Rationale and design of the *S*tudy of a *T*ele-pharmacy *I*ntervention for *C*hronic diseases to *I*mprove *T*reatment adherence (STIC2IT): A cluster-randomized pragmatic trial

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Background Approximately half of patients with chronic cardiometabolic conditions are nonadherent with their prescribed medications. Interventions to improve adherence have been only modestly effective because they often address single barriers to adherence, intervene at single points in time, or are imprecisely targeted to patients who may not need adherence assistance.

Objective To evaluate the effect of a multicomponent, behaviorally tailored pharmacist-based intervention to improve adherence to medications for diabetes, hypertension, and hyperlipidemia.

Trial design The STIC2IT trial is a cluster-randomized pragmatic trial testing the impact of a pharmacist-led multicomponent intervention that uses behavioral interviewing, text messaging, mailed progress reports, and video visits. Targeted patients are those who are nonadherent to glucose-lowering, antihypertensive, or statin medications and who also have evidence of poor disease control. The intervention is tailored to patients' individual health barriers and their level of health activation. We cluster-randomized 14 practice sites of a large multispecialty group practice to receive either the pharmacist-based intervention or usual care. STIC2IT has enrolled 4,076 patients who will be followed up for 12 months after randomization. The trial's primary outcome is medication adherence, assessed using pharmacy claims data. Secondary outcomes are disease control and health care resource utilization.

Conclusion This trial will determine whether a technologically enabled, behaviorally targeted pharmacist-based intervention results in improved adherence and disease control. If effective, this strategy could be a scalable method of offering tailored adherence support to those with the greatest clinical need. (Am Heart J 2016;180:90-97.)

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Although rates of prescribing evidence-based therapies for cardiovascular and other chronic conditions have improved substantially, long-term adherence remains poor.[1-3] Nearly one-half of patients become nonadherent within a year of treatment initiation[1-4] with adverse consequences on morbidity and mortality.[4] The avoidable health care costs attributable to medication nonadherence have been estimated to be anywhere from $100 to $300 billion in the United States (US) annually, representing 3% to 10% of total US health care spending.[5,6]

Barriers to medication adherence arise from a complex interplay among patient, provider, and system-related factors.[7,8] As a result, strategies to improve adherence vary widely and include educational interventions with behavioral support, case management, reminder calls, telephone-based counseling, decision aides, text

Table I. Definitions of poor and worsening disease control

Condition	Age (y)	Poor control	Worsening control
Diabetes[18]	N/A	Latest HbA1c >8%	Latest HbA1c ≥7.5 to ≤8% and previous HbA1c 1% lower
Hypertension[19]	≥60	Latest BP >150/90 mm Hg	Latest BP ≥140/80 to ≤150/90 mm Hg and previous BP 20 mm Hg lower
	<60	Latest BP >140/90 mm Hg	Latest BP ≥130/80 to ≤140/90 mm Hg and previous systolic or diastolic BP 20 mm Hg lower
Hyperlipidemia[20]	N/A	Diagnoses of ASCVD	N/A
	40-75	Type 1 or 2 diabetes and use of glucose-lowering agent	N/A
	40-79	ASCVD risk >7.5%	N/A
	N/A	LDL >190 mg/dL	Latest LDL ≥175 to ≤190 mg/dL and previous LDL 30 mg/dL lower

Abbreviations: *N/A*, Not applicable; *HbA1c*, glycosylated hemoglobin; *ASCVD*, atherosclerotic cardiovascular disease; *LDL*, low-density lipoprotein.

messages, electronic pills bottles, and policy interventions that reduce out-of-pocket expenses for prescription medications.[9-11] Unfortunately, when rigorously tested, many of these approaches have only been moderately successful.[9,12-15] This limited efficacy may reflect that many interventions address a single barrier to adherence, do so at a single point in time, and/or are imprecisely targeted with respect to which patients are most likely to benefit and how the intervention is tailored to meet their specific needs.[16] Among those interventions demonstrating success, many have not been widely adopted because of the substantial resources required to deliver and sustain them.[17]

To address these limitations, we launched the STIC2IT trial.

