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

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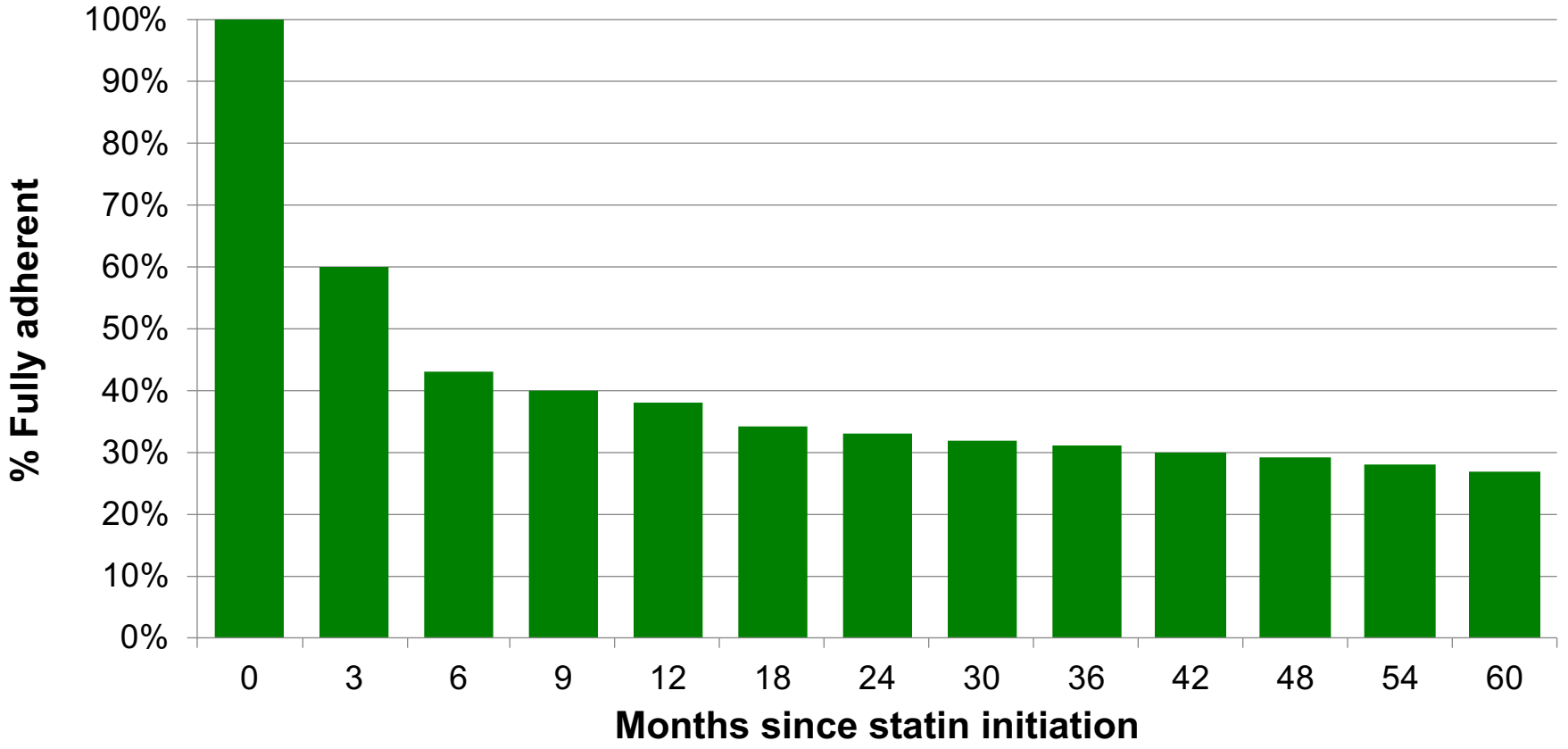
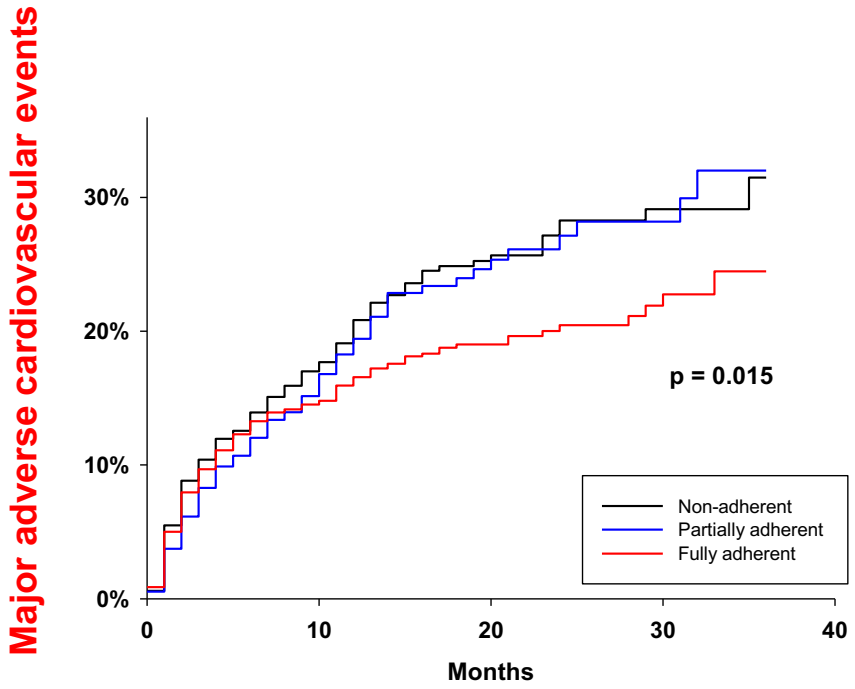
Over the long-term, only half of patients adhere to the evidence-based drugs prescribed to them



