**Application for Review of Human Research**
**IRB Protocol**

## STUDY SUMMARY

**Document Date: Dec 22, 2014**

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|---|---|
| Title | STUDY ON THE EFFECT OF COMBINED USE OF A CONNECTED PILLBOX, PRE-FILLED MEDICATION TRAYS, AUTOMATED TEXT MESSAGE /PHONE CALL REMINDERS, ON MEDCIATION ADHERENCE IN PATIENTS WITH TYPE II DIABETES MELLITUS |
| Short Title | EFFECT OF USE OF A CONNECTED PILLBOX ON MEDICATION ADHERENCE IN PATIENTS WITH TYPE II DIABETES MELLITUS |
| Protocol Number | **821737** |
| Clinical Trial Number | **NCT02593032** |
| Methodology | Randomized Control Trial |
| Study Duration | 6 Months |
| Study Center (s) | Clinics at the Hospital of University of Pennsylvania and Presbyterian Hospital |
| Objectives | Assess the efficacy of a multi-modal intervention on the medication adherence of diabetic patients who were previously nonadherent to their oral hypoglycemic agents according to pharmacy claims data |
| Number of Subjects | Goal of 150 (75 treatment, 75 control) |
| Main Inclusion Criteria | Patients have medical and pharmacy coverage under Independence Blue Cross (IBC), have Type II diabetes (HbA1C ≥ 7.5) and have a proportion of days covered (PDC) or mean PDC <80% for their oral hypoglycemic agents according to pharmacy claims data obtained from IBC/Catamaran |
| Study Product | Connected pillbox and software designed and distributed by TowerView Health Inc. |
| Study Sponsorship | Funding Sponsor: TowerView Health Inc.<br>Site PI: Nalaka Gooneratne, PI |
| Post Study Analysis | Primary Endpoint: Change in medication adherence (PDC) |

## Introduction

Medication adherence is defined as the extent to which a patient takes his or her medication as prescribed by their healthcare provider. One third to one half of all patients in the United States do not take their medication as directed, resulting in nearly $100B in avoidable hospital costs per year.

Much of this cost can be linked to complications secondary to highly prevalent comorbidities such as diabetes, hypertension, and hyperlipidemia. Together, diabetes, hypertension, and hyperlipidemia increase patient risk for microvascular/macrovascular complications and are responsible for the majority of costly cardiac events observed in the US healthcare system. While the etiology of these comorbidities is multi-factorial, such diseases can be managed with a combination of medication and behavioral change, such as increased diet and improved exercise.

Yet despite the low cost, generic status of most oral drugs used to treat diabetes, hypertension, and hyperlipidemia adherence to multi-medication regimens remains poor. Recent efforts to improve medication adherence in patients with multiple comorbidities have turned to case management and disease management programs. Such interventions leverage human interaction and have demonstrated effectiveness; however, they also present operational challenges. Notably, nursing or social work resources must be devoted to patient outreach or home visits thereby greatly increasing program costs.

Connected monitoring devices offer an alternative- or supplement- to frequent nurse visits and outreach. These devices enable frequent monitoring and intervention but can also generate large volumes of data that can be difficult for care teams to manage. Services that can monitor, triage alerts, and encourage patient adherence automatically may fill the void between nurse case management and more frequent biometric monitoring. The present study explores the use of one such device- a technology-enabled, connected pillbox in a population of patients with Type II diabetes mellitus.

## Rationale

The research treatment is targeted at Type II diabetes mellitus due to 1) its growing prevalence in the US population 2) our group's ability to measure a biomarker (A1C) impacted by improved medication adherence and 3) the high prevalence of additional comorbidities (e.g. hypertension, hyperlipidemia) in patients with diabetes. Such concordance increases the risk of costly cardiac events that, when paired with the increased rate of hospital readmissions observed in patients with poorly controlled glycaemia, illustrates why patients with diabetes have per member per month costs (PMPM) that are four to five times as high as that of average health insurance members. Given the continued emphasis on bending the cost curve in US healthcare, clinical validation of tools that may improve the management of costly chronic diseases, such as diabetes, is essential.