Overall study design

STIC2IT is a pragmatic, prospective, intention-to-treat, cluster-randomized controlled trial designed to test the impact of a technologically enabled, behaviorally targeted pharmacist intervention designed to improve medication adherence and disease control among the specific group of individuals who are most likely to benefit from this intervention—those who are nonadherent to their glucose-lowering, antihypertensive, or statin medications and have evidence of poor disease control based on recommended clinical targets. The trial is funded by the US National Institutes of Health National Heart, Lung, and Blood Institute; was approved by the institutional review board of Brigham and Women's Hospital; and is registered with clinicaltrials.gov (NCT02512276). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Study setting and randomization

This trial is being conducted at Harvard Vanguard Medical Associates (Harvard Vanguard), which is a practice of Atrius Health, a large multispecialty medical group and a Pioneer Accountable Care Organization. Harvard Vanguard employs approximately 150 primary care physicians (PCPs) who provide care for approximately 300,000 adult patients at 17 practice sites. Of these, 15 practice sites have integrated retail pharmacies, where approximately 50% of patients obtain their prescription medications.

We randomly selected 1 of the 15 Harvard Vanguard practice sites with onsite pharmacies as a pilot site for intervention refinement. The remaining 14 Harvard Vanguard practice sites were then cluster-randomized such that all PCPs and their patients in a given practice site were assigned to the same study arm. Because the practice sites differ from each other, simple cluster randomization may have resulted in imbalances in patient or provider factors that could potentially bias outcome assessment. Therefore, we categorized the practice sites based on their size (ie, small or large, based on the number of patients receiving care at each site) and whether clinical pharmacists at the sites offered disease management counseling directly to patients (ie, yes or no). Within the resultant 4 blocks, practices were then randomized in a 1:1 ratio to intervention or control using a random number generator.

Participants

Study enrollment began in August 2015 and was completed in July 2016. Follow-up of all trial participants will end in July 2017. In total, 4,076 patients have been randomized. Potentially eligible patients for inclusion were those who (1) were receiving care from a Harvard Vanguard PCP and who are also receiving health insurance from 1 of 4 large health insurers, (2) had evidence of poor or worsening disease control (Table I), and (3) were identified as nonadherent (as defined below) to their oral glucose-lowering, antihypertensive, or statin medications.

Disease control was evaluated using the most recent laboratory or blood pressure (BP) values in the electronic health record and was based on clinical guideline targets from the American Diabetes Association, the Eighth Joint National Committee hypertension guidelines, and the American College of Cardiology/American Heart Association cholesterol guidelines.[18-20] Adherence was assessed using prescription claims data. For each medication used

to treat any one of the targeted conditions, the proportion of days covered (PDC) was calculated as the number of days of medication that a patient filled between the first fill date and the randomization date divided by the number of days in that same period (up to a maximum of 365 days).[2] We considered drugs that are chemically related and not intended for use in combination to be interchangeable (eg, 2 different statins). Using previously described methods,[21] we averaged the PDC for all of the medications used to treat a single condition (eg, all oral hypoglycemics) and then calculated an overall average adherence for all of the conditions that a patient had at the time of their identification. To identify individuals who would benefit most from the intervention, patients were defined as being nonadherent (1) if they had been <80% adherent to the specific class of medications used to treat the condition(s) for which they identified as being poorly controlled and (2) if their "average of averages" PDC for all eligible study drugs was less than 80%. For example, patients with poorly controlled diabetes who were nonadherent to their diabetes medications but adherent to their statins and antihypertensives were only be eligible if their average adherence across all 3 conditions was less than 80%. Patients were excluded if, before randomization, they had less than 6 months of continuous enrollment in the health plan (to allow for adequate assessment of eligibility), are younger than 18 or older than 85 years, or had no available telephone contact information, which would preclude contact for enrollment and delivery of the intervention.