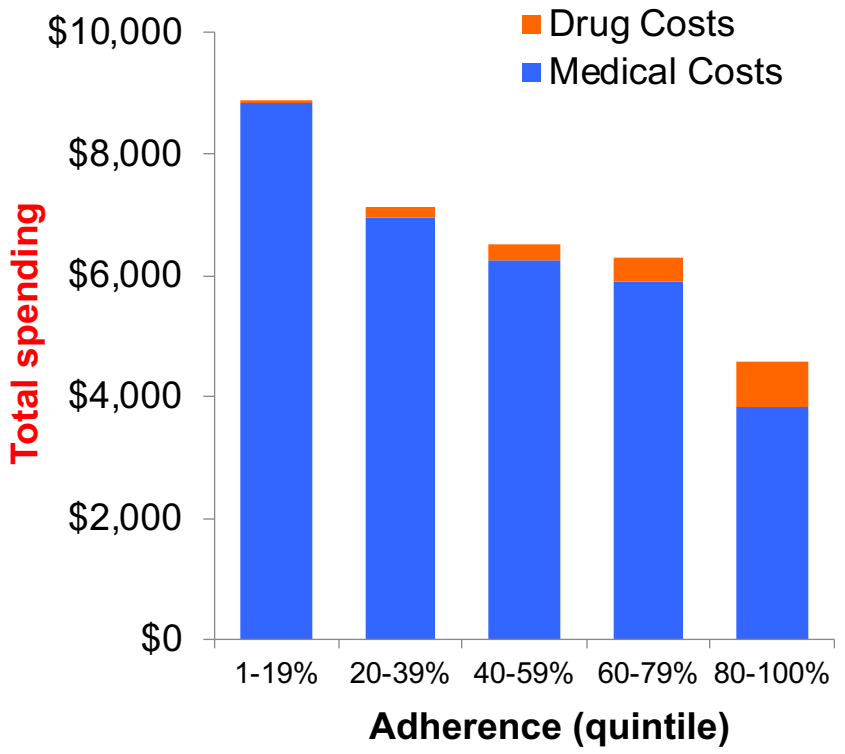
SOURCES: Benner et al. JAMA 2002; 288: 455; Jackevicius et al. JAMA 2002; 288: 462; Akincigil et al. JGIM 2008; 23: 115; Choudhry et al. Circulation 2008;117;1261-1268

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

Worse health outcomes



Higher spending



SOURCE: Choudhry et al. Am Heart J 2014; 167: 51-58; Sokol et al. Med Care 2005; 43: 520

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

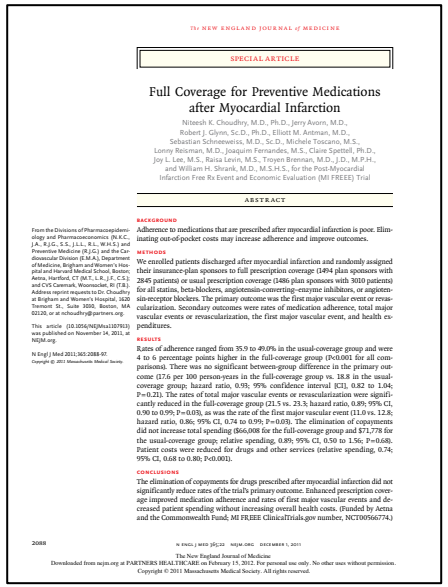
FINANCIAL INCENTIVES

REMINDER DEVICES

TEXT MESSAGES

SMARTPHONE APPLICATIONS

MEDICATION SYNCHRONIZATION



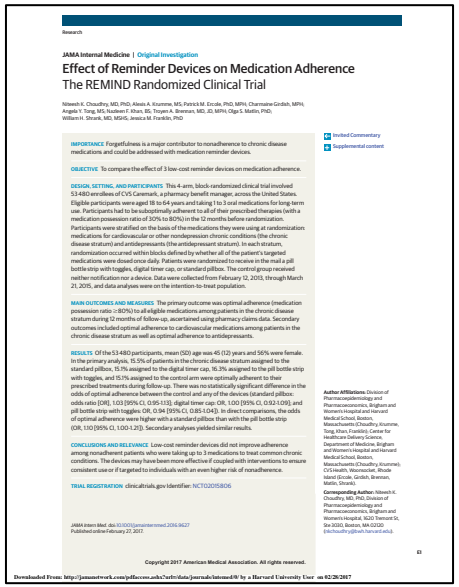
The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Full Coverage for Preventive Medications after Myocardial Infarction

Nitesh K. Choudhry, M.D., Ph.D., Jerry Avorn, M.D., Robert J. Glynn, Sc.D., Ph.D., Elliott M. Antman, M.D., Sebastian Schneeweiss, M.D., Sc.D., Michele Toscano, M.S., Lonny Reisman, M.D., Joaquim Fernandes, M.S., Claire Spettell, Ph.D., Joy L. Lee, M.S., Raisa Levin, M.S., Troyen Brennan, M.D., J.D., M.P.H., and William H. Shrank, M.D., M.S.H.S., for the Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREE) Trial

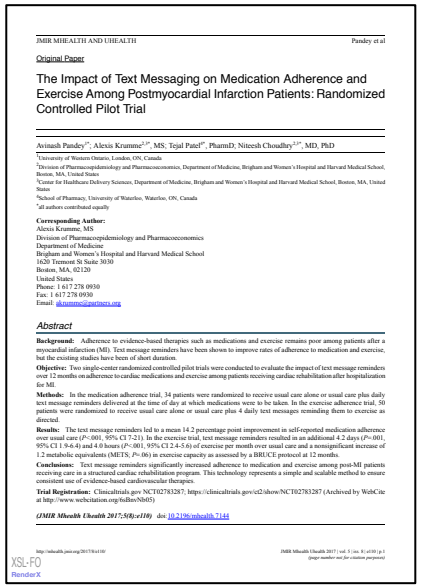
ABSTRACT



Research

JAMA Internal Medicine | Original Investigation

Effect of Reminder Devices on Medication Adherence
The REMIND Randomized Clinical Trial



JMIR MHEALTH AND UHEALTH

Original Paper

The Impact of Text Messaging on Medication Adherence and Exercise Among Postmyocardial Infarction Patients: Randomized Controlled Pilot Trial

Abstract

Research

JAMA Internal Medicine | Original Investigation

Association of a Smartphone Application With Medication Adherence and Blood Pressure Control
The MedISAFE-BP Randomized Clinical Trial

PHARMACEUTICALS & MEDICAL TECHNOLOGY

Medication Synchronization Programs Improve Adherence To Cardiovascular Medications And Health Care Use

ABSTRACT

SOURCES: Choudhry et al. NEJM 2011; 365: 2088-97; **:** Choudhry et al. JAMA Internal Medicine 2017;177:624-31; Pandey et al. *JMIR Mhealth and Uhealth* 201; Morawski et al JAMA Internal Medicine 2018; 178: 802-0; Krumme et al. Health Affairs 2018; 37: 125-33

