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# Mobile diabetes intervention study: Testing a personalized treatment/behavioral communication intervention for blood glucose control

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ABSTRACT

Background: National data find glycemic control is within target (A1c<7.0%) for 37% of patients with diabetes, and only 7% meet recommended glycemic, lipid, and blood pressure goals.
Objectives: To compare active interventions and usual care for glucose control in a randomized clinical trial (RCT) among persons with diabetes cared for by primary care physicians (PCPs) over the course of 1 year.
Methods: Physician practices ($n=36$) in 4 geographic areas are randomly assigned to 1 of 4 study groups. The intervention is a diabetes communication system, using mobile phones and patient/physician portals to allow patient-specific treatment and communication. All physicians receive American Diabetes Association (ADA) Guidelines for diabetes care. Patients with poor diabetes control (A1c≥7.5%) at baseline ($n=260$) are enrolled in study groups based on PCP randomization. All study patients receive blood glucose (BG) meters and a year's supply of testing materials. Patients in three treatment groups select one of two mobile phone models, receive one-year unlimited mobile phone data and service plan, register on the web-based individual patient portal and receive study treatment phone software based on study assignment. Control group patients receive usual care from their PCP. The primary outcome is mean change in A1c over a 12-month intervention period.
Conclusion: Traditional methods of disease management have not achieved adequate control for BG and other conditions important to persons with diabetes. Tools to improve communication between patients and PCPs may improve patient outcomes and be satisfactory to patients and physicians. This RCT is ongoing.


## 1. Introduction

Despite an annual incidence of 1.5 million persons with diabetes in the U.S. (adding to the already diagnosed 24 million) and the availability of evidence-based practice guidelines, only 37% of persons with diabetes meet the A1c target of <7.0%, and only 7% meet combined glycemic, lipid, and blood pressure goals [1–4]. With the inability to achieve control of blood glucose levels, diabetes symptoms and diabetes-related comorbidities through routine provider visits and patient self-management, interventions that use mobile technology have the potential to improve outcomes of diabetes care. We describe a randomized clinical trial (RCT) to evaluate mobile telephones and patient/physician portals providing individualized patient clinical data and feedback to patients and their primary care providers (PCPs) [5].

Increasing concern over the inadequate control of blood glucose levels has led to many behavioral change and monitoring interventions to assist patients and PCPs including regular prompted patient recall, directed patient education and facilitated adherence to treatment [6–8].

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The majority of diabetes care is provided by PCPs in community practices [9–11]. However, primary care providers continue to report lack of time to provide the continuous patient care necessary to manage chronic diseases like diabetes. The average duration of a PCP visit is 17 min [12,13]. The acute complications of diabetes and related chronic symptoms force PCPs to address fewer than two symptomatic problems per office visit rather than the more time-consuming management of diabetes. Studies also document that only 20% of PCPs perceive they have resources necessary to manage patients with diabetes effectively. Diabetes-specific assessments (reviewing blood glucose trends and history of hypoglycemia, providing foot examinations, blood pressure values, assessing nutrition status, adherence to and appropriate timing of diabetes medications) are not always performed during PCP visits [14–16]. Finally, much information about the patient's daily or weekly diabetes self-management strategies or skill set is often not available during a PCP visit, is not usefully organized for PCP action, or may not provide a complete picture of the problems and decisions patients face on an ongoing basis between office visits.

Interventions that use remote patient monitoring, home telehealth, computerized clinical decision support systems, and other new technology are widely available but have had limited feasibility, acceptability, efficacy, or effectiveness evaluations [17–20]. Three major reported problems of remote monitoring studies are: 1) they have limited or unknown applicability in real-world community provider practices [21]; 2) study interventions are not compared to simpler interventions such as regular nurse calls or automated disease management reminders [22,23]; and, 3) technology intervention studies often apply a commercial one-size-fits-all approach and are not patient individualized [20].

Given the public health significance of poor diabetes management and problems with previous remote monitoring studies, we aim to test three interventions of increasing intensity within community provider practices. These interventions are individualized to the patient. Comparing the three interventions to usual care will help to identify the most important intervention component(s).

