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

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Initial protocol

Aims

Evaluate the impact of a novel tele-pharmacist intervention embedded within a multispecialty group practice on the following outcomes over a 12-month period:

a) Adherence to cholesterol-lowering, anti-hypertensive, and oral hypoglycemic agents

b) Achievement of ideal control of HbA1c, blood pressure, and cholesterol levels

Background

Highly effective medications to treat and prevent the complications of chronic disease have been developed and evaluated. While rates of prescribing effective therapies have improved substantially, long-term adherence remains exceptionally poor. Nearly 50% of patients become non-adherent within a year of treatment initiation. Interventions that succeed in improving medication adherence may confer important clinical benefits across large populations, and may even be cost-saving by reducing rates of costly clinical outcomes such as myocardial infarction and stroke.

The success of interventions to improve adherence has been relatively limited, either because of the nature of the intervention or their broad applications to patients who do not require them or will not benefit from them. Prior studies have also been limited by recruiting small samples of volunteers, following patients for short periods, and not evaluating their impact on clinical outcomes. The efficacy of future efforts is likely to be increased by targeting interventions to patients demonstrating both poor adherence and poor disease control, tailoring interventions to individual patient needs, and touching larger and more representative patient populations and care settings. These goals can be achieved by

the innovative use of information technology including electronic health records (EHR) and other advanced communication technologies, including texting.

We propose a cluster randomized controlled trial (RCT) of a novel tele-pharmacist based intervention to improve adherence to medications for hypercholesterolemia, hypertension, and diabetes. We will evaluate an innovative intervention that uses of EHR data to identify approximately 2,000 adult patients cared for by approximately 170 primary care physicians who are both non-adherent and not achieving recommended clinical targets for glycemic, blood pressure, and cholesterol control in a real-world primary care setting. Following EHR-facilitated referral from the treating primary care physicians, a clinical pharmacist will direct an outreach program using multiple communication technologies including text messaging and secure email messaging to improve medication adherence.

Study design and randomization

This study is a randomized, controlled trial of patients treated at Harvard Vanguard Medical Associates. The sites involved in this study are all part of HVMA, located in Boston and surrounding cities and towns. HVMA is associated with the larger organization, Atrius Health. We will enroll all primary care physicians and their eligible patients. Eligible patients include adults 18 years and older with a diagnosis of diabetes, hypertension, or hyperlipidemia; evidence of poor disease control (see below Table); and evidence of medication non-adherence based on medication refill data. We estimate the inclusion of 170 primary care physicians and 2,000 patients.

Table. Definition of Poor Disease Control

Condition	Cardiac Risk*	Poor Control Definition
Diabetes	High	Most recent HbAlc>9
Hypertension	High	Most recent BP>140/80
	Moderate	Most recent BP>140/90
	Low	Most recent BP>150/100
Hyperlipidemia	High	Most recent LDL>100
	Moderate	Most recent LDL>130
	Low	Most recent LDL>160

* High risk defined as Framingham Risk Score (FRS≥20%) or coronary heart disease equivalent.

Moderate risk defined as 10%≤FRS<20%. Low risk defined as FRS<10%.

Intervention

Computerized Alerts to Physicians

Physicians randomized to the intervention group will receive electronic decision support tools to identify patients as non-adherent and facilitate electronic referral to the tele-pharmacist program.

We will identify eligible study patients based on medication adherence and clinical outcomes on a weekly basis and populate a disease registry. We will use this registry to create an automated weekly process that places an electronic "flag" in the EHR to identify these patients. These flags will trigger an electronic alert that intervention physicians will receive upon accessing the patient chart. For patients

that will not be seen by the doctor in an upcoming time period, primary care physicians will receive patient lists through Epic staff messaging asking them to approve their patients fro the intervention. During the initial 3 months of the project, the study team will work with HVMA clinical leadership and primary care physicians to refine the presentation of the alerts. The alert will be directly linked to computerized order entry and will allow the physician to place a referral to the tele-pharmacist program. We have significant experience in this type of innovation. For example, Dr. Sequist currently leads a randomized controlled trial at HVMA, overseen by the Partners IRB, where electronic alerts have been used to facilitate primary care referrals of over 1,000 high risk patients with chronic kidney disease to nephrology specialists. All electronic referrals will be placed in an "electronic pool" to be monitored on a daily basis by the clinical pharmacists. By requiring a direct referral from the primary care physician, we will ensure appropriate and safe selection of patients to receive the intervention, and establish effective integration of the intervention into the primary care team.

