CLUSTER RANDOMIZED TRIALS IN HEALTH CARE DELIVERY SYSTEMS: lessons from STIC2IT

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Over the long-term, only half of patients adhere to the evidence-based drugs prescribed to them.
“Drugs don’t work in people who don’t take them”
-- C. Everett Koop

Worse health outcomes

- Increased spending
- Decreased adherence

"Drugs don’t work in people who don’t take them" -- C. Everett Koop

Non-adherence is a public health problem

- At a national level in the US non-adherence accounts for:
  - 125,000 deaths per year in U.S
  - 11% of hospitalizations
  - $100 billion to $300 billion in annual spending

- Non-adherence also threatens the billions of dollars that have been invested in:
  - Identifying new medications
  - Rigorous evaluation
  - Improving drug prescribing

**SOURCES:** Choudhry and Winkelmayer. JGIM 2008; 23: 216-218
Many interventions to improve adherence have been tested.
Existing adherence improvement interventions have substantial limitations

- **Most interventions have only been modestly effective**
  - Do not adequately address each individual’s unique adherence barriers
  - Imprecisely targeted to patients who do not need adherence assistance

- **Even effective interventions are difficult to sustain**
  - Often require new infrastructure and/or are expensive
OBJECTIVE

STIC2IT: Study of a Tele-pharmacy Intervention for Chronic diseases to(2) Improve Treatment adherence

- To evaluate the effect of a medication adherence intervention for diabetes, hypertension, and hyperlipidemia that was:
  - Targeted ➔ FOCUSED ON PATIENTS MOST LIKELY TO BENEFIT
  - Multi-component ➔ ADDRESSED MULTIPLE BARRIERS
  - Behaviorally-tailored ➔ PERSONALIZED TO PATIENT NEED
  - Delivered by practice-embedded pharmacists ➔ INTEGRATED INTO EXISTING CARE
  - Technologically-enabled ➔ IMPROVED EFFICIENCY

ADULT PATIENTS OF A LARGE MULTI-SPECIALTY GROUP PRACTICE WITH DIABETES, HYPERTENSION OR HYPERLIPIDEMIA

CONTACTED AND OFFERED:
- pharmacist telephone consultation (using brief negotiated interviewing)
- text messages (reminders or motivation)
- automated individual progress reports

RANDOMIZED PRACTICE SITES (N=14)

USUAL CARE

POOR DISEASE CONTROL (based on EHR data)

NON-ADHERENT (based on claims data)

CONTENT tailored to “patient activation” + adherence barriers

FUNDING: NHLBI R01 HL117918 clinicaltrials.gov NCT02512276

- END OF FOLLOW-UP: July 2017
Randomization

- **CLUSTER**: Randomized clinics (practice sites) rather than individual providers or patients to reduce contamination
  - Individual providers (both physicians and pharmacists) care for multiple patients
  - Individual patients are cared for by multiple providers in a given practice site

- **BLOCK**: Practice sites differ from each other in important ways and simple cluster randomization may result in imbalanced groups
  - Practices categorized into “blocks” based on size and whether they had a previous clinical pharmacy program
  - Randomization performed within the blocks
METHODS

Recruitment

Identified potentially eligible patients in intervention practices

Randomly selected 85 every 2 weeks (to achieve timely outreach within resource constraints)

Contacted patients' PCP via EHR to request permission to enroll their patients → if no response, patients were opted into the study

Patients sent a letter (hand addressed, included small gift, signed by their PCP) informing them about the study

Telephone call by a RA and invited to participate, schedule a pharmacist call + administer baseline questionnaires [3 attempts]

Follow-up letter
METHODS

Outcomes assessed using routinely-collected data

- Outcomes assessed during the 12 months after randomization

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Data Source</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication adherence</strong></td>
<td>Prescription health insurance data</td>
<td>Average adherence (“proportion of days covered”) for eligible medications at the time of randomization</td>
</tr>
<tr>
<td><strong>Disease control</strong></td>
<td>Electronic health record data</td>
<td>Proportion of patients meeting guideline targets for: (a) all eligible conditions and (b) at least 1 eligible condition</td>
</tr>
</tbody>
</table>
Primary analyses conducted on an intention-to-treat basis
- Assumed that ~50% of patients would agree to a pharmacist consultation
- Accounted for clustering at the practice level with a design effect of 1.10
- Powered for a 2.5% mean improvement in adherence (assuming a SD of 25%) and 20% between-group difference in the relative risk of our secondary clinical outcome (assuming a baseline risk of 23%)