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

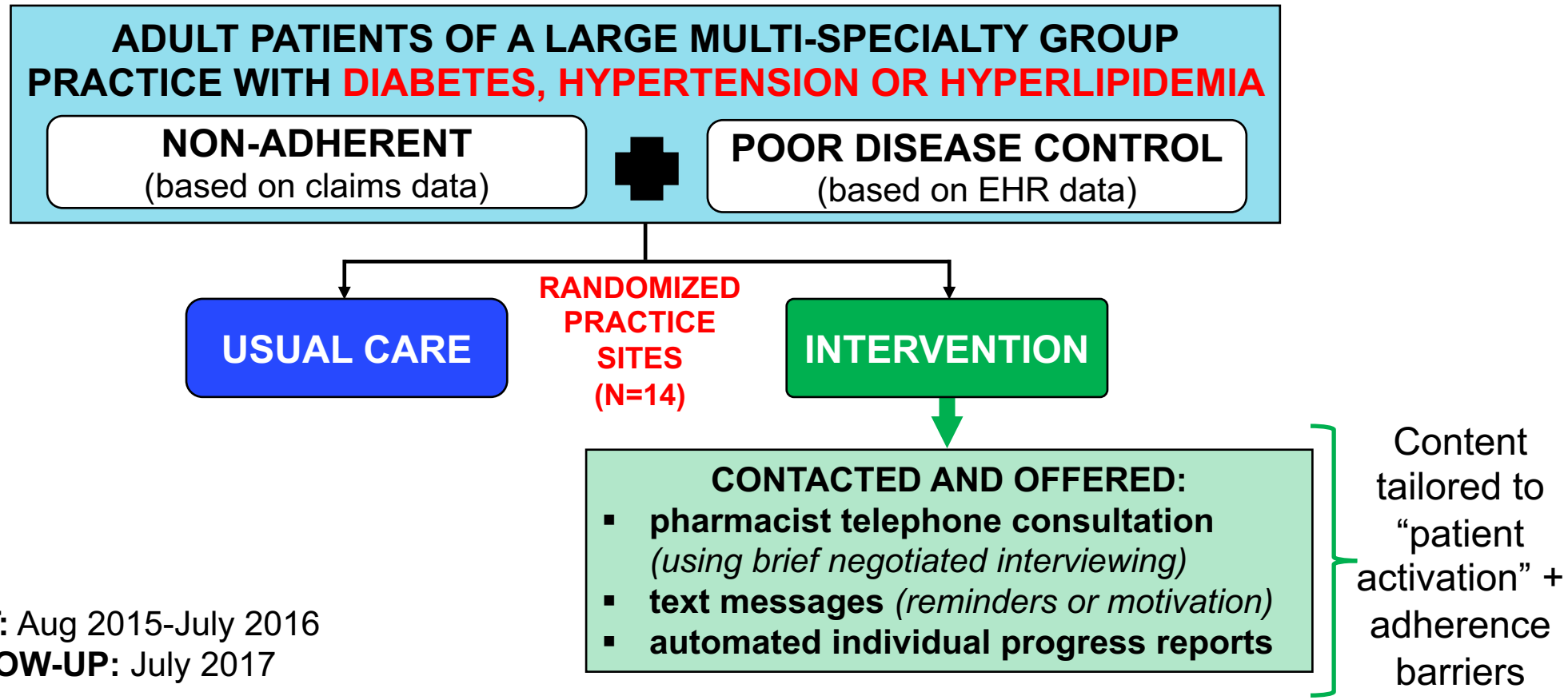
- To evaluate the effect of a medication adherence intervention for diabetes, hypertension, and hyperlipidemia that was:

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**

SOURCE: Choudhry et al. American Heart Journal 2016; 180: 90-97; Choudhry et al. JAMA Internal Medicine 2018; 178: 1174-1181