Study procedures

Once identified, PCPs of potentially eligible intervention group patients were sent a secure message using the electronic health record to ask permission to include their patient(s) in the study. Based on prior agreement with the practices, if a physician did not explicitly respond to approve or disapprove of the identified patient(s) to participate in the study within 5 days, they were sent a reminder message; 1 day later, their patients are automatically opted in to the study.

Patients approved for enrollment in the study were sent a letter informing them about the study along with a simple, 1 compartment per day, pillbox that allows for the storage of 1 week of medication. Patients were then contacted by telephone to schedule a phone consultation with the clinical pharmacist. At this time, they were also administered the Patient Activation Measure (PAM), a questionnaire to assess the knowledge, skills, and confidence to manage one's health and health care.[22,23] As described below, the PAM was subsequently used to tailor the intervention for that individual patient.

Intervention

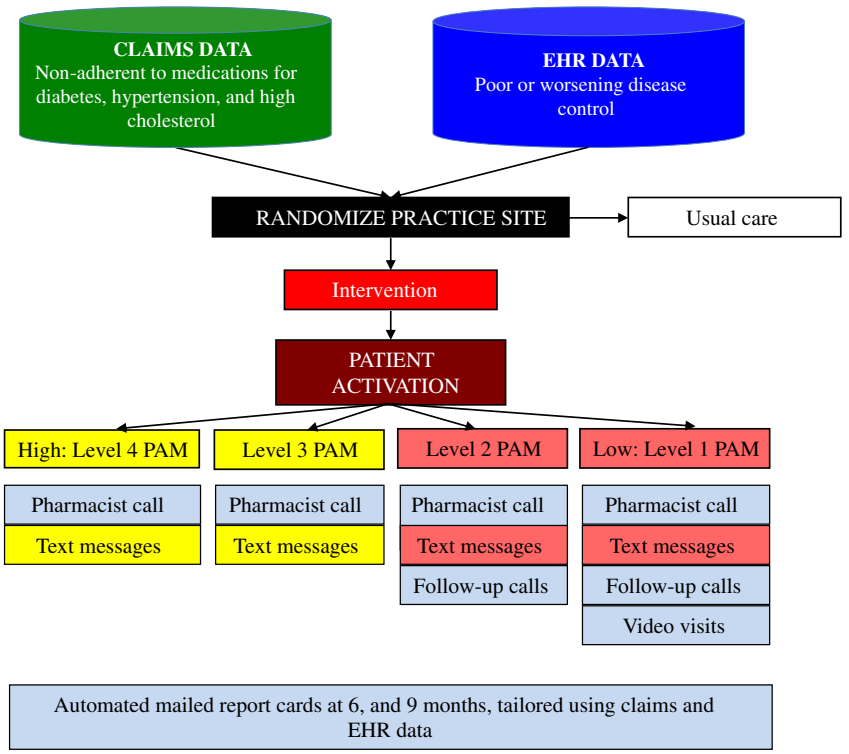
The central component of the multifaceted intervention is an individually tailored telephone consultation conducted by a clinical pharmacist who is part of the Harvard Vanguard care team (Figure). The clinical pharmacists work at multiple sites; to reduce the chances of contamination, they are restricted to providing clinical services only at other intervention sites during the period of this study.

During this consultation, the clinical pharmacist confirmed a patient's treatment regimen, engaged the patient in sharing potential barriers to adherence or other factors that may be contributing to poor disease control, discussed the patient's readiness to modify behaviors, and worked with the patient to agree upon a shared plan of strategies to improve adherence and disease control (see Appendix A). The identified adherence barriers were grouped into 6 distinct groups: treatment complexity/forgetfulness, health perceptions, lack of knowledge/poor health literacy, side effects, cognitive impairment, and cost-related barriers. Patients may had barriers identified in more than 1 category. The solutions and strategies offered to patients by the clinical pharmacists were tailored to their PAM level and their identified adherence barrier(s) (see Table II). Depending on the barrier, patients with lower levels of activation (eg, PAM levels 1 and 2) were offered more intensive solutions, such as daily text messages as reminders or motivational support, pillboxes that allow for multiple times per day dosing, follow-up consultations, and video visits through the WebEx platform (Santa Clara, CA). The video visits allow for one-on-one communication, delivered remotely. Patients with higher levels of activation (eg, PAM levels 3 and 4) were offered less intensive solutions, such as weekly text messages and pillboxes.[23] The clinical pharmacists then worked with the PCPs and other team members at Atrius Health to implement solutions based on the treatment plan. The clinical pharmacists also mailed a copy of the shared plan to the patients after the initial encounter.