## Length and Objectives

This randomized control trial will be carried out in an outpatient geriatric, endocrinology, internal medicine, and family medicine setting at both the Hospital of the University of Pennsylvania (HUP) and Presbyterian Hospital. Patients will be enrolled in the research study for 6 months. The overall study will end when the last patient has completed their 6-month observation period. Independence Blue Cross's informatics department will complete the post study analysis within 2 months of the study completion.

The primary aim of the study is: To determine if a multi-modal intervention focused on improving medication adherence among adults who were previously nonadherent to their oral hypoglycemic agents results in improved medication adherence over a 6-month interval

Secondary (exploratory aims) for the study are: To determine if the multi-modal intervention results in improved blood glucose, blood pressure, reduction in emergency room visits, reduction in absolute healthcare costs, and reduction in overall healthcare utilization

Post study analyses will explore how various demographic factors as well as accompanying comorbidities affect medication adherence in the treatment vs. control groups. Satisfaction with the multi-modal intervention will also be assessed through a survey instrument at the end of the 6-month study period.

Study Intervention

Patients in the research treatment group receive pre-filled, 3x7 disposable trays that separate their medication by dose and time (e.g. morning, afternoon, evening). These pre-filled trays are inserted into a connected, weekly pillbox that detects when pills are removed from its wells. Using this information, TowerView Health's system is able to send automated text messages or phone reminders to patients to take forgotten or ignored medication doses.

Medication adherence data from deployed pillboxes populates a software platform, which a research coordinator can access. Patients who miss *3 consecutive doses or 5 doses out of 12 over a 4-day period* trigger an alert for the study research coordinator who can contact the patient via phone call. The research coordinator follows a scripted motivational interview in his or her outreach to determine the etiology of non-adherence. Patients reporting worrisome symptoms will be instructed to contact their provider directly and/or go to the emergency room for immediate attention.

Our team acknowledges that the current study actually involves multiple interventions:

1. The pre-filled medication trays are provided by a pharmacist, which overcomes medication access issues as well as the inconvenience of manually organizing medications.
2. The electronic pillbox, which monitors adherence that triggers text message or phone reminders in instances where patients forget or ignore medication doses
3. Research coordinator alerts, which trigger outreach events that employ a motivational interview in order to improve patient adherence

A study involving multiple interventions is rooted in literature findings that medication nonadherence has multiple drivers, ranging from forgetfulness and confusion over treatment rationale to logistical difficulties in getting medication refills and drug costs. While our group is unable to address the key cost considerations patients face in remaining adherent, our multi-modal approach improves ease of use and provides reminders that may improve medication adherence.

Future studies may look to add additional research arms in order to isolate the benefits from the various elements of the currently proposed intervention. Such studies may also include larger sample sizes in order to be powered to discern differences between the treatment and control groups for clinical markers such as A1C or blood pressure control.

Hypothesis

Combined use of a technology enabled pill box, targeted text or phone reminders, pre-filled medication trays, and research coordinator outreach will result in a 15% improvement in medication adherence when compared to a usual care control group.

The range of adherence improvements observed in the literature under various adherence interventions varies from 5% improvement to over 40% improvement, however, a number of intervention approaches cluster between a 10-20% improvement (see table below). As a result, our group has conservatively estimated an expected improvement in medication adherence of 15% between the research treatments and usual care arms of the present study. Usual care is defined as the existing clinical practice guidelines used by physicians at the University of Pennsylvania for managing patients with diabetes and additional comorbidities.

| Authors | Intervention | Usual Care PDC (SD) | Intervention PDC (SD) | Study Population |
|---|---|---|---|---|
| Lee et al 2006 | Pharmacist education, multidose blister packaging | 61.2% (13.5%) | 97% (5%) | Geriatrics |
| Murray et al 2007 | Pharmacist Intervention | 67.9% | 78.8% | Heart Failure |
| Morgado et al 2011 | Pharmacist Intervention | 57.6% | 74.5% | Hypertension |
| Dupclay et al 2012 | Single dose blister packaging | 63% (26%) | 76 (25%) | Hypertension |