DESIGN

Open-label, pragmatic cluster-randomized trial



- **ENROLLMENT:** Aug 2015-July 2016
- **END OF FOLLOW-UP:** July 2017

FUNDING: NHLBI R01 HL117918
clinicaltrials.gov NCT02512276

METHODS

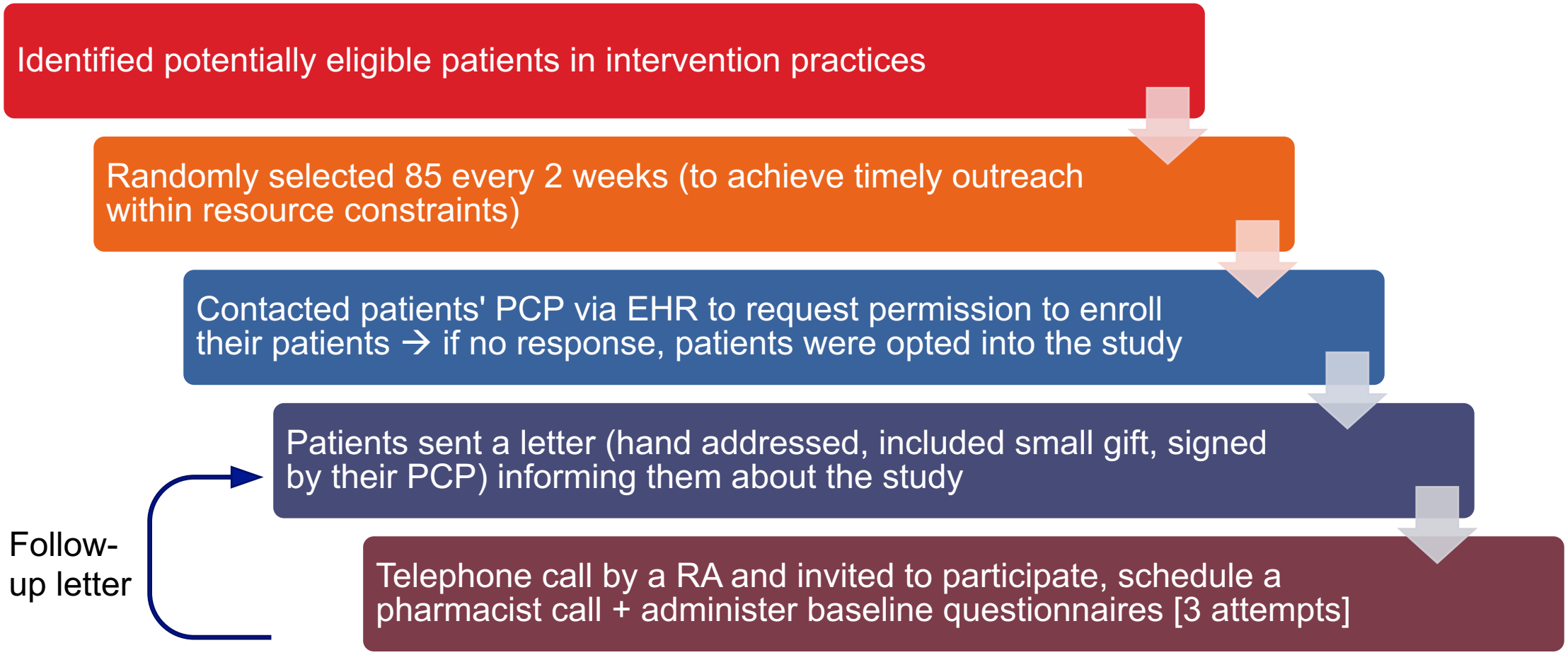
Randomization

- **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



METHODS

Outcomes assessed using routinely-collected data

- **Outcomes assessed during the 12 months after randomization**

	Outcome	Data Source	Definition
1°	**Medication adherence**	Prescription health insurance data	Average adherence ("proportion of days covered") for eligible medications at the time of randomization
2°	**Disease control**	Electronic health record data	Proportion of patients meeting guideline targets for: (a) all eligible conditions and (b) at least 1 eligible condition

METHODS

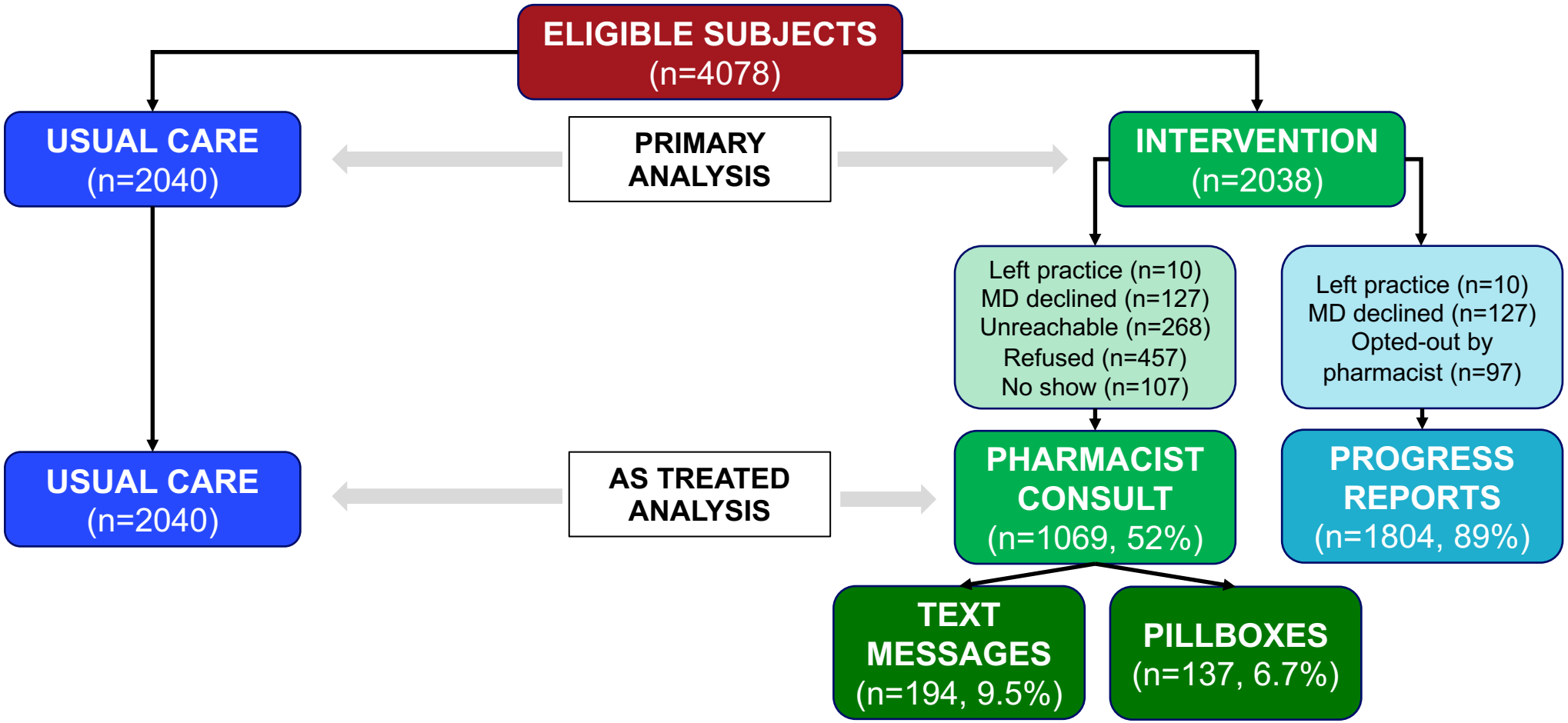
Statistical considerations

- **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)