Tele-Pharmacist Intervention

Once a referral is generated, the clinical pharmacist will deliver a four part intervention that includes 1) motivational interviewing and education, 2) assessing and addressing barriers to medication adherence, 3) employing longitudinal reminders and support via text messaging, secure email messages, or phone calls, and 4) providing feedback to the referring primary care physician via electronic documentation of patient interactions that highlight current care plans.

The initial telephone intake interview conducted by the tele-pharmacist will be 30 minutes in duration. The goal of the initial interview will be to assess a patient's self-reported medication adherence and determine key barriers to adherence including forgetfulness, real or perceived side effects, perceived effectiveness of medications, or financial barriers. The pharmacist will work with the patient during this interview session to provide education regarding their medication regimen and

address all barriers identified, including solutions such as highlighting the effectiveness of the medications, facilitating switches to generic medications to lower costs to patients, or recommending combination pills to simplify regimens.

Complex patients (and patients without access to text messaging or email) will receive ongoing twice-monthly follow-up telephone calls with the pharmacist to provide in-depth consultation. Patients with less complexity who also engage in regular use of either text messaging or the HVMA secure messaging system will receive regular automated, yet interactive, outreach. HVMA has significant experience working with our text-messaging vendor, Mobile Commons, to deliver interactive and tailored text messages with the capacity to store all incoming and outgoing messages in relational databases. We will deliver up to weekly text messages to patients to assess self-reported adherence, remind them of strategies reviewed to address barriers to adherence and to refill their prescriptions. New clinical data such as HbA1c or cholesterol results will be highlighted in the text messages as either within goal or outside of goal. For patients enrolled in our secure email messaging system integrated into the EHR, we will deliver similar email outreach as to the text messages. Dr. Sequist has significant experience using this secure email messaging system to conduct large scale patient outreach.

For those patients deemed to be not improving on either clinical outcomes or medication adherence for 3 consecutive months, the pharmacist will conduct a telephone outreach to readdress barriers to adherence. For those patients that demonstrate improvement in both adherence and clinical outcomes, the frequency of contact will be decreased to a level appropriate to their support needs.

The final component of the intervention will be to provide feedback on patient medication adherence and clinical outcomes to the referring primary care provider

Physician Orientation

Within the first 3 months of the project, Drs. Sequist and Choudhry will travel to each of the 17 health centers to conduct orientation sessions with the primary care physicians, review the goals of the project, and solicit feedback on the intervention components.

Pilot Testing of Interventions

One health center will have been selected for pilot testing the intervention. The pilot will have resolved operational issues and clarified roles.

Randomization of Primary Care Physicians

We will employ a cluster randomized study design, with primary care physicians serving as the unit of randomization and patients clustered within physicians. We believe the possibility of contamination between intervention and control physicians practicing side-by-side is minimal due to the current lack of focus on routine assessment and action based on medication adherence.

Moreover, control physicians will not have any way of accessing the lists of patients eligible for medication adherence intervention that we will identify for intervention physicians.

Randomization of individual physicians will be stratified by practice site. Within each of the 17 practices, we will array physicians into blocks of 2 based on eligible patient sample size and one physician in each block will be randomly assigned to intervention group. Because the intervention will be embedded in the EHR and approved by the HVMA leadership, individual providers will not be able to opt-out.

Outcomes

We will leverage HVMA's rich EHR data and prescription data. The study sample will consist of patients with poorly controlled diabetes, hypertension, and hyperlipidemia as identified by using lab values and other coded clinical data such as blood pressure and clinical diagnosis codes contained in the EHR. HVMA prescription data, available with a one-month lag, will be used to identify patients with suboptimal medication adherence.

Adherence

Adherence will be assessed for each medication prescribed for diabetes, hypertension, and hyperlipidemia and compared between intervention and control patients. The main measure of patient adherence will be proportion of days covered (PDC) for the intervention and control groups, as assessed with HVMA pharmacy data. This will be computed using the date the prescription was filled, the 'days supplied' field in dispensed drug data, and the dates on which the prescription was refilled.

Clinical outcomes

Clinical outcomes of interest are the proportion of patients achieving the following clinical targets: HbA1c values for patients with diabetes, systolic and diastolic blood pressure for patients with hypertension, and LDL values for patients with hypercholesterolemia. All laboratory values are available within the EHR.

Analytic plan

Statistical analyses

We hypothesize that the intervention will improve medication adherence and disease control.

All analyses will use intention-to-treat principles. Medication adherence based on the proportion of days covered will be compared using generalized estimating equations, with adjustment for the cluster and block randomized design. We will use an identity link function and normally distributed errors. The proportion of patients considered adherent by achieving clinical goals will be compared using a logit link function and binary distributed errors. We will censor patients if they die, lose insurance eligibility, or at the end of the study period. Analyses will be run unadjusted as well as after controlling for the potential confounders listed below.