## 2. Trial design and methods

### 2.1. Overview

The Mobile Diabetes Intervention Study trial is evaluating a diabetes coaching system, using mobile phones and patient/physician portals to allow patient-specific treatment and

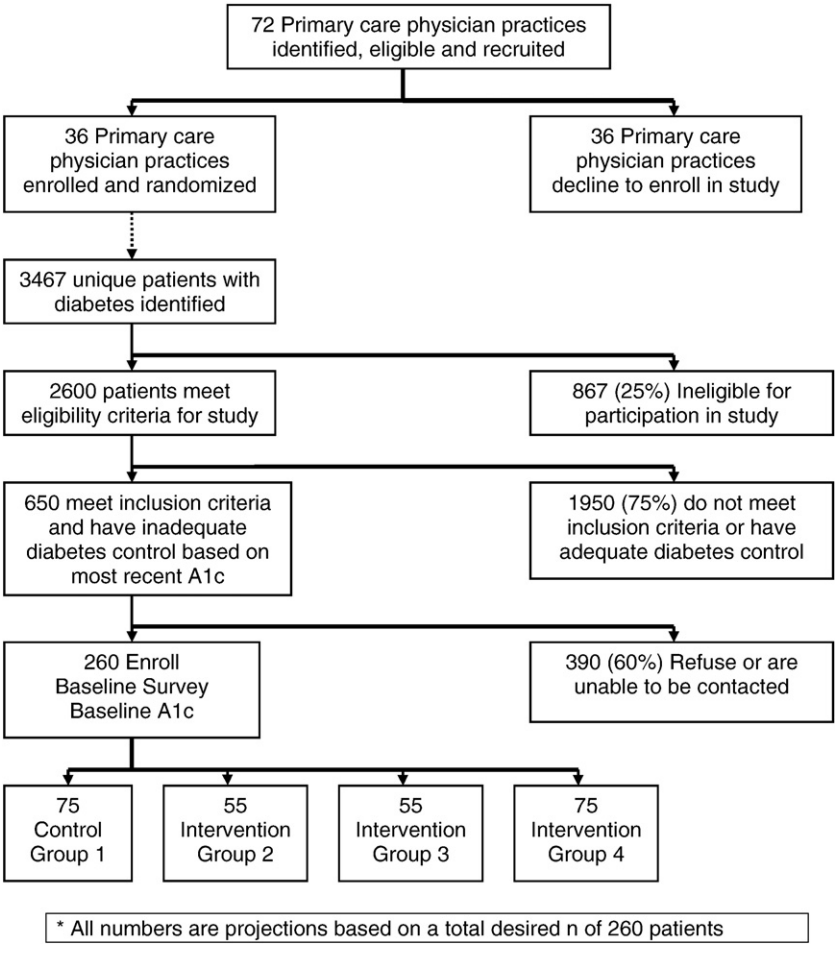


**Fig. 1.** Study design.

communication. We hypothesize that timely information provided to patients and their physicians can result in reduction of A1c over 1 year. This randomized clinical trial (RCT) is ongoing.

### 2.2. Study setting

General practice physicians (internal medicine, family medicine) are recruited from four areas in Maryland, including urban, suburban and rural practices. Physicians in academic settings are not included because these physicians regularly participate in other clinical studies, and their practices do not reflect usual care in the community. Our goal is to evaluate the intervention in the most common primary care setting where the majority of diabetes care is provided. The University of Maryland Baltimore (UMB) Institutional Review Board (IRB) approved the study, and a Data Safety and Monitoring Board (DSMB) was appointed to review study procedures and adverse advents.

### 2.3. Inclusion and exclusion criteria

Patients must meet all of the following criteria to be recruited for the study:

- Type 2 diabetes diagnosed by a physician at least six months prior to study enrollment
- A1c $\geq$ 7.5%, within most recent 3 months
- 18–64 years of age

Patients are excluded if they meet any of the following criteria:

- Medicare or Medicaid beneficiaries
- Uninsured
- Using an insulin pump
- Pregnant
- Active substance abuse, alcohol or drugs (must be sober for 1 year)
- Psychosis or schizophrenia under active care
- Uncorrected severe hearing or visual impairment
- Lack access to internet or email address

### 2.4. Recruitment

#### 2.4.1. Physician recruitment

To identify physicians, study leadership reviewed physician practice lists provided by a statewide health insurer which maintains publicly available physician practice information including practice location, number of insured patients, physician practice identification number, and physician contact information. Potentially eligible physicians and their practice information were verified using other publicly reported data. Physicians are contacted by office visits, letter, phone and/or email inquiring about their interest in the study and offered a 15–30 min presentation describing the study. Physicians practicing in academic settings or listed as specialists other than primary care, family care, or internal medicine were removed from the eligible physician list. After recruitment from the original list of approximately 300 physicians was completed, the study team identified a smaller number of large multi-site practices and other physicians known in the geographic areas but not on the insurer's list of physicians. This resulted in 72 PCP practices determined to be eligible and willing to participate (Fig. 1).