Statistical Analysis

Mean medication adherence was calculated as the proportion of days covered (PDC) for hypoglycemic medications. The change in medication adherence (pre-intervention PDC subtracted from the post-intervention PDC = change score) will be compared using unpaired t tests. For the primary endpoint, analyses will be performed according to the intention-to-treat principle. Change in mean medication adherence between the 2 study groups (usual care and intervention) will be compared by using a t test for independent groups. Patients who do not complete the randomized trial (because of death or withdrawal) will be analyzed by the imputation method of last observation carried forward, using the medication adherence level of the time available. A similar methodology will be used for the secondary (exploratory) endpoints of diabetes control and re-admission rate.

Exploratory analysis: To control for baseline differences between study groups, a multivariable analysis will be performed for the randomized trial primary end point. The dependent variable for this analysis will also be the change score (the change in medication adherence between pre-treatment and post-treatment). The independent variables will be those baseline characteristics that had between group comparisons with $P<.20$, in addition to the randomized trial group assignment, clinic site and the baseline (run-in phase) medication adherence. The criteria for statistical significance for the primary outcomes will be a two-sided $p<0.05$. The above statistical methodology is based on the approach used by Lee et al., JAMA 2006.

Target Population

We will recruit adults with independence Blue Cross medical and pharmacy coverage, Type II DM, HbA1C ≥ 7.5, and a current medication regimen that only includes oral therapy. If patients are eligible for participation an initial meeting will be arranged with a trained research coordinator to enroll them in the study. This meeting will occur either in the clinic or in the patient's home in the case the patient is unable to commute to the clinic. Eligible participants will be randomized to either treatment or control arms with a target allocation ratio of 1:1. With the estimated sample size (75 treatment, 75 control) we have 80% power to detect up to a 15% change in medication adherence. This assumes a dropout rate of 15% percent and a standard deviation of 30%.

Inclusion Criteria

We have structured the criteria to include patients who are most likely to benefit from the intervention. This includes patients are nonadherent based on pharmacy benefit claims data and whose blood sugar is not well controlled (HbA1C $\geq$ 7.5). Key inclusion criteria are:

- Insurance and pharmacy coverage with Independence Blue Cross (IBC)
- 18 years or older
- Current diagnosis of Type II Diabetes Mellitus
- HbA1C $\geq$ 7.5 (standards defined by the American Diabetes Association) as recorded in the clinical chart at last determination
- Less than 80% medication adherence for hypoglycemic medications as determined by pharmacy benefit data in the 9 months prior to the study
- Able to communicate in English
- Willing to give informed consent

Exclusion Criteria

Participants whose medications are dispensed are excluded because the intervention focuses on the patient, not their care facility. Not agreeing to use TowerView's connected pillbox is an exclusion because it is central to our intervention. Finally, not having access to a phone is an exclusion criteria because it is the only way our group can contact the patient if needed.

- Known alcohol or illicit drug abuse
- Significant cognitive impairment at baseline as defined by a Montreal Cognitive Assessment (MoCA) exam
- Residence in a care facility that provides medication on schedule
- Unwilling to use TowerView Health's connected pillbox and accompanying medication trays
- Any active medical or psychiatric diagnosis that, based on the clinical assessment of the research team, would prevent the study participant from completing the trial such as: markedly shortened life expectancy (e.g. diagnosis of metastatic cancer, end stage renal disease on dialysis, New York Heart Association (NYHA) Class III or IV heart failure, active psychosis or suicidal ideation, etc.) or dexterity/motor impairments (e.g. severe arthritis, neuromuscular disorders, etc)
- Lack a mobile or landline phone

Subject Recruitment and Screening

We will recruit 150 patients identified through the Pennsylvania Integrated Clinical and Administrative Research Database system and Independence Blue Cross/Catamaran databases. Patients with Type II DM, an HbA1C ≥ 7.5, and IBC medical and pharmacy coverage will be identified.

