Quantifying Medication Adherence: Practical Challenges and an Approach to Linking Alternative Measures

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Part 1: Medication Adherence

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Eli Lilly and Company
Needs for Better Measure of Medication Adherence

- Value-based pricing and performance-based contracting align incentives of payer and pharmaceutical companies to find ways to reduce cost and improve medication adherence and outcomes.
- Medication adherence as a quality measure: Percent of patients with Proportion of Days Covered (PDC) ≥80% used for quality rating for health plans in the US.
- Observational studies assume greater importance in demonstrating value to payers, and adherence data will be routinely collected in such settings.
Adherence is Poor

US Adults Receive Only About Half of Recommended Care, and Quality Varies Significantly by Medical Condition

Medication Non-adherence leads to Bad Outcomes: Delay in Initiation

AMI or Death rate

Ho et al. Circulation Quality Outcomes 2010: 300-00
Medication Non-Adherence leads to Bad Outcomes: Premature Discontinuation

Better Adherence Reduces HCRU

Adherence Level

- **n = 182, 1%-19%**
- **n = 259, 20%-39%**
- **n = 419, 40%-59%**
- **n = 599, 60%-79%**
- **n = 1801, 80%-100%**

Hospitalization Risk, %

* Indicates significantly higher cost vs the 80%-100% adherence group (P < .05); Adherence was defined as the percentage of days during the 1-year analysis period that patients had a supply of 1 or more maintenance medications for the condition.

Incentive Works: A Case of Warfarin Lottery Experiment

Incentive works while it is offered.

Part 2: Combining Approaches to Studying Adherence – Proof of Concept

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Type 2 Diabetes

- **Global diabetes prevalence in 2010: 285 million**
  - 90-95% have type 2 diabetes
  - Approximately 8% prevalence in the US
- **Extensive and effective range of therapies to manage glycaemia**
  - Yet, only about 50% of patients achieve HbA1c of <7.0%
- **32.5% of patients nonadherent to diabetes treatments**
  - In an administrative claims database, 29% nonadherent to oral agents
- **Nonadherence associated with health impacts and higher costs**
  - 10% decrease in adherence ≈ 0.14% increase in HbA1c
  - Nonadherence increases risk of complications, hospitalizations, and death => increased costs

Medication Adherence in Type 2 Diabetes (continued)

• Factors affecting adherence to therapies

  - Polypharmacy
  - Regimen complexity
  - Patient understanding of therapeutic value, dosing regimen
  - Depression
  - Side effects
  - Racial, ethnic, and socioeconomic factors
  - Cost of medications, need for refills
  - Social support

Which interventions work?

• **Need to study the disease and population of interest**
  – E.g., disease severity, managed care organization participant

• **Evaluating interventions in any particular population can be complex**
  – E.g., prospective study (e.g., survey, randomized-controlled trial, observational cohort study, or quasi-experimental study) of patients in administrative claims database

• **This workshop explores an alternative approach**
Combining Types of Adherence Studies to Evaluate Interventions: Proof of Concept

Question:
Which interventions are effective in increasing adherence to oral type 2 diabetes treatment in a managed care population?

Answer:
Simulates intervention in survey sample
Likely effect of treatment attributes on adherence

Sample matched to population
Stated Adherence Survey
Combining Types of Adherence Studies to Evaluate Interventions: Proof of Concept

• This is just one of many ways to combine approaches.
  • Key idea: combine sources of information to enhance the value/meaning of studies
  • Leverage strengths and overcome limitations in any single approach
Part 3: Estimating likely adherence using patient preference studies

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## Approaches to measuring adherence to current therapy