Potential confounders

The independent variable of interest is exposure to the pharmacist intervention. We will measure several variables to assess the degree of balance between patients and physicians randomized to intervention versus control, to adjust for chance imbalances, and to assess whether the efficacy of the intervention is modified by particular patient characteristics. Patient demographic characteristics and major comorbid conditions, as identified based on EHR data, will be included as independent variables

Description of standard of care and how study procedures differ from it

HVMA currently has an existing clinical pharmacy program. These clinical pharmacists already work collaboratively with the primary care physicians in the clinics to provide patient education and advice around medication management. Primary care physicians can currently refer patients to the clinical pharmacist using an electronic referral in the electronic health record.

Our intervention differs from standard of care in two ways:

1) We will use data from the EHR and medication refill data to prospectively identify patients that might benefit most from referral to a clinical pharmacist (e.g. those who are not achieving clinical targets and are non-adherent to medications). We will create an alert in the electronic health record that advises primary care physicians to refer these patients to the clinical pharmacists.

2) We will have equipped the clinical pharmacist with a new set of educational tools and outreach mechanisms that facilitate better communication with patients and support medication adherence.

Minimizing risks and ensuring safety of subjects

Our study involves both physician-subjects and patient-subjects. We believe that the risks to participation for both sets of subjects are no more than minimal.

Physician-subjects in the intervention arm will only be asked to refer their eligible patients demonstrating non-adherence to chronic medications to the clinical pharmacist via an alert in the electronic health record. The information in the alerts is already available to the physicians in the electronic health record, and the alerts are only meant to highlight the information for the physicians to assist in patient management. Indeed, the alerts will facilitate a clinical practice that is already in place within HVMA – referral of patients on chronic medications to the clinical pharmacist for education. All physicians will be assigned a scrambled identifier by the implementation team at HVMA, and only these scrambled identifiers will be shared with the evaluation team at BWH.

Patient-subjects may be referred by their physician to a visit with the clinical pharmacist as part of an educational intervention to improve chronic medication adherence. The study team will not provide direct care to patients, and all treatment decisions will ultimately be made by the patient's medical team at HVMA. The risk to patient-subjects is no more than minimal as we will collect health

care data that was generated as a result of routine care, including clinical diagnoses of diabetes, hypertension, or hyperlipidemia; as well as relevant laboratory results and medication prescription data. The primary risk to patients will be privacy of health information.

We will minimize the risk to privacy by taking appropriate steps to limit access to data to study investigators, creating scrambled patient identifiers, and sharing only deidentified data with Partners Healthcare investigators, and ensuring that all team members have received appropriate training in data privacy. The link between the identifiers and the medical record number will remain at HVMA in a password protected file.

We will ensure the safety of patient-subjects by leaving ultimate clinical decision making in the hands of the evaluating physician and the clinical pharmacist who are in charge of caring for the patient. These clinicians already have an established professional relationship in caring for patients at HVMA, and we are mainly focused on facilitating referral of appropriate patients between the primary care physician and pharmacist. We do not anticipate any safety issues to arise with regards to physician-subjects that receive the electronic alerts. Given the minimal risks involved in participation in this study, we do not anticipate any unacceptable adverse events or need to drop subjects from the study.

Foreseeable risks

There is no more than minimal risk involved to the physician subjects, as they will only receive electronic alerts within the medical record. Patient risks should also be minimized, as our intervention aims to promote adherence to medications already prescribed by their primary care physician under the guidance of a referral from their physician. Any clinical risks will be minimized in our protocol by prompting the evaluating doctor to make a clinical decision as to whether referral to a clinical pharmacist is appropriate. The clinical pharmacist intervention is primarily supportive and educational,

and all management decisions will be made by the primary care physicians. This model is already in place at HVMA, and we are studying the facilitation of this process for patients in most need of education and support.

Expected benefits

This study is designed to improve the management of patients with diabetes, hypertension, and hyperlipidemia. The physician-subjects randomly assigned to the intervention may benefit from becoming more aware of patient adherence to medications and its importance to achieving improved clinical outcomes. Patient-subjects randomly assigned to the intervention may also benefit from the receipt of education from clinical pharmacist, gaining a better understanding of their chronic disease and the role of their prescription medications. By evaluating three of the most common chronic conditions, this study also has the potential to improve care for similar patients in other health care organizations across the United States by providing a new model of care.

