real world” and with usual care and is intended to help support a decision on whether to deliver an intervention

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

**PRECIS-2**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility</td>
<td>To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?</td>
</tr>
<tr>
<td>Recruitment</td>
<td>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?</td>
</tr>
<tr>
<td>Setting</td>
<td>How different are the settings of the trial from the usual care setting?</td>
</tr>
<tr>
<td>Organization</td>
<td>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?</td>
</tr>
<tr>
<td>Flexibility (delivery)</td>
<td>How different is the flexibility in how the intervention is delivered and the flexibility anticipated in usual care?</td>
</tr>
<tr>
<td>Flexibility (adherence)</td>
<td>How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?</td>
</tr>
<tr>
<td>Follow-up</td>
<td>How different is the intensity of measurement and follow-up of participants in the trial from the typical follow-up in usual care?</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>To what extent is the trial's primary outcome directly relevant to participants?</td>
</tr>
<tr>
<td>Primary analysis</td>
<td>To what extent are all data included in the analysis of the primary outcome?</td>
</tr>
</tbody>
</table>

**SOURCE:** BMJ 2015;350:h2147 | doi: 10.1136/bmj.h2147
The PRECIS Tool
PRAGMATIC/EFFECTIVENESS TRIAL DESIGNS

How can pragmatic trials be made more efficient?

**BURDEN OF DATA COLLECTION**

- Use of routinely collected data
- Simplified prospective data collection
- Detailed prospective data collection
- Strict criteria applied to subjects actively identified from selected care settings
- Limited criteria applied to patients actively identified from typical care settings
- Limited criteria applied to patients identified using routinely collected data

**BURDEN OF SUBJECT IDENTIFICATION**

**SOURCE:** Choudhry NK. N Engl J Med 2017; 377: 957-964
How can pragmatic trials be made more efficient?

- Burden of data collection
  - Use of routinely collected data
  - Simplified prospective data collection
  - Detailed prospective data collection
  - Strict criteria applied to subjects actively identified from selected care settings

- Burden of subject identification
  - Traditional efficacy trials
  - Typical pragmatic trials
  - Trials using health insurance data

How can pragmatic trials be made more efficient?

**BURDEN OF DATA COLLECTION**
- Simplified prospective data collection
- Detailed prospective data collection

**TRADITIONAL EFFICACY TRIALS**
- Strict criteria applied to subjects actively identified from selected care settings

**TYPICAL PRAGMATIC TRIALS**
- Limited criteria applied to patients actively identified from typical care settings

**BURDEN OF SUBJECT IDENTIFICATION**

**SOURCE:** Choudhry NK. N Engl J Med 2017; 377: 957-964
How can pragmatic trials be made more efficient?

<table>
<thead>
<tr>
<th>BURDEN OF DATA COLLECTION</th>
<th>TRADITIONAL EFFICACY TRIALS</th>
<th>TYPICAL PRAGMATIC TRIALS</th>
<th>TRIALS USING ROUTINELY-COLLECTED DATA</th>
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</thead>
<tbody>
<tr>
<td>Use of routinely-collected data</td>
<td>Strict criteria applied to subjects actively-identified from selected care settings</td>
<td>Limited criteria applied to patients actively-identified from typical care settings</td>
<td>Limited criteria applied to patients identified using routinely-collected data</td>
</tr>
<tr>
<td>Simplified prospective data collection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detailed prospective data collection</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SOURCE:** Choudhry NK. N Engl J Med 2017; 377: 957-964
Efficacy and implementation could be evaluated simultaneously
Niteesh K. Choudhry, MD, PhD
Center for Healthcare Delivery Sciences
Brigham and Women’s Hospital
Harvard Medical School

W: www.c4hds.org
E: nkchoudhry@bwh.harvard.edu
Study Designs to Evaluate Tracking, Improvement in Medication Adherence, and Impact on Clinical Outcomes
Trial Design Considerations for Adherence Interventions

Real World Relevance Without Sacrificing Rigor

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

Medication Adherence: Landscape, Strategies, and Evaluation Methods
December 10, 2019
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
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
Better Intervention Science Needed

THE INSTITUTE OF MEDICINE SAYS IT TAKES AN AVERAGE OF 17 YEARS FOR PROFESSIONALS TO CHANGE THE WAY THEY PRACTICE MEDICINE, BASED ON EVIDENCE

IOM 2001 Crossing the Quality Chasm
Relevance and Rigor via Pragmatic Trials

Methodologic Rigor

Pedantic

Puerile

Relevance in Diverse Real World Practice Contexts

Pragmatic

Populist

Geng, Peiris, & Kruk 2017 PLOS Medicine
Relevance and Rigor via Pragmatic Trials

PRECIS-2 criteria

Primary analysis
To what extent are all data included?

Eligibility
Who is selected to participate in the trial?

Recruitment
How are participants recruited into the trial?

Setting
Where is the trial being done?

Organisation
What expertise and resources are needed to deliver the intervention?

Follow-up
How closely are participants followed-up?

Primary outcome
How relevant is it to participants?

Flexibility: adherence
What measures are in place to make sure participants adhere to the intervention?

Flexibility: delivery
How should the intervention be delivered?

Loudon 2015 BMJ
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

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
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
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
Patients respond “Fine” or “Problem” & nurses call back those with problems

Weekly text message asks “How are you?”