With consent from their physician, eligible patients will be sent an initial contact letter informing them of their eligibility to participate in the study. Approximately, 1-2 weeks later a research coordinator will call the patient and educate the patient on the study objectives, benefits, and risks. Patients may verbally confirm their participation in the study at this time, allowing the coordinator to prepare a connected pillbox for their upcoming appointment. Verbal confirmation is not considered formal consent, which will be obtained during the in-person, scheduled appointment. The initial contact letter will also notify the patients that they can decline the informational phone call and provide the patient an email/phone number to directly communicate this request.

At the scheduled appointment patients who have verbally confirmed their interest in participating will be approached to formally enroll in the study. This appointment may occur in the primary care clinic, endocrinology clinic, internal medicine clinic, in the Clinical and Translational Research Center (CTRC), or at the patient's home. All patients retain the right to not participate despite having verbally confirmed prior interest in enrolling.

Early Withdrawal of Subjects

Participants may be withdrawn from study participation without their consent if: 1) the PI feels it is best for their safety and/or health, 2) they have not followed the study instructions, or 3) the PI sponsor, or Office of Regulatory Affairs at the University of Pennsylvania decide to stop the study.

Participants also have the right to drop out of the research study at anytime. If a participant wishes to withdraw from the research study he or she need only notify the study coordinator. Participants will be able to keep any compensation for study activities they have participated in, however, they will not receive compensation for study activities they have not participated in. All participants will be made aware of withdrawal procedures when informed consent is obtained.

Vulnerable Populations

Children, pregnant women, neonates, or prisoners are not included in this research study. Economically or educationally disadvantaged persons may participate in this study. We will minimize the risk of coercion by making clear in the consent process that participation in the study is voluntary and separate from their medical care and that non-participation will not affect how they are treated clinically.

Study Design

We propose a randomized control clinical trial. Random number generation will be used to randomize patients to either the treatment group (connected pillbox) or control group (usual care). The patient will only be randomized after he or she has been briefed on the intervention and consented to participating. In this way both patients in the treatment and control groups will receive the same education regarding adherence so as to not bias the study. Patients in both the research treatment and control group will be compensated equally for their participation in the study.

Study Intervention

The study intervention is multi-modal and consists of 1) prefilled medication trays that are shipped to patient's home 2) a connected pillbox that senses when doses are missed and can initiate phone call or text reminders and 3) research coordinator outreach triggered by nonadherence. A detailed overview of each component of the intervention is presented below:

*Prefilled Medication Trays*

The study sponsor, TowerView Health, has developed plastic trays designed to hold all the medications in a patient's regime. Each tray has 21 medication compartments- 3 compartments (morning, afternoon, nightly meds) for each day of the week. Patients in the research intervention will receive monthly shipments of 5 prefilled medication trays from Friendship Pharmacy, Inc., an IBC participating long-term care and retail pharmacy, located at 3300 Cottman Avenue, Philadelphia, PA 19149.

After consenting to participate in the study, the patient or patient's caregiver will provide the research coordinator with a complete list of pharmacies used by the patient. This information will be shared with the Friendship Pharmacy pharmacist who will initiate the transfer of all scripts from patient's existing pharmacy to Friendship Pharmacy. A nurse practitioner or physician at Penn Medicine will initiate any scripts that need to be rewritten. In instances where prior authorization is required or a script is denied at adjudication the Friendship pharmacist will reach out to the physician or nurse practitioner to receive authorization or make an appropriate medication change.