Equitable selection of subjects

We will enroll all primary care physicians at Harvard Vanguard Medical Associates (HVMA), as well as all of their patients with diabetes, hypertension, or hyperlipidemia; and evidence of poor disease control and medication nonadherence. We estimate that 61% of eligible patients are female. The racial composition of this population is 72% White, 23% Black, and 5% Hispanic.

Women and minority patients will be fully eligible for inclusion as study subjects and randomized to the intervention or control groups consistent with their proportions in the population of patients meeting the eligibility criteria. Physician-subjects will be selected based on current employment by HVMA as a primary care physician.

All participating clinicians are fluent in English. We will enroll patients regardless of language based on referral from the primary care physician.

Recruitment procedures

Primary care physicians will be enrolled in the study by virtue of being an actively practicing clinician in internal medicine at HVMA. Prior to the beginning of the study, we will conduct site visits to each of the health centers and provide a 1-hour lunchtime lecture to review the scope of the intervention and entertain questions for physicians. Patients will be recruited into the study by a review of electronic medical record data to identify patients with diabetes, hypertension, or hyperlipidemia; evidence of poor disease control; and evidence of medication nonadherence. Physicians will be prompted to refer these patients to the clinical pharmacist via an alert in the electronic health record. We will only evaluate clinical outcomes for patients referred by their primary care physicians to the clinical pharmacist. The clinical pharmacist will conduct an intake interview with the patient, emphasizing the referral from the primary care physician. The pharmacist will describe the educational program to the patient and create a treatment plan based on the patient's needs and desires. The patient can decline the referral from the primary care physician (consistent with any clinical referral that the primary care physician recommends), and can also decline to participate in any educational offerings from the clinical pharmacist. There will be no remunerations to any study subjects.

Consent procedures

A waiver of informed consent and HIPAA authorization applies to all physician-subjects and patient-subjects. This study relies on the PHRC as the IRB of record for HVMA's participation, through an existing umbrella IRB agreement between HVMA and Partners.

Data and safety monitoring

The research subjects in this study will be subject to no more than minimal risk and we do not anticipate the occurrence of any adverse events. We will be in routine contact with the practice managers and internal medicine chiefs at each health center to obtain any feedback from clinicians regarding the study. Our plan for data and safety monitoring also includes oversight by the project principal investigator (Dr. Sequist) throughout the study period, as well as an independent DSMB that will consist of three members of the Harvard Medical School and Brigham and Women's Hospital faculty with experience in health information technology, patient safety, and biostatistics. This committee will meet on a semi-annual basis to review data related to the study protocol, and ensure protection of patient confidentiality and safety, as well as to monitor the quality of the data collected via the study protocol. Our protocol primarily involves delivery of electronic risk alerts to primary care physicians to facilitate referral to clinical pharmacists for appropriate education. We will not provide any direct treatment, and do not anticipate any adverse events for patients as a result of this study.

Privacy and confidentiality

All physicians will be assigned scrambled identifiers by the HVMA project manager, and only these identifiers will be made available to investigators at Brigham and Women's Hospital, thereby limiting any risks to privacy for physician-subjects.

All patients will be assigned scrambled identifiers by the HVMA project manager. Following medical chart reviews, only these scrambled identifiers will be included in analytic datasets at Brigham and Women's Hospital, thereby limiting any risks to privacy for patient-subjects. The link between the identifiers and the medical record number will remain at HVMA in a password protected file.

Finally, all project staff will have received training in research subject protection.

Sending specimens/data to research collaborators outside Partners

Once data is received at Partners from HVMA, we will not share these data with any outside collaborators. No data will be stored at collaborating sites outside Partners for any use not described in this protocol.

Final protocol

Background

Highly effective medications to treat and prevent the complications of chronic disease have been developed and evaluated. While rates of prescribing effective therapies have improved substantially, long-term adherence remains exceptionally poor. Nearly 50% of patients become non-adherent within a year of treatment initiation. Interventions that succeed in improving medication adherence may confer important clinical benefits across large populations, and may even be cost-saving by reducing rates of costly clinical outcomes such as myocardial infarction and stroke.

The success of interventions to improve adherence has been relatively limited, either because of the nature of the intervention or their broad applications to patients who do not require them or will not benefit from them. Prior studies have also been limited by recruiting small samples of volunteers, following patients for short periods, and not evaluating their impact on clinical outcomes. The efficacy of future efforts is likely to be increased by targeting interventions to patients demonstrating both poor adherence and poor disease control, tailoring interventions to individual patient needs, and touching larger and more representative patient populations and care settings. These goals can be achieved by the innovative use of information technology including electronic health records (EHR) and other advanced communication technologies, including texting.