<table>
<thead>
<tr>
<th></th>
<th>Viral suppression at 12 months</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>57%</td>
<td>0.85 (0.72-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Standard care</td>
<td>48%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RCT outcomes at 12 mos. (N = 538 drug naïve ART initiators in Kenya)

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
“EPIC” HIV PrEP Adherence Trial

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

![Protective Drug Levels](chart)

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

Liu et al *CID* 2018
• 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)
• 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

Take Away Messages

• Pragmatic aspects
  ▪ Real world care settings
  ▪ Limited exclusion criteria* and participants with co-morbidities
  ▪ Comparator is typically usual care
  ▪ Tailored intervention delivery OK
  ▪ Employ attention to treat analysis

• Adding rigor (explanatory aspects)
  ▪ Only enroll those with 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

THANKS!

Michael Stirratt
stirrattm@nih.gov
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
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\(^4\)

---

1. GOLD 2020. www.goldcopd.org
2. GINA 2019. www.ginasthma.org
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.
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

---

**Weekly Adherence Summary**

This week you took your medicine on schedule only 71% of the time. Propeller can help you get back on track.

- Last Week: 29%
- This Week: 71%

*View Adherence Details*

---

**Alert Reminder**

- Dose Status: Did you take your 7:00 AM dose of Breo Ellipta?

---

**Forgetting something?**

Have you taken your Tuesday 7:00 AM dose of Breo Ellipta? Our sensors don’t have any record of it yet... Make sure you stay on schedule!
Study design considerations

**Efficacy**
- E.g., younger, tech savvy

**Population**

**Effectiveness**
- General asthma / COPD

**Setting**
- Clinical, RCT
- 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

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

---

Stanford et al. Am J Respir Crit Care Med. 2019; A5930–A5930  
Van Sickle et al. Eur Respir J. 2016;48:PA1018
Design: Multicenter RCT, in clinic
Treatment: Sensor vs. Sensor+app vs. Sensor+app+HCP
Duration: 6 months
Outcome: ICS/LABA adherence (%)
N: ~250

- Common that efficacy does not translate to effectiveness
- Efficacy $\rightarrow$ effectiveness
  - Define target population
  - Generalizability
  - Study duration
  - Setting
  - Comparator
  - Broader outcome

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

5. Woodcock et al. Eur Respir J. 2018 Feb 1;51(2):1701531
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\(^6\)

<table>
<thead>
<tr>
<th>Practice 1</th>
<th>Practice 2</th>
<th>Practice 3</th>
<th>Practice 4</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

Usual care  Intervention

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

Adherence and clinical outcomes
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 be 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
Improving Medication Adherence

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

Effective in the hospital, interrupted in the ambulatory setting
Pharmacotherapy Feedback Loop

Effective in the hospital, interrupted in the ambulatory setting
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
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

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

Sara H. Browne\textsuperscript{1*}, Anya Umlauf\textsuperscript{1†}, Amanda J. Tucker\textsuperscript{1†}, Julie Low\textsuperscript{2}, Kathleen Moser\textsuperscript{3}, Jonathan Gonzalez Garcia\textsuperscript{1}, Charles A. Peloquin\textsuperscript{4}, Terrence Blaschke\textsuperscript{5}, Florin Vaida\textsuperscript{1}, Constance A. Benson\textsuperscript{1}

1 University of California San Diego, La Jolla, California, United States of America, 2 Orange County Health Care Agency, Santa Ana, California, United States of America, 3 Health and Human Services Agency, San Diego, California, United States of America, 4 University of Florida, Gainesville, Florida, United States of America, 5 Stanford University, Stanford, California, United States of America
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

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

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

- After 12 weeks with digital medicines: 98%
- After 12 weeks with regular medicines: 51%

Change in SBP (mm Hg)

- Usual Care: -15.2
- Proteus: -24.6

Change in LDL (mg/dL)

- Usual Care: -10.9
- Proteus: -30.1

Change in A1c (%,
Baseline ≥8)

- Usual Care: -0.3
- Proteus: -0.31

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


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%

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 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)

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
Feedback Effective in Curing HCV in High-Risk Population

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

<table>
<thead>
<tr>
<th>Number of Sites</th>
<th>18 (including Johns Hopkins, Providence, UCSF, Mount Sinai, Duke and Henry Ford)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>Adults newly initiating treatment for chronic HCV</td>
</tr>
</tbody>
</table>
| 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**

<table>
<thead>
<tr>
<th></th>
<th>SVR4</th>
<th>SVR12</th>
<th>ADHERENCE</th>
<th>PATCH WEAR</th>
<th>Net Promoter Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=205</td>
<td>100%</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>N=217</td>
<td>99.5%</td>
<td></td>
<td>93.0%</td>
<td>93.5%</td>
<td>76.5%</td>
</tr>
<tr>
<td>N=235</td>
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</tbody>
</table>

Sułkowski M, et al AASLD 2019
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)

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

- **100% SVR4**
  - N=205
- **99.5% SVR12**
  - N=217
- **93.0% ADHERENCE**
  - N=235
- **93.5% PATCH WEAR**
  - N=235
- **76.5% Net Promoter Score**
  - N=230

Sułkowski M, et al AASLD 2019
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

---

**Mean Adherence by Drug**
- Mean Adherence by Patient
  - Click on a bar to filter the box plot on the right

**Mean Adherence by Patient**
- Hover over each data point for more details

---

**Patch Wear by Patient**
- Hover over each data point for more details

---

**Cumulative Patch Wear over Time**
- Filter data range from
  - 1/1/2015
  - 12/5/2019
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))

Recommendation of Proteus to a Friend with a Similar Health Condition

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<th>Overall Rating</th>
<th>Number of Respondents</th>
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<td>0</td>
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</tbody>
</table>
Study Designs to Evaluate Tracking, Improvement in Medication Adherence, and Impact on Clinical Outcomes
Closing Remarks
Adjournment
Thank You!

Contact Us

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Washington, DC 20004

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