RESULTS

Enrollment



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

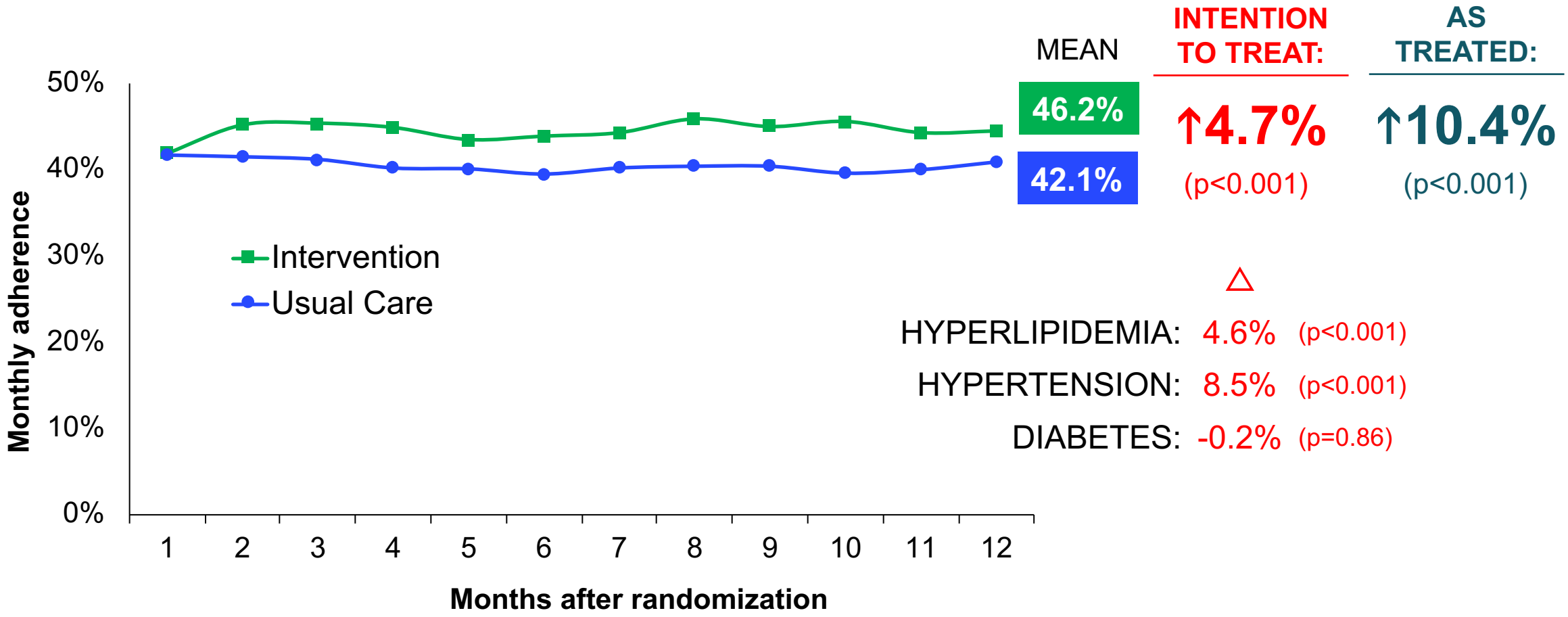
Baseline characteristics

CHARACTERISTIC	USUAL CARE (N=2040)	INTERVENTION (N=2038)
Age, mean years*	60.4	59.2
Male sex	54.7%	55.0%
White race*	53.6%	60.6%
Qualifying conditions		
Hyperlipidemia	72.0%	73.7%
Hypertension	25.9%	23.8%
Diabetes	12.1%	11.9%
Charlson comorbidity score, mean	0.90	0.74
Baseline disease control		
LDL cholesterol, mean mg/dL,	204.8	207.8
Systolic blood pressure, mean mmHg	149.9	149.2
Hemoglobin A_{1c}, mean	9.8	9.5
Baseline adherence, mean	57.0%	57.2%