<table>
<thead>
<tr>
<th>Approach</th>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td><strong>Self-reported</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interviews</td>
<td>Easy to use, inexpensive</td>
<td>Social desirability and interviewer bias, measurement error</td>
</tr>
<tr>
<td>Diaries</td>
<td></td>
<td>Diaries must be returned</td>
</tr>
<tr>
<td>Questionnaires</td>
<td>Easy to use, inexpensive, some are validated</td>
<td></td>
</tr>
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<tr>
<td>(indirect)</td>
<td></td>
<td></td>
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<tr>
<td>Administrative claims</td>
<td>Noninvasive, long-term data, large populations</td>
<td>Validity of measures</td>
</tr>
<tr>
<td>Electronic monitors</td>
<td>Regimen adherence</td>
<td>Expensive, inconvenient</td>
</tr>
<tr>
<td>Pill count or canister weight</td>
<td>Easy to use, inexpensive</td>
<td>No information on regimen adherence, alteration</td>
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<td>Plasma drug concentration</td>
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</tr>
<tr>
<td>Biological marker</td>
<td></td>
<td></td>
</tr>
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<td>Directly observed therapy</td>
<td>Verifies use</td>
<td>Impractical in outpatient settings</td>
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<td><strong>Non-self-reported (Direct)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stated adherence</td>
<td>Questionnaire: Easy to use, inexpensive, assess unavailable options</td>
<td>Conditional and hypothetical, measurement error</td>
</tr>
<tr>
<td>Assesses likely adherence conditional on treatment and personal attributes</td>
<td></td>
<td></td>
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<tr>
<td>Plasmid drug concentration</td>
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Previous Approaches to Studying Likely Adherence Using Patient Preference Studies

• **Prospective Adherence**
  – Attempts to use preferences to predict future adherence behavior

• **Previous studies**
  – For a given profile or pair of profiles ask respondents to rate likely adherence or non-adherence
  – Elicit preferences over adherence and outcomes jointly
  – Collect data on preferences and actual adherence simultaneously (revealed and stated preference)
## Likely Adherence Ratings

Source: Hauber et al., Diabetic Medicine 2009

<table>
<thead>
<tr>
<th>Medication Feature</th>
<th>Medication A</th>
<th>Medication B</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c change</td>
<td><img src="HbA1cLevels.png" alt="HbA1c Levels" /></td>
<td><img src="HbA1cLevels.png" alt="HbA1c Levels" /></td>
</tr>
<tr>
<td>Number of hypoglycemic events per month</td>
<td>1 to 2</td>
<td>More than 2</td>
</tr>
<tr>
<td>Water retention</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Weight gain in first 6 months</td>
<td>None</td>
<td>10 pounds</td>
</tr>
<tr>
<td>Mild stomach upset</td>
<td>Mild nausea and vomiting or diarrhea that continues as long as you take the medicine</td>
<td>No stomach problems</td>
</tr>
<tr>
<td>Chance of a heart attack</td>
<td><img src="NoAdditionalPerson.png" alt="No additional person" /></td>
<td><img src="10AdditionalPeople.png" alt="10 additional people out of 1,000 (1.0%) will have a heart attack" /></td>
</tr>
</tbody>
</table>

### Which medication would you choose?
- I would choose Medication A □
- I would choose Medication B □

### How likely would you be to miss or skip doses of each medication?
- Much more likely to miss or skip doses with Medication A □
- A little more likely to miss or skip doses with Medication B □
- Equally likely to miss or skip doses with Medication A and Medication B □
- A little more likely to miss or skip doses with Medication B □
- Much more likely to miss or skip doses with Medication B □
Predicted Likely Adherence

Source: Hauber et al., Diabetic Medicine 2009
Part 4: Combining Approaches to Studying Adherence

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Steps in Combination Approach

1. Select off-the-shelf stated adherence study
2. Select “cases” from survey sample:
   • Drop stated adherence survey respondents with characteristics not observed in administrative claims database
3. Select matched “controls” from administrative claims data
4. Compare retrospective adherence measures for cases and controls
   • Did matching yield groups that were similar in terms of retrospective adherence?
5. Examine likely adherence in “cases” as proxy for results for the “controls”
Patients’ Stated Preferences for Type 2 Diabetes Mellitus Treatments

- Elicit patient preferences for oral type 2 diabetes mellitus (T2DM) treatments
  - Estimate relative preference weights for levels of treatment attributes
  - Estimate likely effect of treatment attributes on adherence

- Survey structure:
  - Respondent socioeconomic and demographic characteristics
  - Health and treatment history, including current treatment adherence
  - Description of treatment attributes
  - Choice questions
Example Treatment-Adherence Question

Imagine your blood sugar level is 206 (uncontrolled). Please think about the following medicines, Medicine A and Medicine B.