A pharmacist at Friendship Pharmacy will load a patient's complete medication schedule and seal each medication tray using a heat-sealing system that uses compressed air. The system will seal each individual medication compartment in order to minimize drug waste in instances when the patient drops the pillbox or tray. Each medication compartment will be labeled with all the drug names and respective doses housed within it for quality and safety purposes. Complete printed labels identical to those found on the exterior usual care medication vials will accompany the trays in order to comply with Pennsylvania state pharmacy regulations. PRN (e.g. opioids) and frequently titratable medications (e.g. warfarin, tacrolimus) will not be included in the tray and will be provided to the patient in usual care medication vials.

Friendship Pharmacy will refill medication trays on a monthly basis only at patient request. An automated reminder will be initiated 10 days prior to the patients refill date. Failure to refill will be followed up by a personalized call from Friendship Pharmacy 7 days prior to the patients expected refill date. Refill reminders will continue every 3 days after initial outreach until patients initiate a tray refill.

*Connected Pillbox*

After consenting to participate in the study patients will receive a connected pillbox that has been activated for use on the Verizon Wireless network. Using embedded sensors, the pillbox senses volume changes within individual compartments and sends this raw, encrypted data to a dedicated server in the cloud. TowerView's algorithms process capacitance data and determine whether a patient took his or her medications. In instances when patients did not take their medications, TowerView can send the patient an automated text message, phone call, or email reminder. For patients who prefer not to receive such notifications the pillbox comes equipped with visual (flashing blue light) and audio (loud beeping) reminders as well.

Initial notification schedules will be assigned based on patient preference by the research coordinator (ex: 9AM, 3PM, 9PM). Using TowerView's web based software, however, patients can alter their notification

schedule at any time; furthermore, notifications can be set for medications that do not reside within the pre-filled trays. This feature has been added to accommodate PRN, frequently titratable and injectable medications that are unable to be included as part of the tray.

*Targeted Reminders*

The technology being deployed has customizable reminders, however, for the present study reminder variations will be limited in order to maintain a level of consistency within the research treatment group. Patients will be thoroughly briefed on the reminder program both orally and in writing at enrollment. The reminder program is as follows:

1. Patients can opt for either text messages OR phone call reminders at the dosage time of their choosing (e.g. 9:30AM morning dose)
    a. The TowerView system will send the patient a reminder text OR phone call at a variable time between 5-15 minutes after the dosage time of their choosing
    b. The reminder delivered by phone will be: "Please don't forget to take your [morning, afternoon, or nightly] medication! Please press "1" if you took your medication before receiving this call or "2" if this call prompted you to take your medication. –The Penn Medicine Team"
    c. The reminder delivered by text will be: "Please don't forget to take your [morning, afternoon, or nightly] medication! Please text "Y" if you took your medication before receiving this message or "P" if this message prompted you to take your medication. – The Penn Medicine Team."
2. The system will continue to sense if patients took their medication. 30 minutes after the first notification our software will make a determination as to whether a dose was actually taken
    a. If the dose WAS taken no reminder is initiated until the next dose becomes due
    b. If the dose WAS NOT taken we will reach out again with another text OR phone call reminders
        i. The reminder delivered by phone will be: "Please don't forget to take your [morning, afternoon, or nightly] medication! Please press "1" if you took your medication before receiving this call or "2" if you'd like to be reminded again later. –The Penn Medicine Team"
        ii. The reminder delivered by text will be: "Please don't forget to take your [morning, afternoon, or nightly] medication! Please text "Y" if you took your medication before receiving this message or "P" if this message prompted you to take your medication. –The Penn Medicine Team."
3. If a patient responds (Y or 1) or does not respond at all reminders cease until the next dose of their medication. If they respond (P or 2) the system will sense for a medication dose until 30 minutes elapse at which point it will send the following message by either text message OR phone call.
    a. "This is the last reminder to take your [morning, afternoon, and nightly] medication! There is no need to respond to this notification –The Penn Medicine Team
4. All patients will receive an automated phone call reminder to refill their medication tray 10 days prior to their refill date. Patients with cell phones will also receive a text message reminder.
    a. "Please be sure to refill your medications by calling 215-624-0440 during regular business hours"-The Penn Team

Patients will have the option to turn on or off the pillbox's light and sound feature. The rationale for introducing the "P" or "2" option into the reminder system is to better understand if reminders before a medication dose are constructive when compared to simply reminding a patient after they have already forgotten their dose. Notifications after a dose is due may reduce reminder fatigue as the patient is given the opportunity to remember their dose from memory alone.