We propose a cluster randomized controlled trial (RCT) of a novel tele-pharmacist based intervention to improve adherence to medications for hypercholesterolemia, hypertension, and diabetes. We will evaluate an innovative intervention that uses of EHR data to identify 4076 adult patients cared for by approximately 150 primary care physicians who are both non-adherent and not achieving recommended clinical targets for glycemic, blood pressure, and cholesterol control in a real-world primary care setting. Following EHR-facilitated referral from the treating primary care physicians, a clinical

pharmacist will direct an outreach program using multiple communication technologies including a telephone consultation, text messaging and video visits to improve medication adherence.

Study setting

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. Within each site, all PCPs and their eligible patients will be randomized to the same study arm.

Study design and randomization

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 non-adherent to their glucose lowering, anti-hypertensive, or statin medications and have evidence of poor disease control based on recommended clinical targets. 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 (i.e., 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 (i.e., 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.

Subjects

We will enroll all primary care physicians and their eligible patients. Eligible patients include adults ≥18 years and <85 years with a diagnosis of diabetes, hypertension, or hyperlipidemia; evidence of poor or worsening disease control (see Table 1); and evidence of medication non-adherence based on medication refill data. Disease control is evaluated using the most recent lab or blood pressure values in the electronic health record and is based on clinical guideline targets from the American Diabetes Association (ADA), the Eighth Joint National Committee (JNC 8) hypertension guidelines, and the American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines. Adherence is assessed using prescription claims data. HVMA prescription data are available with a one-month lag. For each medication used to treat any one of the targeted conditions, the proportion of days covered (PDC) is 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). We consider drugs that are chemically related and not intended for use in combination to be interchangeable (e.g., two different statins). We average the PDC for all medications used to treat a single condition (e.g., all oral hypoglycemics) and then calculate an overall average adherence for all of the conditions that a patient had at the time of their identification.

TABLE 1. Definitions of poor and worsening disease control

Condition	Age (years)	Poor control	Worsening control
Diabetes	…	Latest HbA1c > 8	Latest HbA1C 7.5 ≤ to ≤ 8, and previous HbA1C 1% lower
Hypertension	≥ 60	Latest BP > 150/90	Latest BP 140/80 ≤ to ≤ 150/90, and previous BP 20 mmHg lower
	< 60	Latest BP > 140/90	Latest BP 130/80 ≤ to ≤ 140/90, and previous systolic or diastolic BP 20 mmHg lower
Hyperlipidemia	…	Diagnoses of ASCVD	…
	40-75	Type 1 or 2 diabetes and use of glucose lowering agent	…
	40-79	ASCVD risk > 7.5%	…
	…	LDL>190 mg/dl	Latest LDL 175 ≤ to ≤ 190, and previous LDL 30 mg/dl lower

…= N/A; Abbreviations: HbA1c, glycosylated hemoglobin; BP, blood pressure; ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein

To identify individuals who would benefit most from the intervention, a patient is defined as being non-adherent if they (1) have been less than 80% adherent to the specific class of medications used to treat the condition(s) for which they were being identified as being poorly controlled and (2) if their "average of averages" PDC for all eligible study drugs is less than 80%. For example, patients with poorly

controlled diabetes who are non-adherent to their diabetes medications but adherent to their statins and antihypertensives, would only be eligible if their average adherence across all 3 conditions is less than 80%. Patients are excluded if, prior to randomization, they have less than 6 months of continuous enrollment in the health plan (to allow adequate assessment of eligibility), are < 18 or > 85 years of age, or have 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 will be sent a secure message using the electronic health record to ask permission to include their patient(s) in the study. If a physician does not explicitly respond to approve or disapprove of the identified patient(s) to participate in the study within 5 days, they are sent a reminder message; one day later, their patients will automatically be opted in to the study.

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

Intervention

The central component of the multi-faceted intervention is an individually-tailored telephone consultation conducted by a clinical pharmacist who is part of the Harvard Vanguard care team. The

clinical pharmacists work at multiple sites; in order to reduce the chances of contamination, they are restricted to providing clinical services only at other intervention sites during the time period of this study.