<table>
<thead>
<tr>
<th>Medicine Feature</th>
<th>Medicine A</th>
<th>Medicine B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in average blood sugar level</td>
<td>![Graph showing decrease from 206 mg/dL to 140 mg/dL controlled]</td>
<td>![Graph showing decrease from 206 mg/dL to 151 mg/dL controlled]</td>
</tr>
<tr>
<td>Dosing schedule</td>
<td>![Table showing dosing schedule]</td>
<td>![Table showing dosing schedule]</td>
</tr>
<tr>
<td>Chance of stomach problems</td>
<td>30 out of 100 (30%)</td>
<td>25 out of 100 (25%)</td>
</tr>
<tr>
<td>Frequency of low blood-sugar episodes</td>
<td>No low blood-sugar episodes</td>
<td>No low blood-sugar episodes</td>
</tr>
<tr>
<td>Weight change</td>
<td>6-pound weight gain</td>
<td>3-pound weight gain</td>
</tr>
<tr>
<td>Increased chance of CHF</td>
<td>3 additional people out of 100</td>
<td>3 additional people out of 100</td>
</tr>
<tr>
<td>Personal medicine cost</td>
<td>$200 per month</td>
<td>$25 per month</td>
</tr>
</tbody>
</table>

Which medicine would you choose if these were the only two medicines available?  

- Medicine A
- Medicine B

How likely would you be to miss or skip doses of each medicine?  

- Much more likely to miss or skip doses with Medicine A
- A little more likely to miss or skip doses with Medicine A and Medicine B
- Equally likely to miss or skip doses with Medicine A and Medicine B
- A little more likely to miss or skip doses with Medicine B
- Much more likely to miss or skip doses with Medicine B
Study Sample

- **Inclusion criteria**
  - Age 18 years or older
  - Resident of the United States
  - Not currently using insulin
  - Not currently using injectable T2DM medicines
  - Both currently taking and not taking oral T2DM medicines

- **Survey participant recruitment**
  - Approved by RTI International’s institutional review board
  - Recruited from Knowledge Networks’ Web panel

- **Final sample size for choice modeling was 923**
“Case” Selection

• **Part 1: Keep survey respondents diagnosed at most 5 years ago and with private health insurance**
  
  – Admin claims has 5 years of data on privately insured individuals
  
  – Kept 172 out of 923 survey respondents
Part 5: Measuring adherence using administrative claims data

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Data Source

• A large, US-based, commercial insurance administrative claims database

• Data include:
  – Enrollment and demographic information
  – Medical claims (inpatient, outpatient, office) with information on payments, date of service, place of service, diagnoses, procedures, and admission and discharge dates for inpatient stays
  – Pharmacy claims with information on payments, date of fill, drug name, drug class, strength, quantity, and days supplied
Selection of Matched “Control”

- **Patients with at least one medical claim with a primary or nonprimary diagnosis on or after January 1, 2009, through December 31, 2011, for type 2 diabetes**

- **Further restricted to enrollees with one or more pharmacy claims for an oral antidiabetic agent (OAD)**
  - For each patient, the index date was defined as the date of the earliest observed OAD prescription
    - OADs identified using NDCs, and brand and generic drug names

- **Enrollees were required to be continuously enrolled in the health plan between January 1, 2007, and December 31, 2011**

- **At least 40 years of age**
Matching Approach

- **Simple matching without replacement used**
  - Sought to match patients from the enrollees in the administrative claims to the survey “cases” 5:1
  - Matched on
    - Sex
    - Age
    - Geographic region
    - Comorbidities (i.e., depression/anxiety; renal insufficiency; diabetic foot issues; hypertension; hyperlipidemia; retinopathy; neuropathy; osteoporosis; osteoarthritis; rheumatoid arthritis; angina; MI; history of stroke; liver disease; cancer; and stomach ulcer)
Adherence Measure and Analysis

• Proportion of days covered by an OAD, assessed during the 360 days following each patient’s OAD index date