*Research Coordinator Outreach*

In addition to patient facing software through which patients and can view their medication adherence and make changes to notification schedules, TowerView has designed a care coordinator/nurse dashboard. Using this dashboard the research coordinator is able to view the adherence of all patients using the connected pillbox. Patients who are continuously nonadherent- 3 consecutive missed doses or 5 doses out of 12 over a 4-day period receive targeted outreach from the research coordinator. This call is designed to explore the etiology of patient nonadherence as well as potentially change patient behavior using motivational interviewing techniques.

*Primary Endpoint:*

- Medication adherence as defined by PDC rates for both the treatment and control group

*Secondary (Exploratory) Endpoints:*

- Time to treatment discontinuation (rate of medication persistence)
- Glycated hemoglobin (HbA1C), which is generally collected every three months as part of routine clinical care for diabetic patients with HbA1C over 7.5
- Blood pressure
- Body Mass Index (BMI)
- Emergency Room (ER) visits
- Absolute cost
- Overall healthcare utilization
- Patient Satisfaction with research treatment
- Time to research coordinator outreach event
- Number of research coordinator outreach event
- Automated phone or text message reminder trends (e.g. number of reminders required)

<u>Post Enrollment Events</u>

Patients in both the treatment and control arms will receive an identical overview regarding the proposed intervention and randomization will only occur after the consent process has been completed. Patients in the control arm will receive usual care and can continue using their existing pharmacy. Patients in the treatment group will begin receiving their medications in pre-filled medication trays from Friendship Pharmacy. Patients will receive 5 trays on a monthly basis in order to accommodate a 30-day, insurance-reimbursed fill schedule.

As much as possible our group will attempt to collect data as part of usual clinical practice. For example, we will attempt to consent patients with upcoming clinic visits who meet enrollment criteria on the same day as their existing appointment. For patients whose appointment schedule does not permit us to do so we'll look to schedule a research visit on a day and time that is most convenient.

We will also attempt to utilize existing laboratory tests so as to not duplicate services. Given the present study assesses patient adherence for hypoglycemic medications, we would like to have an HbA1c measure for each patient at the onset and conclusion of the study. Rather than simply re-order this test we have set a 45 day window such that if an A1C was ordered as part of usual care in the 45 days before the patient's study start date or end date we will abstract that value from the patients chart for use in our analysis.

As clinical guidelines recommend that patients with poorly controlled glycaemia have an A1C taken quarterly, we reserve the right to request an A1C for patients who have not had one as part of usual care. If none of the conditions previously described are met we will order an A1C under the research protocol, thereby incurring a research expense on behalf of the patient.

LDL, HDL triglycerides, and total cholesterol levels are also of interest to our group in instances where the patient has both diabetes and hyperlipidemia. As a lipid panel is typically ordered once a year for patients with hyperlipidemia our group has set a 3 month window from the study start and end date. If the patient's lipid panel was drawn as part of usual care during this 3-month time window we will abstract the value from the patient's chart. Below is a summary of the information we will collect at the two visits common to all patients participating in the study.

*Induction Visit*

Patients will be consented by a trained research coordinator and have the following information collected from them:

- Electronic mailing address and phone number
- Blood pressure-once at the beginning and once at the end of the visit
- Demographic survey
- Montreal Cognitive Assessment (MoCA exam)- a screen for cognitive impairment
- Cumulative Illness Rating Scale (CIRS)- a measure of comorbid illness burden
- Short Form 12 (SF-12)- a measure of general quality of life
- Brief Medication Question (BMQ)- a self reported assessment of medication adherence and medication adherence related factors (e.g. cost burden of drugs)

*Concluding Visit*

Patients will return their connected pillbox and have the following information collected from them:

- Blood pressure- once at the beginning and once at the end of the visit
- HbA1c test and lipid panel if data cannot abstracted from the chart
- Patient satisfaction and attitudes toward adherence system

The care coordinator will also assist the patient in transitioning from the tray to another method of receiving their medications. Patients will have the option of either remaining with Friendship Pharmacy or be transferred back to their original pharmacy.