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

STIC2IT: PRIMARY OUTCOME

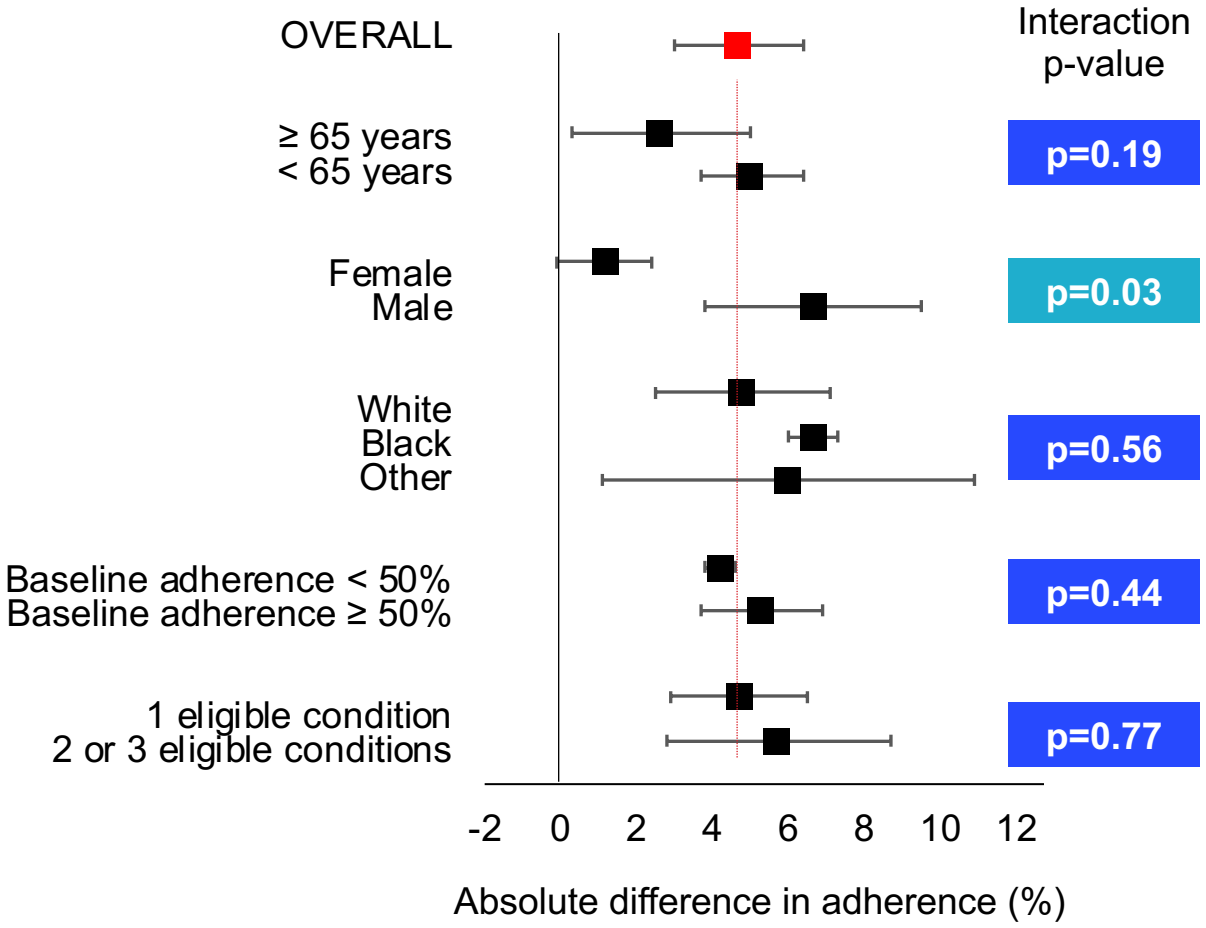
Adherence



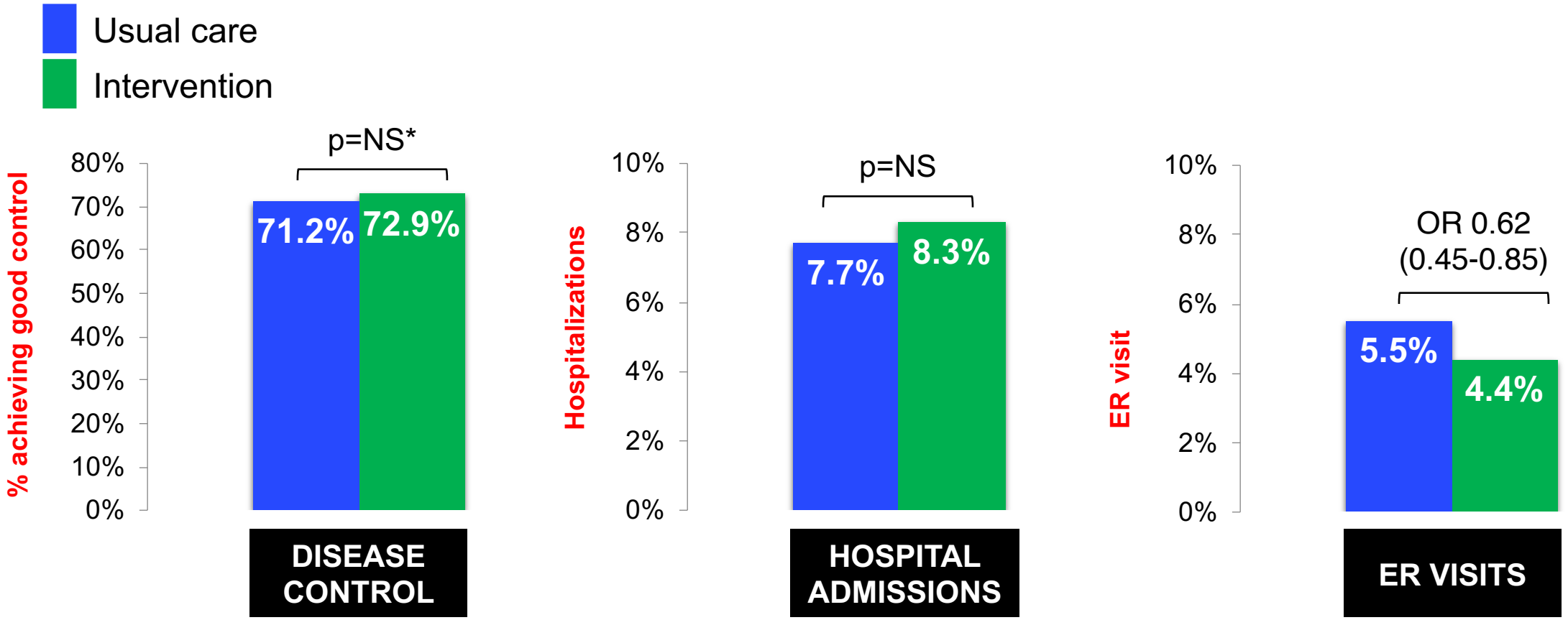
Median (IQR) time from randomization to pharmacist call (when it occurred): 22 (17 to 32) days

SUBGROUP ANALYSES

Adherence



Disease control and resource utilization

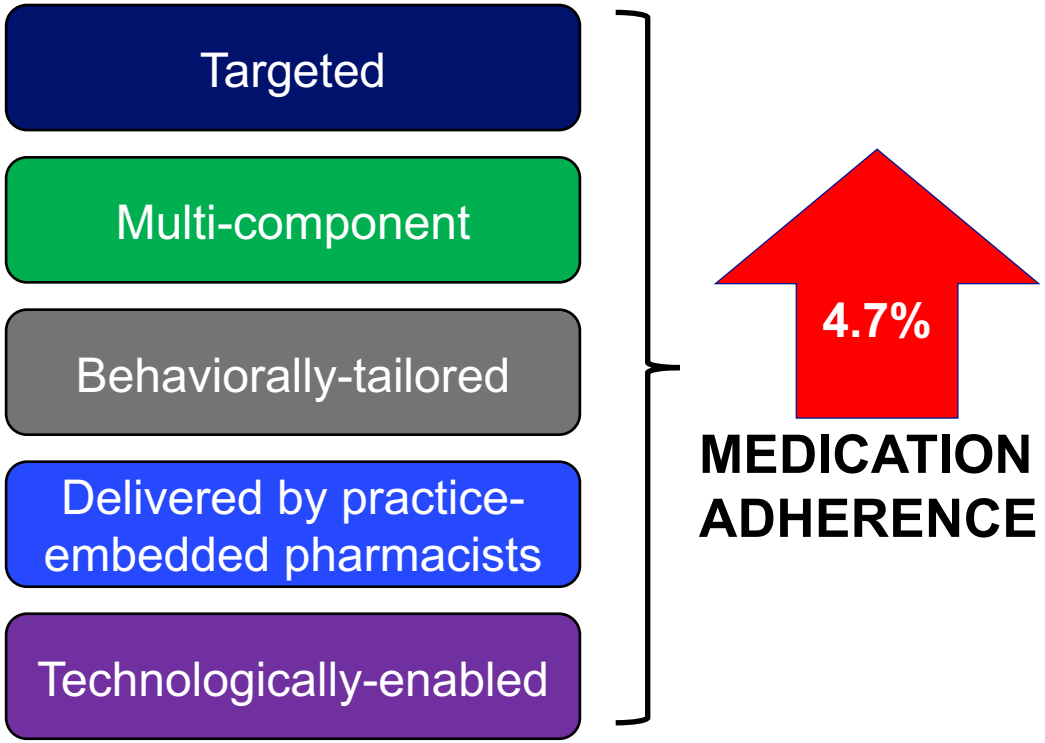


*As treated OR for good disease control (≥1 eligible condition): 1.24 (1.03-1.50)