• PDC = Sum of days in observation period with an OAD on hand / Days in observation period (i.e., 360)
  – Both continuous PDC and related categories were generated

• Following matching, PDC among the control group was summarized with simple descriptive analyses (i.e., mean; frequency distribution)
Results

- 5 controls were matched to 130 (out of 172) “cases” with survey data (N=650 controls)
- Mean (SD) PDC was 77.3% (28.3%)
- Nearly 40% of the control group was nonadherent to their OAD treatment (i.e., PDC < 80%)

<table>
<thead>
<tr>
<th>PDC</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19%</td>
<td>40</td>
<td>6.15</td>
</tr>
<tr>
<td>20-39%</td>
<td>52</td>
<td>8.00</td>
</tr>
<tr>
<td>40-59%</td>
<td>74</td>
<td>11.38</td>
</tr>
<tr>
<td>60-79%</td>
<td>88</td>
<td>13.54</td>
</tr>
<tr>
<td>80%+</td>
<td>396</td>
<td>60.92</td>
</tr>
<tr>
<td>Total</td>
<td>650</td>
<td>99.99</td>
</tr>
</tbody>
</table>
Limitations

• Assumes a prescription filled is a prescription consumed
• Do not know if patient was told by clinician to alter medication taking (e.g., decrease dose; stop taking medication entirely)
• Cannot account for prescriptions filled outside the insured setting
• What to do if more than one medication is apparent?
  – Only count a day as covered if both medications are on hand?
Part 6: Combining Approaches to Studying Adherence, continued

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Self-reported adherence from survey

- Qualitative responses
- Tend to indicate higher level of adherence than nonself-reported measures

Comparing Adherence Measures

Self-reported adherence from survey
- Qualitative responses
- Tend to indicate higher level of adherence than nonself-reported measures

PDC from Administrative Claims Data
- Quantitative response

Comparing Adherence Measures (continued)

- Need to quantify qualitative categories
- Different concepts underlying retrospective adherence measures
Treatment Adherence

• We modeled treatment adherence using an ordered probit model
  – Dependent variable = Relative adherence rating
  – Independent variables = Treatment attribute levels
  – The model estimated the impact of treatment characteristics on ratings of likely treatment adherence

• The estimated parameters measure the effect of treatment attributes on likely treatment adherence
What Could Affect Treatment Adherence? (N = 172)

I denotes 95% confidence interval
Limitations in this application

- **Different adherence measures**
  - Self-reported ≈ day-to-day average adherence
  - PDC ≈ whether medicine is on-hand
  - Likely adherence ≈ likely relative adherence conditional on treatment attribute levels

- **Limited number of “cases” due to use of existing survey data**
  - Lack of precision in likely adherence analysis
  - Representativeness

- **“Controls” selected on basis of selected observable characteristics**
  - Survey “cases” may differ in terms of other observables or unobservables

- **Treatment attribute levels similar to current levels**

- **Usual suspects in patient preferences:**
  - Hypothetical bias, measurement error, statistical error, sampling error
Possible Extensions

- **Use larger administrative claims data as source of “cases” and design survey sample prospectively to recruit matched “controls”**
  - Would ensure larger survey sample to match to claims sample
  - Tailor survey items to better align with measures in claims data
  - Select treatment attribute levels outside of currently available levels
- **Link different adherence measures via behavioral model**
- **Combine different types of studies or sources of information, e.g.,**
  1. Combine data on “cases” in retrospective chart review with data on matched “controls” from insurance claims database
     - Insurance claims data would provide broader data on health care use than chart review
  2. Explore similar topics in different data sources (e.g., Cook et al. 2005 J Am Pharm Assoc)
  3. Combine data on “cases” in observational studies with data on matched “controls” from surveys
     - Provide an understanding of potential behavior with respect to currently unavailable treatments
Conclusion

- Administrative claims databases often lack person-level characteristics that might influence adherence
  - E.g., education; social support systems; other living arrangements

- A survey on a sample matched to enrollees in administrative databases may offer a relatively easy way to generate interesting data about a population of interest
  - Less complex than collecting data directly from enrollees in administrative database
Part 7: Summary of survey and discussion