<u>Methods</u>

*Measuring Adherence*

Proportion of Days Covered (PDC) is the metric currently used by CMS and NCQA to assess patient medication adherence; the metric is calculated using pharmacy benefit data. The present study utilizes an interval-based PDC calculation defined as medication possession during the interval from the index date (the patient's study start date) to the end of the period being assessed (the patient's end date). In this way, the number of days of medication supplied throughout the period becomes the numerator and is divided by the number of days in the overall period itself. Intervals during which patients are hospitalized or in hospice are excluded from the PDC calculation

As PDC is an assessment of medication adherence for a single drug the calculation must be modified for patients taking multiple medications. Of interest in this study is patient adherence to oral hypoglycemic drugs. Our group recognizes the following categories as oral hypoglycemic agents: sulfonylurea, metformin hydrochloride, glitazones, acarbose, and meglitinides.

For patients taking multiple hypoglycemic agents the PDC for each drug is calculated then averaged to arrive at a mean group PDC. Mean group PDC will be used as a patient inclusion criteria as well as in the post study analysis for patients taking multiple hypoglycemic agents. Pre-study adherence rates will be determined using a 9-month estimate of PDC for the hypoglycemic drugs in a patient's medication schedule.

*Measuring Persistence*

Medication persistence relates to the length of time a patient remains on a medication without discontinuation. Patients are deemed to have discontinued therapy when more than 30 days have elapsed without a prescription refill. The persistence length will be calculated from the study start date to the expected end date of the last prescription prior to the patient discontinuing therapy.

*Post Study Analysis*

The primary outcome of interest in the present study is improvement in adherence; however, our group also plans to analyze the following secondary variables if the sample size allows:

- Medication Persistence
- Blood glucose (A1C)
- Blood pressure control
- Body mass index,
- ER visits
- Absolute costs,
- Overall healthcare utilization,
- Patient satisfaction with service,
- Time to first research coordinator outreach
- Number of research coordinator outreach events
- Text message and phone call trends

We also plan to perform regressions that explore how the following factors influence study outcomes:

- Age and Gender
- Insurance Line of Business (e.g. HMO, PPO, POS, MA HMO, MA PPO, etc)
- Pre-study medication adherence
- Pharmacy preference
- Type and number of comorbidities
- Patient drop-out from the study

Risks

Patients in the treatment group face potential confusion over use of new of device and mode of receiving their medication. This risk will be mitigated through patient education. Each patient will be trained on how to use the device as well as sent home with a detailed document highlighting how to use their smart pillbox and how to navigate the TowerView Health platform. Patients will also be given a number they can call at anytime to receive detailed assistance if challenges arise.

The transition to a single, new pharmacy also poses a risk as many patients have grown comfortable with their existing pharmacy or may fill at multiple facilities, introducing a risk of omitting medications from the tray. This risk will be mitigated by conducting medication reconciliation at study onset. Patients will be asked to bring all their medications to the consenting visit in order to cross-reference them with the complete medication list in the EPIC system, the electronic health record currently being used by the University of Pennsylvania Health System. Patients will also be asked for a complete list of the pharmacies they frequent in order to ensure that all medications are transitioned to Friendship Pharmacy appropriately.

Another potential risk is device failure; in such instances patients may not be notified to take their medication as expected. Our group has anticipated the possibility for device failure and will therefore test each pillbox prior to its deployment during the study. Furthermore, the pillbox has been programmed to alert the server if it is experiencing mechanical difficulties. This will allow a member of our team to promptly reach out to patients in order to service or replace any malfunctioning units.