Nurse practitioners and physician assistants are contacted if they are the main health care providers managing diabetes patients in an office practice. Enrolled physicians receive a standard reimbursement to cover office expenses for each patient enrolled in the study ($250 per enrolled patient). Physicians can choose to distribute a portion of the payment to their office managers for effort assisting study staff in obtaining patient charts to abstract and patient contact information. Physicians agreeing to participate provide HIPAA waiver access to patient records to screen for the eligible patient population.

#### 2.4.2. Patient recruitment

Potentially eligible patients are identified through physicians' practices and chart review. Once identified, patients are sent a letter from their physicians explaining the study and that they may be eligible to participate. Response post cards for return to the study investigator team are included in the letters for patients to indicate willingness to be called by study staff. Following a first mailing, patients are contacted by study staff by phone.

At the first screening contact, participants give verbal informed consent by phone to be interviewed, and study staff confirm eligibility. If patients are determined eligible, patients are mailed informed consent documents for signature. Individual patient informed consent is obtained by University of Maryland School of Medicine study staff independent of physician office involvement. Informed consent is confirmed for intervention subjects face-to-face at the beginning of the training session. Control subject consenting information is verified by study staff during all follow-up phone interviews occurring every 3 months for the one-year study period.

Based on experience in patient recruitment for a pilot study [5], we estimated that physician practices would provide an average of 93 patients with Type 2 diabetes, which would result in 3467 patients available for the study. Of these 3467 patients, we estimated 25% (867) would not be eligible to participate in the study for reasons including mistakenly coded diagnoses and age. Further, we estimated that of the remaining 2600 patients, 25% would meet the inclusion criteria and have inadequate diabetes control (650) and 40% of these patients would enroll in the study. These estimates are shown in Fig. 1.

### 2.5. Random assignment

We randomized at the physician practice level in order to prevent potential contamination of the study intervention, i.e., all participating physicians at a practice site were randomized to the same study group. When a physician practice is contacted, agreement of individual physicians within the practice is sought, and they are added to the study physician group. Physicians are not told of their practice intervention (Groups 1–4) assignment until they agree to participate. If a participating physician leaves the practice, he/she is dropped from the study. For newly enrolled (<3 months) study patients of departing physicians, we have established a process for recruiting the patients' new physicians. If physician departure occurs at 3 months or later

and new physicians are not recruited, patients are offered continuation in the study by an enrolled physician in the same physician practice group (if available). Treatment study patients who object are offered the option of continuing as a Group Two enrolled patient (no physician–patient interaction required). Patient assignment follows the physicians' randomized assignment. Patients under the care of non-participating physicians are not enrolled in the study. Thus, this clinical trial is cluster-randomized for individuals.

The Study Coordinator provided a list of physician practices, by location in the four geographic areas ordered within zip code, to the study biostatistician. The first list ordered physicians by patient practice size (numbers of patients) based on information obtained from a statewide private health insurer. An initial set of six groups of practices was created by size (large $\geq 20$, small $<20$) and location (Baltimore City, Baltimore County, Anne Arundel County). Only practices with $\geq 10$ patients were randomized in this initial contact. We randomly assigned physician practices to treatment within practice categories to obtain the desired distribution of patients according to treatment study groups ($n=75$ for Groups One and Four, each, and $n=55$ for Groups Two and Three, each, to achieve a total study size of $n=260$ based on power and study logistic considerations). After recruitment from the original list of approximately 300 practices was completed, but the goals for eligible patients had not been met, a small number of additional practices and an additional county, were added with simple, random treatment assignment. The study biostatistician conducted the randomization by a pseudo-random number generator in the software package R (version 2.7.0) [24].