Clinical outcomes were evaluated using routinely collected data
- Used values that were closest to the end of each patient’s 12-month follow-up period
- Used multiple imputation (with 20 imputations to achieve in-range values and 99% relative efficiency)
Clinical pharmacist telephone consultations lasted a mean of 24.9 minutes; 1050 (98.2%) patients completed at least 2 calls and 175 (16.4%) patients received 3 or more calls.

8 intervention and 11 control patients lost insurance eligibility within 2 weeks of randomization.
## RESULTS

### Baseline characteristics

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>USUAL CARE (N=2040)</th>
<th>INTERVENTION (N=2038)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years*</td>
<td>60.4</td>
<td>59.2</td>
</tr>
<tr>
<td>Male sex</td>
<td>54.7%</td>
<td>55.0%</td>
</tr>
<tr>
<td>White race*</td>
<td>53.6%</td>
<td>60.6%</td>
</tr>
<tr>
<td>Qualifying conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>72.0%</td>
<td>73.7%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25.9%</td>
<td>23.8%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12.1%</td>
<td>11.9%</td>
</tr>
<tr>
<td>Charlson comorbidity score, mean</td>
<td>0.90</td>
<td>0.74</td>
</tr>
<tr>
<td>Baseline disease control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol, mean mg/dL,</td>
<td>204.8</td>
<td>207.8</td>
</tr>
<tr>
<td>Systolic blood pressure, mean mmHg</td>
<td>149.9</td>
<td>149.2</td>
</tr>
<tr>
<td>Hemoglobin A(_1)c, mean</td>
<td>9.8</td>
<td>9.5</td>
</tr>
<tr>
<td><strong>Baseline adherence, mean</strong></td>
<td><strong>57.0%</strong></td>
<td><strong>57.2%</strong></td>
</tr>
</tbody>
</table>

* Standardized mean difference for age and race/ethnicity were >0.1; there were no other significant differences
STIC2IT: PRIMARY OUTCOME

Adherence

<table>
<thead>
<tr>
<th>Months after randomization</th>
<th>Monthly adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
</tr>
<tr>
<td>1</td>
<td>45%</td>
</tr>
<tr>
<td>2</td>
<td>44%</td>
</tr>
<tr>
<td>3</td>
<td>43%</td>
</tr>
<tr>
<td>4</td>
<td>42%</td>
</tr>
<tr>
<td>5</td>
<td>41%</td>
</tr>
<tr>
<td>6</td>
<td>40%</td>
</tr>
<tr>
<td>7</td>
<td>40%</td>
</tr>
<tr>
<td>8</td>
<td>40%</td>
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<tr>
<td>9</td>
<td>40%</td>
</tr>
<tr>
<td>10</td>
<td>40%</td>
</tr>
<tr>
<td>11</td>
<td>40%</td>
</tr>
<tr>
<td>12</td>
<td>40%</td>
</tr>
</tbody>
</table>

Median (IQR) time from randomization to pharmacist call (when it occurred): 22 (17 to 32) days

Intention to Treat: $\uparrow 4.7\%$ (p<0.001)

As Treated: $\uparrow 10.4\%$ (p<0.001)

- Hyperlipidemia: 4.6% (p<0.001)
- Hypertension: 8.5% (p<0.001)
- Diabetes: -0.2% (p=0.86)
SUBGROUP ANALYSES

Adherence

OVERALL

≥ 65 years
< 65 years

Female
Male

White
Black
Other

Baseline adherence < 50%
Baseline adherence ≥ 50%

1 eligible condition
2 or 3 eligible conditions

Interaction p-value

p=0.19
p=0.03
p=0.56
p=0.44
p=0.77

Absolute difference in adherence (%)
STIC2IT: SECONDARY OUTCOMES (INTENTION TO TREAT)