Finally, while patients on oral diabetic drugs experience much lower rates of hypoglycemia than patients taking insulin there is a chance that improved adherence will lead some patients to experience periods of low blood sugar. Patients will be educated on the signs of hypoglycemia and how to quickly raise their blood sugar (e.g. drink fruit juice, eat hard candy). Patients will also be instructed to take their blood sugar as directed by their physician and report hypoglycemia to the research coordinator using the number provided at study onset[1]. In such instances, the research coordinator will work with physicians to determine whether dosing changes need to be made to the patient's medication.

Benefits

Society at large may gain additional information about whether a multi-modal, technology-centered intervention can improve medication adherence in nonadherent patients with Type II DM and additional comorbidities. Such knowledge may improve the management of chronic diseases, reducing the need for

[1] Under Pennsylvania law, patients who have diabetes are eligible to receive a blood glucose monitor and strips free of charge under their insurance benefit. Patients who have not yet utilized this IBC benefit will be assisted by the research coordinator to do so as part of the study.

costly interventions involving case or disease management programs. There is also a chance there is no benefit associated with the study intervention.

Subject Confidentiality

All aspects of this study are conducted in HIPAA compliant environment. The TowerView Health software is hosted on a dedicated, HIPPA compliant server using Amazon Web Services (AWS). Use of encrypted computer files, de-identified documents, and storage of all patient questionnaires in locked offices/cabinets will reduce the risk of loss of confidentiality. No verbal or written information concerning study participants will be released without their express written consent, unless required under federal law. All data analyses will be performed using participants' identification numbers rather than names so as to minimize the number of study team members who know the identity of the research participants.

Compensation

Participants can receive up to $100 for participating in this study. Checks will be distributed in two stages $20 at the 3 month study mark, and $80 at the 6 month study mark. If participants withdraw from the study before the next milestone they will be able to keep the monies for their existing enrollment but will not be able to receive compensation for upcoming milestones.

In addition to compensation for participating in the study there are also out of pocket costs for medications. These costs may change for certain patients given that they are being transferred to Friendship Pharmacy from their existing pharmacy. Wherever possible we will work closely with IBC/Catamaran to ensure cost parity between patient's previous pharmacy choice and Friendship Pharmacy. In instances where this is not possible TowerView Health will make up the difference by compensating patients for their increased cost sharing. We acknowledge that for some medications the difference in cost between Friendship and existing pharmacy may be too high for our group to make up the difference. In these cases we will have to disenroll patients from the study unless they agree to accept the higher out of pocket costs associated with the study.

Risk/Benefit Assessment

The proposed study will provide patients in the treatment group with a comprehensive medication adherence system that may offset the inconveniences of participation (e.g. changing pharmacies). Anticipated benefits to society include new knowledge pertinent to improving patient medication adherence. Such knowledge is broadly applicable across a number of disease states that require oral medication. Overall, the risks are minimal and the possibility of improving medication adherence and associated improvement in BP control/glucose control make the risks reasonable for the anticipated benefits.

Informed Consent

The consent process will consist of both an oral briefing conducted by a trained research coordinator as well as giving patients ample time to read the written consent form and ask questions or have family/friends ask questions about their participation. We will not enroll any participants for whom we are unsure of their comprehension of the study and/or its risks, despite their stated desire to enroll. We will also minimize the risk of coercion by making it clear in the consent process hat participation in the

study is truly voluntary and separate from their medical care and that their non-participation will not affect how they are clinically treated in any way.

If an individual expresses interest in participating, a trained research coordinator will administer informed consent. The information communicated will include the goals of the study, the fact that the group assignment is random, that their participation is purely voluntary and not part of their medical care, that they lose none of their rights regarding medical care, that they can withdraw at any time, and that they will be kept informed if there are changes in care or standard-of –care that would affect their willingness to participate, and the fact that they will be compensated for their participation. Consent will be documented by having the participant and research coordinator sign and date the consent form.

Waiver of Informed Consent

We are not requesting a waiver of informed consent.