During this consultation, the clinical pharmacist confirms a patient's treatment regimen, engages the patient in sharing potential barriers to adherence or other factors that may be contributing to poor disease control, discusses the patient's readiness to modify behaviors, and works with the patient to agree upon a shared plan of strategies to improve adherence and disease control. The identified adherence barriers are grouped into six distinct groups: treatment complexity/forgetfulness, health perceptions, lack of knowledge/poor health literacy, side effects, cognitive impairment, and cost-related barriers. Patients may have barriers identified in more than one category. The solutions and strategies offered to patients by the clinical pharmacists are tailored to their PAM level and their identified adherence barrier(s). Depending on the barrier, patients with lower levels of activation (e.g., PAM Level 1 and 2) are 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 (e.g., PAM Level 3 and 4) are offered less intensive solutions, such as weekly text messages and pillboxes. The clinical pharmacists then work with the primary care physicians and other team members at Atrius Health to implement solutions based on the treatment plan. The clinical pharmacists also mail a copy of the shared plan to the patients after the initial encounter.

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 are 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 subjects who opted to receive them (see Appendix C). In addition to the motivational text messages, patients are asked questions 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 will differ depending on patients' PAM levels and adherence barrier. The Mobile Commons platform can store all incoming and outgoing messages in relational databases. We will deliver text messages to patients to assess self-reported adherence, remind them of strategies reviewed to address barriers to adherence and to refill their prescriptions (see Text_messages). Requested responses are structured (e.g. the number of days that they took their medication last week). If the patient sends anything other than an expected response to the question being asked (for example, if they provide their blood pressure reading rather than their level of adherence), they will receive an automated message telling them that the text message system is not monitored by a live individual and instructing them, in the case of the need for urgent medical attention, to call 911, go to their nearest emergency department or calling the 24-hour nurse helpline for their HVMA primary care practice. In addition, the study PIs and the HVMA Site PI (Dr. Thomas Isaac) will receive an automated and instant email from the Mobile Commons platform with a copy of any such unanticipated texts, and if necessary based on the content will call the 24-hour HVMA nurse helpline to have them attempt to address the patient's concern.

At the conclusion of the initial pharmacist call, the pharmacists will provide feedback to the referring PCP via electronic documentation of patient interactions that highlight current care plans. In situations where the pharmacist is recommending a change in therapy (e.g. a switch from the branded version to the generic version of a given drug to reduce cost-related barriers to adherence), they will ask the PCP to review their consultation note and based on this to write a new prescription, if appropriate.

All intervention patients who do not opt out of trial participation are mailed progress reports at 6 months 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 (e.g., for patients who only use their prescription insurance plan to pay for their prescriptions), the progress reports will also provide patient-specific medication adherence information. For those patients deemed to be not improving on either clinical outcomes or medication adherence for 3 consecutive months, the pharmacist will conduct a telephone outreach to readdress barriers to adherence. For those patients that demonstrate improvement in both adherence and clinical outcomes, the frequency of contact will be decreased to a level appropriate to their support needs

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, will be explicitly tracked to facilitate future reproducibility and scalability.

At the conclusion of the 12-month follow-up period, a brief survey will be administered to intervention patients who did not decline to speak to a clinical pharmacist. These surveys will assess each patient's self-reported medication adherence, activation, and perceptions of the clinical pharmacist program. The surveys will also be used to validate medication adherence collected by retail pharmacy filling data and administrative pharmacy claims. These surveys will be delivered via a paper mailing on behalf of the PCP. Within these paper surveys, patients will be given the option to complete the survey online through Qualtrics. Non-respondents will receive a second copy of the survey with a $5 gift card as an incentive (see "12-month survey" in attachments section).

Outcomes

The trial's primary outcome is medication adherence assessed at 12 months after randomization. For this outcome, medication adherence will be assessed using prescription claims data and measured as the mean PDC over 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. 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 sensitivity analyses, we will measure medication adherence by calculating PDC beginning from the first fill of a medication after randomization until the end of the 12-month follow-up period. We will also repeat our analyses censoring patients with diabetes when they initiate insulin.

The secondary outcomes for the study include disease control and rates of healthcare utilization. Disease control will be measured as the following two 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 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. If more than 10% of subjects have missing data we will repeat our analyses using multiple imputation

Rates of healthcare utilization will also be measured using administrative claims data and will include all-cause emergency room visits, physician office visits, and all-cause hospitalizations during the 12-month follow-up period.

Analytic plan

We will report the means and frequencies of pre-randomization variables separately for intervention and control subjects. Comparisons of these values will be performed using t-tests and chi square tests and their non-parametric 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 subjects 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 for disease control and rates of healthcare utilization, respectively.

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 a standard deviation of 0.25 (a conservative assumption), clustering at the practice level with a design effect of 1.10, and a 15% non-differential 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 4000 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.