Disease control and resource utilization

Usual care
Intervention

% achieving good control

DISEASE CONTROL

71.2% 72.9%

p=NS*

Hospitalizations

HOSPITAL ADMISSIONS

7.7% 8.3%

p=NS

ER visit

ER VISITS

5.5% 4.4%

OR 0.62 (0.45-0.85)

*As treated OR for good disease control (≥1 eligible condition): 1.24 (1.03-1.50)
The STIC2IT intervention improved adherence

- An intervention for patients with diabetes, hypertension, and hyperlipidemia with poor medication adherence and suboptimal disease control:
  - Effect size was similar to those achieved by more labor intensive interventions
  - Used highly-pragmatic research methods to facilitate the generalizability of the results
SUMMARY AND IMPLICATIONS

Intervention did not improve secondary clinical outcomes

- Routinely-collected data used inaccurate?
- Adherence improvement too small?
- Patients may have required therapeutic intensification?

FUTURE INTERVENTIONS MAY NEED TO:
- Be more intensive while still pragmatic
- Focus on a more impactable patient population
- Simultaneously address adherence and other barriers to optimal disease control
LESSONS FROM STIC2IT FOR FUTURE DELIVERY BASED RCTS

Multi-level engagement is critical

- **SYSTEM**
  - Many systems have multiple competing priorities
  - Some do not want to randomize practices
  - **STIC2IT**: High-level engagement (but still required many months of negotiation after the grant was awarded)

- **PHYSICIANS**
  - Patients are being cared for in real care environments
  - Disconnecting PCPs could have implications for safety and patient willingness to participate
  - **STIC2IT**: “opt-out” approach for PCP approval + pharmacist consultation notes saved in the HER

- **PATIENTS**
  - Amplified by cluster randomization and an ITT analytic approach (i.e. non-receipt of the intervention = little likelihood of benefit)
  - **STIC2IT**: patient outreach all signed by patients’ PCPs
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Introduction

Review study medications

Assess self-reported adherence
  - If no self-reported non-adherence:
  - If self-reported non-adherence:
    - Elicit primary adherence barrier
    - Assess other adherence barriers

Continue to assess non-adherence
  - Rephrase/ask adherence barrier questions
  - If still no self-reported non-adherence:

Focus BNI on disease control

Enhance motivation

Negotiate a plan
  - Summarize/Offer resources
  - Schedule follow-up (PAM 1 and 2)

STIC2IT: Brief Negotiated Interviewing
STIC2IT: Intervention Tailoring

**Intervention**

- **PATIENT ACTIVATION**
  - **High (PAM 56-100)**: Pharmacist call, Text messages
  - **Medium (PAM 48-55)**: Pharmacist call, Text messages, Follow-up calls
  - **Low (PAM 0-47)**: Pharmacist call, Text messages, Follow-up calls, Video visits

Automated report cards at 6, 9 and 12 months using claims and EHR data

**SOURCE:** Choudhry et al. American Heart Journal 2016;180:90-97
PATIENT ACTIVATION MEASURE (PAM)

- Assesses individual’s willingness, knowledge, skills and confidence for managing one’s health

<table>
<thead>
<tr>
<th>LEVEL 1</th>
<th>LEVEL 2</th>
<th>LEVEL 3</th>
<th>LEVEL 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predisposed to be passive</strong></td>
<td><strong>Building knowledge and confidence</strong></td>
<td><strong>Taking action</strong></td>
<td><strong>Maintaining behaviors, pushing further</strong></td>
</tr>
<tr>
<td>Patients lack the confidence to play an active role in their health.</td>
<td>Patients have some knowledge but large gaps remain. They can set simple goals.</td>
<td>Patients have the key facts and are building skills. They are goal-oriented.</td>
<td>Patients have adopted new behaviors but may struggle in times of stress or change. Healthy lifestyle is a key focus.</td>
</tr>
<tr>
<td>‘My doctor is in charge of my health.’</td>
<td>‘I could be doing more.’</td>
<td>‘I’m part of my healthcare team.’</td>
<td>‘I’m my own advocate.’</td>
</tr>
</tbody>
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**GENERAL POPULATION:**

<table>
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<tr>
<th>Level 1</th>
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<tbody>
<tr>
<td>10-15%</td>
<td>20-25%</td>
<td>25-30%</td>
<td>20-25%</td>
</tr>
</tbody>
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Source: Insignia Health