The structure of the initial and follow-up clinical pharmacists phone calls was developed by the study team (see Appendices A and B) based on the principles of the brief negotiated interview,[24-26] a behavioral interviewing technique with foundations in motivational interviewing, and refined during the pilot phase of the trial. Before the start of the study, the clinical pharmacists underwent a full-day training program that included script development and role-playing exercises with feedback by the study team. These role-playing exercises were then repeated 2 more times. The initial calls last 30 to 45 minutes. Follow-up calls are scheduled with all patients with low levels of activation but only if clinically indicated for highly activated individuals.

Depending on the barrier(s) identified, patients were offered the opportunity to receive SMS text messages via a secure messaging platform (Mobile Commons; Brooklyn, NY) for the 12-month follow-up period or until the patient opts out. These 50 unique text messages were developed by the study team to provide reminders and motivation to participants who opted to receive them

Figure



Study design and intervention components.

(see Appendix C). In addition to the motivational text messages, patients are asked questions on an ongoing basis about their adherence behavior to which they can provide answers by directly replying to the text message and receive automated responses using a feedback response system. The response system provides different encouraging feedback or advice, depending on the patients' inputs. The content and frequency of the text messages differ depending on patients' PAM levels and adherence barrier. For example, patients with lower levels of activation are more frequently asked specific questions about their adherence behavior, are encouraged to reply more often, and are also offered the choice of receiving daily or weekly texts, whereas patients with higher levels of activation are only offered weekly texts.

All intervention patients who do not opt out of trial participation are mailed progress reports at 6, and 9 months after randomization on behalf of their PCP. These progress reports provide personalized and updated information about disease control generated using data from the electronic health record. For patients whose administrative claims data are believed by the clinical pharmacist to be an accurate representation of actual filling behavior (eg, for patients who exclusively use their prescription insurance plan to pay for their prescriptions), the progress reports also provide patient-specific medication adherence information.

The specific components of the intervention that are administered to each patient, including the number, frequency, and length of the phone consultations that they receive, are being explicitly tracked to facilitate future reproducibility and scalability.

Outcomes

The trial's primary outcome is medication adherence assessed at 12 months after randomization (see Table III). Medication adherence will be assessed using prescription claims data and measured as the mean PDC for the 12 months after randomization using the "average of averages" approach used for study eligibility. Adherence will be measured only for medications that qualified a patient for inclusion in the study, and follow-up will begin at the point of randomization.[21] Medications that were filled before randomization but had a supply that extended into the follow-up period will have their carry-over supply included in the adherence calculation. In a sensitivity analysis of this outcome, medication adherence will be measured by calculating PDC beginning from the first fill of a medication after randomization until the end of the 12-month follow-up period. As a second sensitivity analysis, we will also censor patients when they initiate insulin.