### 2.6. Interventions

The interventions are a diabetes coaching system, using mobile phones and patient/physician portals to allow patient-specific treatment and communication (Fig. 2). All physicians receive the most recent American Diabetes Association (ADA) Guidelines for diabetes care and are notified when their patients enroll in the study [25]. Physicians assigned to the control group (Group One) are told to care for patients as usual, including checking patient self-management blood glucose (SMBG) log books and downloading blood glucose meter readings, if made available by the patient. Active treatment physicians (Groups Two, Three, and Four) are informed that their patients receive the mobile phone and web-based Diabetes Manager™ system. The physicians receive different quantities of analyzed data

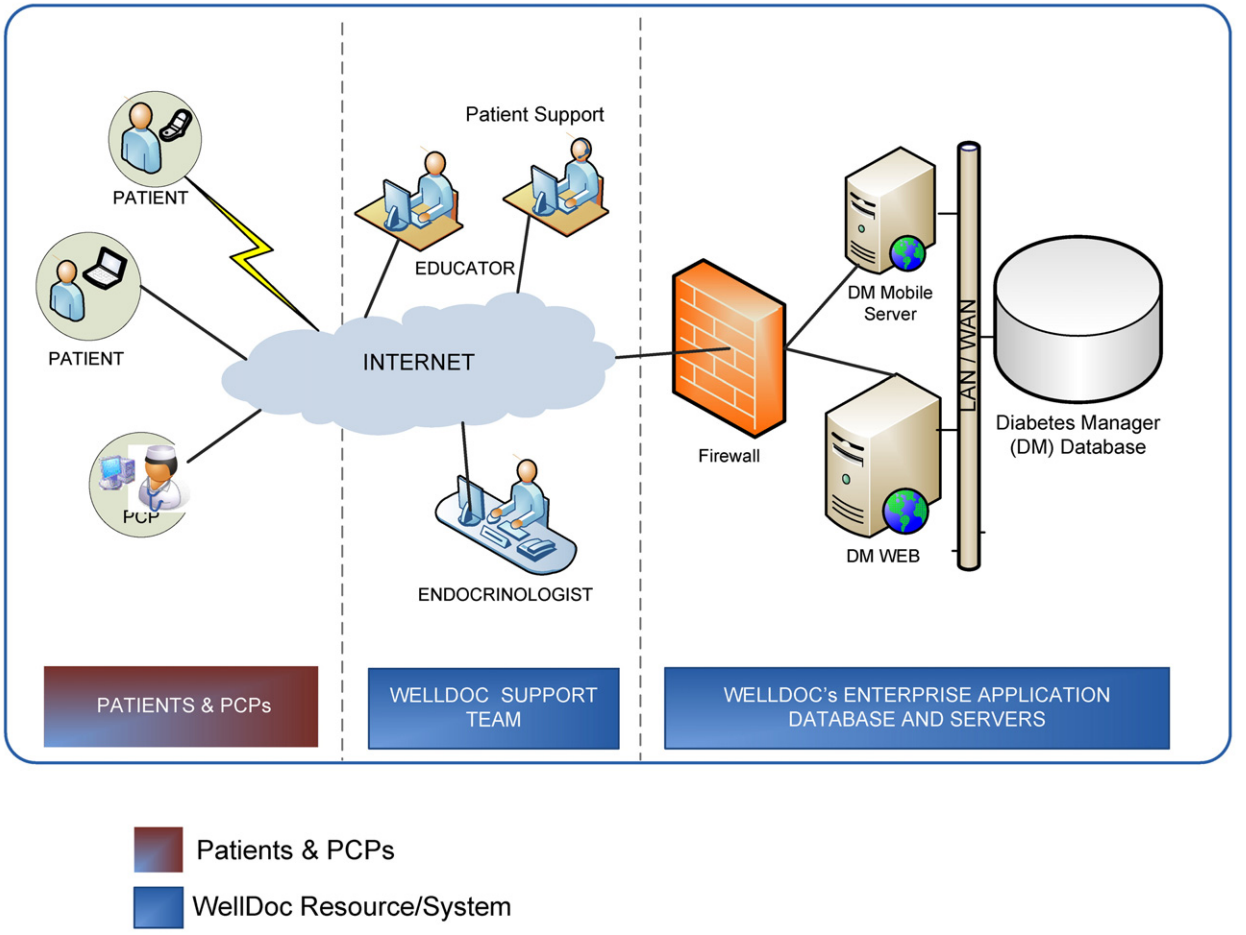


**Fig. 2.** Schematic to show patient mobile phone connection, patient/physician web portals, and servers.

and clinical support depending upon which treatment group they are assigned. Physicians assigned to study treatment Group Two do not have web access to the patient data. It is the responsibility of the patient to forward data to the physician. Group Two data are captured and organized in an electronic logbook. The logbook data are not analyzed. Study treatment providers in Groups Three and Four receive training and access to the HIPPA compliant, password-protected physician portal from their office PCs. The web portal for physicians in Group Three hosts their patient's raw BG in a logbook form and laboratory data. These PCPs do not receive reminders or prompts to review the data. Other patient-entered data (laboratory data, screening exams, etc.) are also available for viewing but, again, are unanalyzed.