Summary of changes to protocol

Date of submission	Description of modification	Rationale for modification	Approval date
11/20/2013	1- Adding new funding source: NIH - 1 R01 HL117918-01	Our NIH application will be funded	12/31/2013
07/01/2014	1- Adding that this will utilize HVMA sites, which is part of a larger organization (Atrius). 2- Including information clinical QI efforts have been removed and language simplified. 3- Discussing how roles will be determined from the pilot study 4- Updating the number of sites/ health centers 5- Discussing waiver of informed consent as well as stating that HVMA is relying on PHRC for IRB through an already existing umbrella IRB agreement between Partners and HVMA.	These changes have been updated as part of a continuing review as noted during the review process.	07/03/2014
03/13/2015	1- Updating definitions of "poor disease control" to reflect current practice guidelines. 2- Changing randomization process from the level of the physician to the level of the practice site. 3- Outlining the process by which physicians will approve patients for study participation in greater detail 4- Describing the actual tele-pharmacist intervention in more detail. 5- Increasing the number of patients included in the study has increased from 2000 to 3000, as this is roughly the number of eligible patients at our practice sites. 6- Uploading new documents including the letter notifying patients of the intervention, the research assistant telephone script, a list of FAQs that may be relevant when the research assistant (RA) calls a patient, a list of text messages that will be sent to patients, and the letter that will be sent to patients summarizing their new relevant clinical data.	Processes have been updated to reflect realistic work flows per the request of our partners at HVMA and the number of patients in the study based on eligible patients at the practice sites. We also included new documents that the research assistants will use to schedule patients for a telephone visit with their clinical pharmacist.	04/14/2015
05/19/2015	1- Slighting revising several documents including: the patient recruitment letter,	The first three documents propose minor updates,	06/22/2015

	research assistant FAQs, research assistant call script, and reminder call message to patients for their clinical pharmacist call.	such as "clinical pharmacist" as opposed to "pharmacist" and wording in an automatic reminder call that will be sent to patients prior to their appointments	
06/26/2015	1- Submitting revised text messages to be sent to patients who consent to receiving this service. 2- Including the text for a follow-up recruitment letter that will be sent to patients who could not be reached with the first recruitment letter mailing.	1- The new text messages better address specific barriers that may hinder optimal medication adherence. 2- The follow-up recruitment letter will allow us to re-contact patients who could not be reached with the first mailing.	07/02/2015
07/22/2015	1. Updating with Spanish-translated versions of the initial and follow-up patient recruitment letters 2. Updating the initial patient recruitment letter to include verbiage about the enclosed pillbox 3. Providing voicemail messages that RAs will leave to patients who could not be reached via phone 4. Adding additional questions to the RA FAQs 5. Revising the RA script	1. Spanish translations of the patient recruitment letters will allow us to appeal to patients whose primary language is Spanish. 2. We changed our workflow to mail a pillbox with the initial recruitment letter, so we want to reference this tool in the letter. 3. Voicemail messages will provide patients with the opportunity to return the RAs' calls. 4. Additional information in the RA FAQs will help RAs answer any questions about clinical pharmacist responsibilities. 5. Edits to the RA script reflect improved verbiage for recruitment.	08/04/2015
09/03/2015	1- Revising RA permissions to include access to contact patients via MyHealth, a secure, web-based program that allows patients to contact their physician's office about non-urgent medical matters. 2- Revising the re-contact letter that is already IRB approved to include reference	1- RA access to MyHealth would provide an alternative method to contact patients who could not be reached via telephone.	09/24/2015

	to a small nominal collapsible drinking cup with pill container that will be included in the envelopes.	2- A small collapsible drinking cup with pill container could serve as a useful tool to increase adherence.	
01/12/2016	1- Updating the report card (progress report), which contains information on medication adherence and disease control according to each patient's claims data and most recent lab values.	The updated version of the report card reflects changes in both content and language. We included patients' most recently filled medications, last filled dates (according to claims data), and most recent lab values and incorporated more verbiage about medication adherence and next steps for better disease control.	01/25/2016
02/18/2016	1- Changing the enrollment number target from 3,000 to 4,080 patients to reflect findings from the first few months of enrollment.	After randomization, the referral rates by the PCPs were somewhat lower than originally estimated. Second, fewer patients randomized to the intervention were able to be reached by the RAs. We previously expected that 60% of patients would be reachable; that estimate is closer to 40%. Lastly, patients are censored when they lose insurance eligibility during follow-up, and more patients than originally estimated lose insurance. These affect the sample size estimates.	03/03/2016
06/29/2016	1- Adding the specific patient surveys and processes that will be conducted at the conclusion of the 12-month follow-up period for intervention patients who did not decline to speak to a clinical pharmacist. The surveys will be delivered via paper mailing with an online survey. Non-respondents will be mailed a second copy of the survey with an enclosed $5 gift card as an incentive.	These surveys will be used to evaluate the effectiveness of the telepharmacist intervention on patient adherence and activation. The surveys will also be used to validate the adherence measures collected by retail pharmacy data and	07/22/2016