Table II. Patient barriers to adherence and available solutions

Barrier	Solution	Specific strategy: Low activation (PAM 1 and PAM 2)	Specific strategy: High activation (PAM 3 and PAM 4)
Treatment complexity and/or forgetfulness	Medication review	▪ Reduce dosing frequency ▪ Switch to combination ▪ Stop unnecessary medications	▪ Reduce dosing frequency ▪ Switch to combination ▪ Stop unnecessary medications
	Pill organization and reminders	▪ Pill box reminder ▪ Use of apps/alarms ▪ Mail order service	▪ Pill box reminder
	Counseling	▪ Counsel about disease/medications as needed	▪ Counsel about disease/ medications as needed
	Text messaging	▪ Reminder text messages (weekly or daily)	▪ Reminder text messages (weekly)
	Family and/or social work involvement	▪ Family member support ▪ Social work referral	▪ None
Health perception	Counseling	▪ Counsel as needed	▪ Counsel as needed
	Text messaging	▪ Motivational text messages (daily or weekly)	▪ Motivational texts (weekly)
Cognitive impairment	Family and/or social work involvement	▪ Family member support ▪ Social work referral	▪ Family member support ▪ Social work referral
	Counseling, education	▪ Counsel as needed	▪ Counsel as needed
Lack of knowledge and/or poor health literacy	Counseling	▪ Counsel about disease/medications	▪ Counsel about disease/ medications
	Family and/or social work involvement	▪ Family member support ▪ Social work referral	▪ None
Experiencing side effects	Medication review	▪ Switch to alternative, adjust dose, or stop ▪ Other strategies to reduce side effects ▪ Refer to PCP if needed	▪ Switch to alternative, adjust dose, or stop ▪ Other strategies to reduce side effects ▪ Refer to PCP if needed
	Counseling	▪ Counsel about expected side effects ▪ Plan for contact if side effects persist	▪ Counsel about expected side effects ▪ Plan for contact if side effects persist
Costs	Medication review	▪ Switch to less expensive option/generic ▪ Switch to combination medication ▪ Stop unnecessary meds	▪ Switch to less expensive option/generic ▪ Switch to combination medication ▪ Stop unnecessary meds
	Mail order, social work support	▪ Use of mail order service ▪ Social work referral	▪ Use of mail order service
	Counseling	▪ Refer patients to co-pay assistance program ▪ Counsel about disease/medications as needed	▪ Refer patients to co-pay assistance program ▪ Counsel about disease/ medications as needed
All barriers	Follow-up calls	▪ All patients receive follow-up calls	▪ Follow-up calls only if clinically indicated

The secondary outcomes for the study include disease control and rates of health care utilization. Disease control will be measured as the following 2 different outcomes: (1) the proportion of patients achieving good disease control for all of their eligible conditions and (2) the proportion of patients achieving good disease control

Table III. Study outcomes and their measurements

Type	Outcome	Definition*
Primary	Medication adherence	Average PDC for medications to treat eligible conditions
Secondary	Disease control	Proportion of patients achieving good disease control for all eligible conditions
		Proportion of patients achieving good disease control for at least 1 eligible condition
	Health care utilization	Rates of all-cause emergency room visits, physician office visits, and hospitalizations

* Please see text for additional details.

for at least one of their eligible conditions. Because disease control will be evaluated using biometrics that are collected during routine care rather than at study-prescribed intervals, we will use those values that are closest to each patient's 12-month end of follow-up period.

Rates of health care utilization will also be measured using administrative claims data and will include all-cause emergency room visits, physician office visits, and hospitalizations during follow-up. In addition, patients in the intervention group will be administered a mailed survey 12 months after randomization to assess self-reported adherence. Self-reported adherence will be assessed as the proportion of patients who are deemed adherent according to the validated 3-item self-report measure for medication adherence.[27]

Analytic plan

We will report the means and frequencies of prerandomization variables separately for intervention and control participants. Comparisons of these values will be performed using *t* tests and χ^2 tests and their nonparametric analogs, as appropriate. The outcomes will be evaluated using intention-to-treat principles among all randomized patients. In the primary analysis, the outcomes will be compared using generalized estimating equations with an identity link function and normally distributed errors to account for the clustering of participants within practice sites. Our primary models will also adjust for the block-randomized design. If there are differences in baseline characteristics between study groups that are believed to be confounders of the intervention-outcome association, we will repeat our analyses after adjusting for these covariates. A similar approach will be taken for the analysis of the secondary outcomes, except using logit link functions with binary errors and log link functions with Poisson errors, as appropriate. If more than 10% of participants have missing outcome data, we will repeat our analyses using the latest postrandomization laboratory values available and using multiple imputation.[28]

Several additional analyses will also be conducted. First, we will assess the correlation between calculated adherence based on insurer claims, self-reported adherence, and pharmacy transaction records (for patients filling prescriptions at Harvard Vanguard pharmacies). Second, we will use Markov modeling to assess the long-term impact of the intervention on cost, quality-adjusted survival, and cost-effectiveness of the intervention.