SUMMARY

The STIC2IT intervention improved adherence

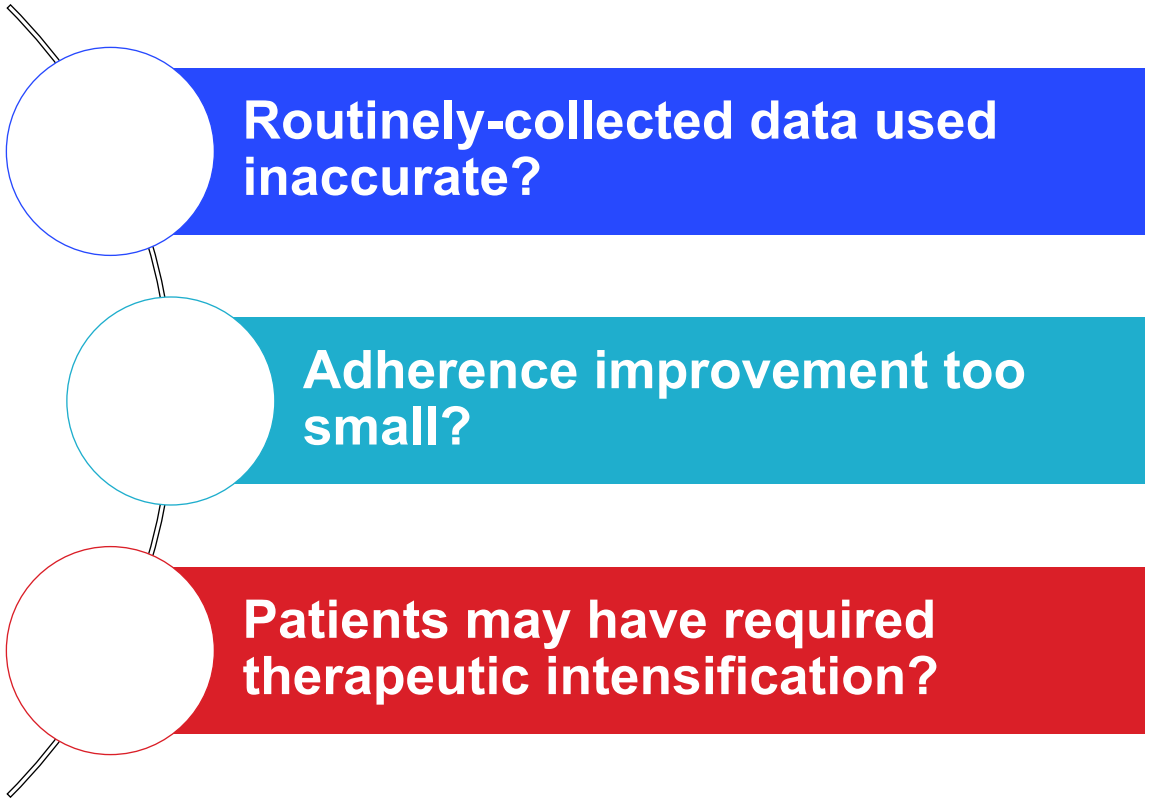
- An intervention for patients with diabetes, hypertension, and hyperlipidemia with poor medication adherence and suboptimal disease control:



- 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



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

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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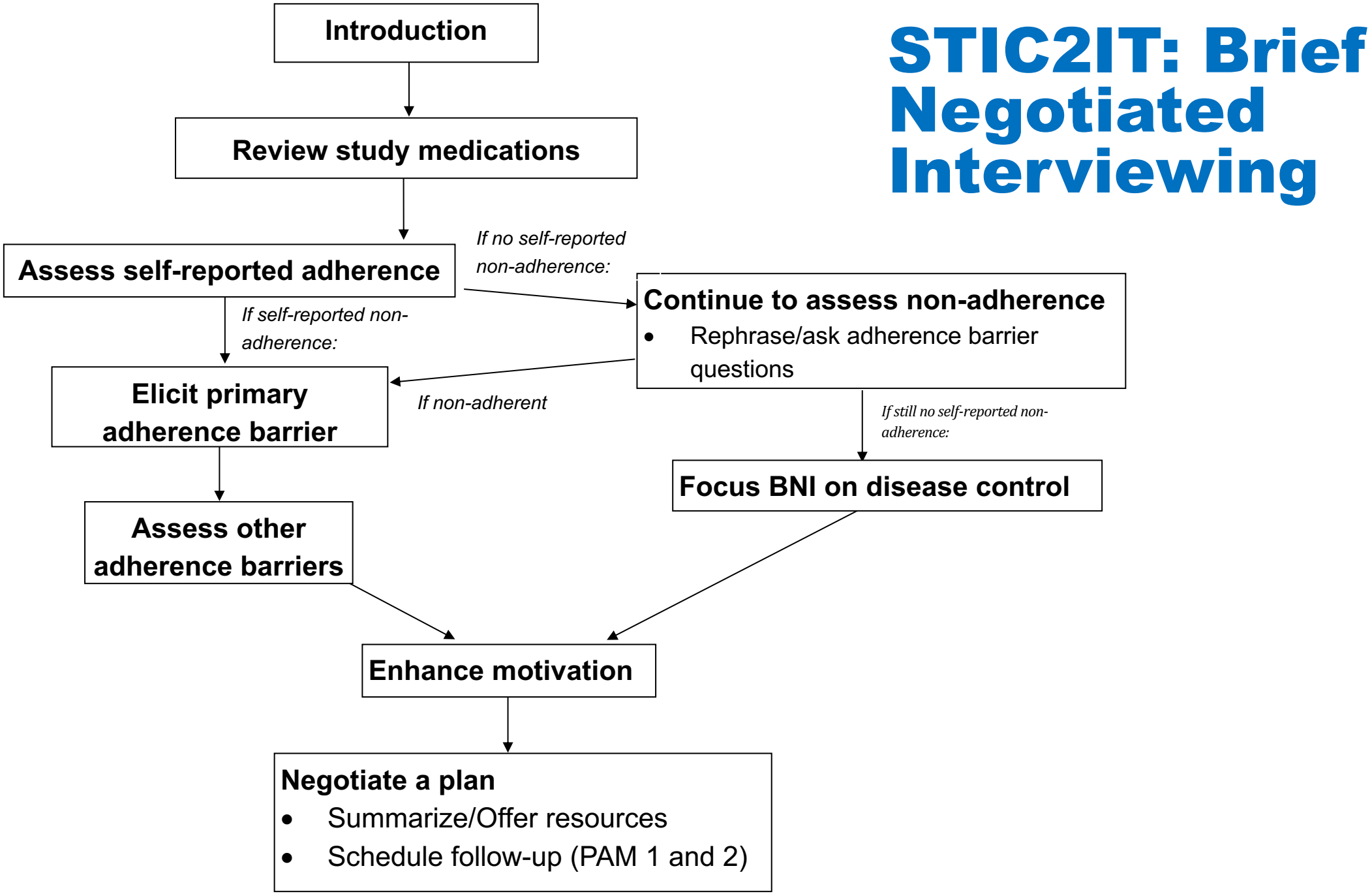
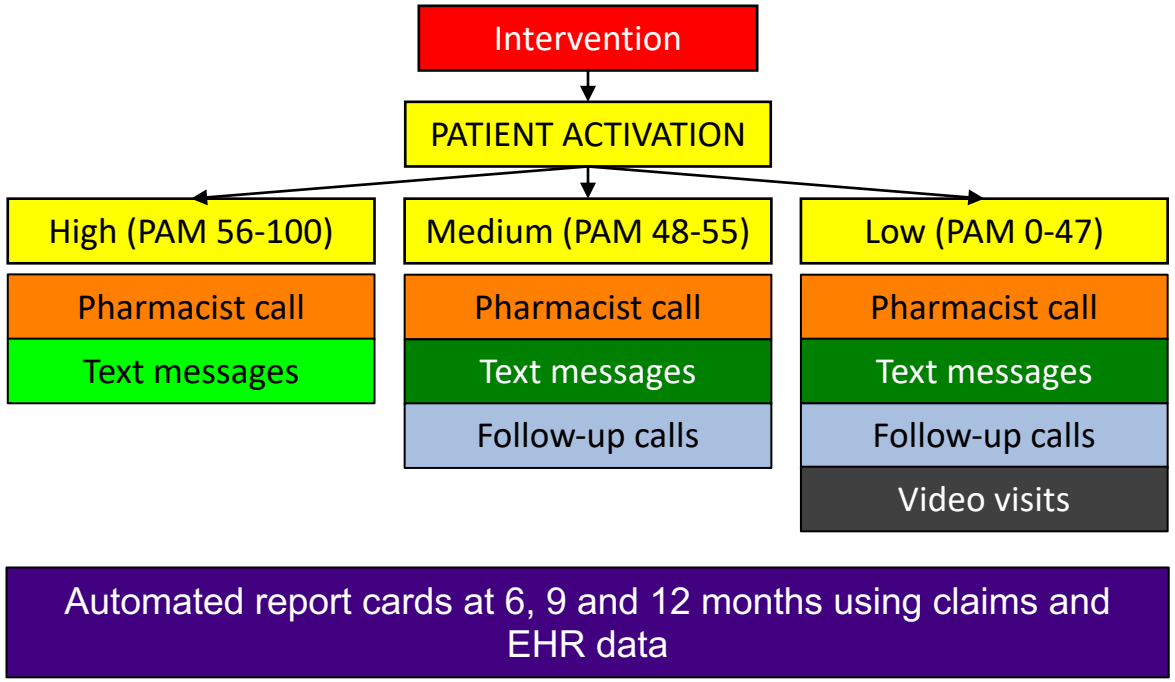
STIC2IT: Brief Negotiated Interviewing