		pharmacy claims. We will compare adherence and assess the validity of these alternative measures.	
11/02/2016	1- Slightly modifying the protocol to clarify which data are being used by Partners investigators for the purposes of analysis. The present amendment includes this clarification in the protocol and in the related data forms, as applicable.	The study team will use HIPAA-limited PHI data from HVMA for the purpose of analyzing the study. The only PHI that will be shared with Partners investigators are dates (e.g., date of birth, admission/discharge dates, and dates of procedures).	12/16/2016
03/08/2017	1- Slightly modifying the protocol to clarify how the data are being used by Partners investigators for the purposes of analyses to inform the DUA between the BWH and HVMA.	Like other insurer administrative claims, these data may contain some diagnosis codes and procedures for potentially sensitive information (e.g., HIV diagnosis, reproductive history) as these are adjudicated claims from insurers. In this study, except for mental health conditions, we will not be specifically looking at these sensitive conditions as comorbidities, effect modifiers or outcomes. We are only planning to include these in aggregated counts of resource utilization.	04/27/2017

Original analysis plan

Outcome Measures

Adherence

Adherence will be assessed for each medication prescribed for diabetes, hypertension, and hyperlipidemia and compared between intervention and control patients. The main measure of patient adherence will be proportion of days covered (PDC) for the intervention and control groups, as assessed with HVMA pharmacy data. This will be computed using the date the prescription was filled, the 'days supplied' field in dispensed drug data, and the dates on which the prescription was refilled.

Clinical outcomes

Clinical outcomes of interest are the proportion of patients achieving the following clinical targets: HbA1c values for patients with diabetes, systolic and diastolic blood pressure for patients with hypertension, and LDL values for patients with hypercholesterolemia. All laboratory values are available within the EHR.

Statistical analyses

We hypothesize that the intervention will improve medication adherence and disease control.

All analyses will use intention-to-treat principles. Medication adherence based on the proportion of days covered will be compared using generalized estimating equations, with adjustment for the cluster and block randomized design. We will use an identity link function and normally distributed errors. The proportion of patients considered adherent by achieving clinical goals will be compared using a logit link function and binary distributed errors. We will censor patients if they die, lose insurance eligibility, or at the end of the study period. Analyses will be run unadjusted as well as after controlling for the potential confounders listed below.

Potential confounders

The independent variable of interest is exposure to the pharmacist intervention. We will measure several variables to assess the degree of balance between patients and physicians randomized to intervention versus control, to adjust for chance imbalances, and to assess whether the efficacy of the intervention is modified by particular patient characteristics. Patient demographic characteristics and major comorbid conditions, as identified based on EHR data, will be included as independent variables

HVMA currently has an existing clinical pharmacy program. These clinical pharmacists already work collaboratively with the primary care physicians in the clinics to provide patient education and advice around medication management. Primary care physicians can currently refer patients to the clinical pharmacist using an electronic referral in the electronic health record.

Final analysis plan

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 a standard deviation of 0.25 (a conservative assumption), clustering at the practice level with a design effect of 1.10, and a 15% non-differential 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 4000 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.

Outcome Measures

Primary outcome - Adherence

The trial's primary outcome is medication adherence assessed at 12 months after randomization. Medication adherence will be assessed using prescription claims data and measured as the mean PDC over 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

Secondary outcomes

The secondary outcomes for the study include disease control and rates of healthcare utilization.

Disease control will be measured as the following two 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 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 up to a maximum of 15 months after randomization

Rates of healthcare 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

Statistical analyses

We will report the means and frequencies of pre-randomization variables separately for intervention and control subjects. Comparisons of these values will be performed using t-tests and chi square tests and their non-parametric 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 subjects 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 subjects have missing outcome data, we will repeat our analyses using the latest post-randomization lab values available and using multiple imputation.

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

Potential confounders

We will measure several variables to assess the degree of balance between patients and physicians randomized to intervention versus control, to adjust for chance imbalances, and to assess whether the efficacy of the intervention is modified by particular patient characteristics such as baseline patient demographic characteristics, major comorbid conditions, medication use, and healthcare utilization as identified based on claims and EHR data.

Summary of changes to the analysis plan

Detailed sample size calculations are now provided which was not included in the original plan. The primary and secondary outcomes are now clarified along with the specific analytic strategy for these outcomes.