Sample size considerations

Our study should be sufficiently powered to detect small clinically meaningful changes in the primary outcome. We powered the study to detect a 2.5% mean change in adherence between the intervention and control groups, assuming an SD of 0.25 (a conservative assumption), clustering at the practice level with a design effect of 1.10,[29,30] and a 15% nondifferential loss to follow-up rate. We assumed that 95% of potentially eligible intervention patients would be approved for study inclusion by their PCPs and that 50% of these patients would agree to a pharmacist consultation. With these assumptions, we estimated that we would need a total sample size of 4,000 eligible patients to provide more than 80% power to detect differences in our primary study outcome of medication adherence. In other words, if those patients receiving the intervention demonstrate a 4.6% improvement in adherence, we will still have more than 80% power to detect an improvement of 2.5% in the overall sample. We also have substantial power to detect improvements in disease control, assuming a rate of controlled disease of 30% based on our pilot data.

To reach our enrollment target while ensuring that all identified patients could be contacted and intervened upon in a timely fashion, we queryied the electronic health records and claims data every 2 weeks and selected a random sample of 85 patients from all eligible patients for each of the intervention and control groups. After identification, selected patients were removed from the pool of potentially eligible patients in subsequent rounds. Each patient's randomization date was defined as the day of the biweekly data query on which they were identified as being eligible for inclusion in the study.

Limitations

There are several limitations to this trial that should be acknowledged. First, patients who fill their prescriptions

by paying cash or using low-cost generic programs will not have adjudicated claims reflecting these transactions and thus may be misclassified as being nonadherent.[31,32] Although we are prospectively tracking intervention patients who are identified as having missing or inaccurate claims because of cash payments, we expect any misclassification introduced by this claims inaccuracy to be nondifferential between the study arms. Furthermore, our ability to assess the impact of the intervention on disease control is unaffected by this claims inaccuracy. Second, claims-based methods of adherence estimation may be prone to misclassification because they cannot differentiate between patients who discontinue or switch medications based on their doctors' orders as opposed to not filling their medication because of nonadherence. We will assess the robustness of our results using alternate definitions of the primary outcome measure of adherence, as described above. In addition, our primary outcome definition is more conservative by design, because clinical pharmacist-directed switching may be more likely to occur in the intervention group. Furthermore, claims-based methods of adherence assessment have been shown to correlate highly with patient self-report, pill counts, and serum drug levels[33,34] and are also the basis for quality metrics currently being used by Medicare and other agencies.[35] Third, patients may not have a laboratory value or BP reading in the 12-month follow-up period, particularly given the newer cholesterol-lowering guidelines, which may lead to incomplete assessment of clinical outcomes. Fourth, although multicomponent adherence interventions have consistently been found to be more effective than those addressing single barriers, should the trial meet its primary outcome, we will not be able to identify which aspect of the intervention was responsible for the effect. Finally, although our trial is pragmatic in its design and leverages, to the extent possible, interventions that are relatively low cost, there is substantial infrastructure necessary to administer the intervention. As such, our results may not be generalizable to all existing care settings or patients, such as those without reliable access to a telephone or the other technologies we are using. However, because telephone and cell phone access is almost universal in the US, our results should apply to most patients being treated in the rapidly expanding number of accountable care organizations, patient-centered medical homes, and other similar integrated care models.

Conclusion

This cluster-randomized controlled trial will determine whether a novel technologically enabled, behaviorally targeted, pharmacist-based intervention improves adherence to medications for chronic diseases and disease control. This study will also provide generalizable information about how to tailor patient interventions and integrate advance communication technologies into clinical practice.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ahj.2016.07.017.

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