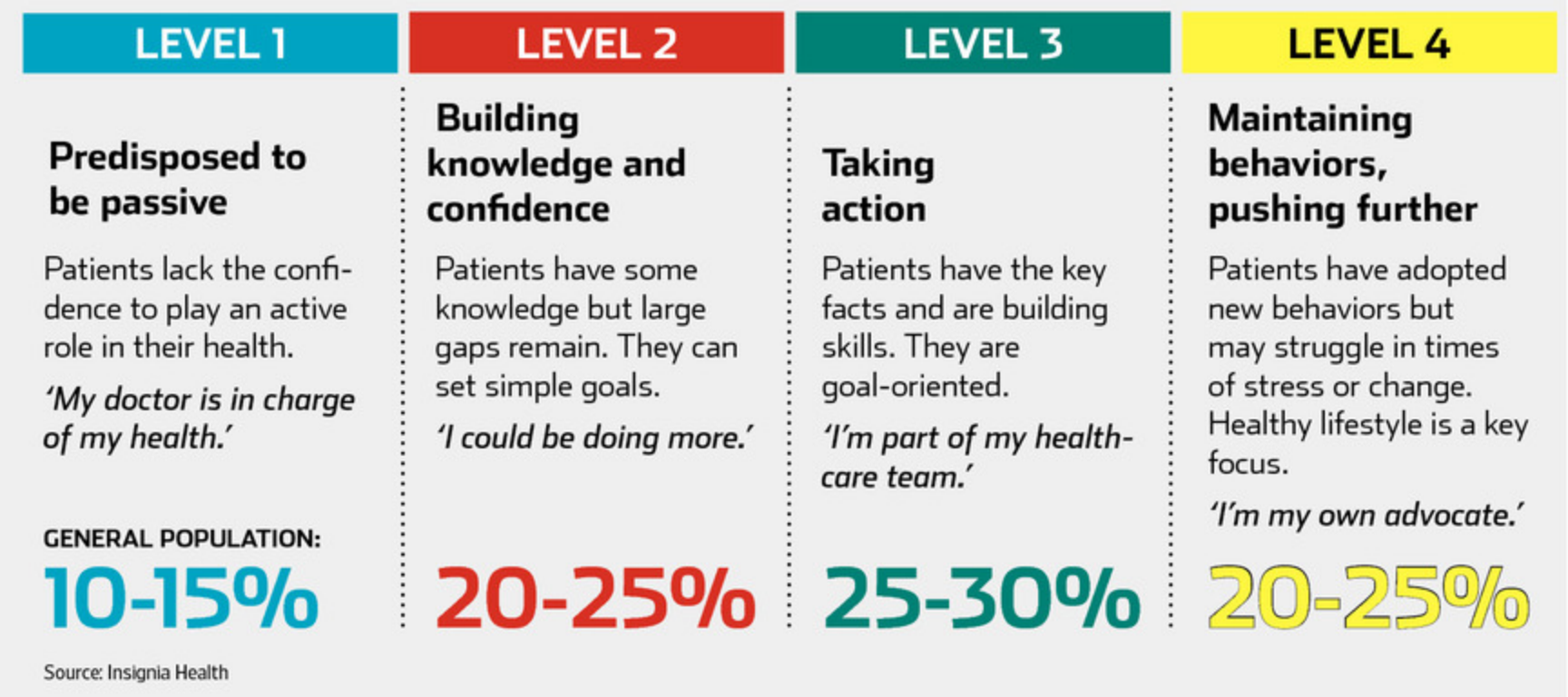
STIC2IT: Intervention Tailoring



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



SOURCES: Hibbard et al. 2004 *HSR*; Hibbard et al. 2005 *Health Serv Res.;* Mosen et al. 2007 *J Am Care Manag;* Begum N et al. 2011 *Diabetes Res Clin Pract.* Lorig K et al. 2010 *Diabetes Care;* Hibbard et al. 2009 *Am J Manag Care*; Hibbard et al. 2013 *Health Aff ;* Kinney et al. 2015 *Patient Educ Couns*