Physicians in Group Four differ from Group Three PCPs in that every 3 months (or sooner if critical issues are identified) they receive via fax and/or email an analyzed report of all patient-entered data (BG and laboratory values, screening exams). The report is a summary of the patient's glycemic and metabolic (lipids, blood pressure, weight) control, and adherence to medication, self-management skills, and compliance with other key measures of care (eye examinations, immunizations, aspirin use, screening for microvascular complications). Based on the data summaries, the PCPs are also presented with treatment recommendations. These patient reports are generated by automated, proprietary analytical models and may also have additional endocrinologist and/or diabetes educator directed treatment recommendations individualized to the study patient's clinical status and diabetes self-management behaviors. The Group Four PCPs may also access the reports at any time on their PC web portal. Groups Two, Three and Four are ordered so that the Group Two intervention is the simplest and the Group Four intervention is the most complex.

Providers in Groups Three and Four receive training on access and use of the HIPAA compliant, password-protected physician portal.

All study patients receive a One Touch Ultra 2™ glucose (BG) meter and a year's supply of testing materials. Based on their physicians' random assignment, patients are enrolled to the study groups summarized below (Table 1).

*2.6.1. Group 1: control — usual care*

Patients receive a One Touch Ultra 2™ (LifeScan, Milpitas, CA) glucose meter and supplies for a year. Patients are told to use the glucose meter as recommended by their physicians. Patients in Group One provide SMBG information based on their individual physicians' instructions, including the physician practice option to download SMBG from the study patient glucose meter. Group One PCPs provide care as usual.

*2.6.2. Groups 2–4: intervention groups*

Patients in the three active treatment groups select one of two mobile phone models, receive a one-year unlimited mobile phone data and phone service plan, receive the study treatment phone software, and have access to the web-based individual patient portal. All patients in the intervention groups are given system-driven guidance on when to test their BG based on their disease status, medication regimen, and time of poorest control (for example, preprandial versus postprandial) so that the most useful, patient-specific multi-point BG profile can be created and used for data analysis and future self-management coaching for the patient. For quality assurance, diabetes educators and endocrinologists periodically review patients' electronic logbook data and the summary analysis reports, generated for patients and physicians.

After random treatment assignment, patients in the intervention groups are risk stratified by the coaching system based on comorbidities, complexity of medication regimen and diabetes status. This risk-stratification is used to direct the level of diabetes educator interaction with patients. Those patients who are determined highest risk level are contacted by a diabetes educator via the web-based messaging center, at most, four times a month. Other patients receive communication updates every 2–3 months. These communications are directed by patterns in patient data and focus on such topics as self-management skills, blood glucose control, and medication adherence. The majority of the patient communication is delivered by automated feedback on the mobile phone and messaging through the message center in the patient web portal. If the content material has not been created at the time a particular patient problem has been identified that needs to be addressed, a diabetes educator writes a message to the patient. This material is then catalogued by the coaching system and added for future automation. Outbound patient phone calls by the educators are discouraged and limited to those patients who display high-risk glycemic patterns (i.e., repeat severe hypoglycemia) or who request to be contacted by phone for self-management issues.

**Table 1**
Overview of study intervention design

| | Group one | Group two | Group three | Group four |
|---|---|---|---|---|
| Intervention arm (sample size) | Usual care ($n=75$ patients) | Tailored patient intervention ($n=55$ patients) | Tailored patient–physician intervention ($n=55$ patients) | Combined with patient data analyzed intervention ($n=75$ patients) |
| Intervention components | a. Provider-driven care, based in office, no special diabetes management<br><br>b. Patient SMBG | a. Home diabetes monitoring by patient using mobile phone to communicate information and receive feedback | a. Home diabetes monitoring by patient using mobile phone to communicate information and receive feedback<br>b. Physician can access unanalyzed information from the patient's electronic logbook | a. Home diabetes monitoring by patient using mobile phone to communicate information and receive feedback<br>b. Physician can access raw and analyzed patient data<br><br>c. Physician receives report summary and treatment recommendations |

*2.6.2.1. Group 2: intervention — patient only data.* Patients receive the coaching software system on the mobile phone. Patients enter BG data, carbohydrates consumed, diabetes medications taken, and miscellaneous comments regarding diabetes self-care. "Just-in-time" (real-time) messaging is sent to the patient's mobile phone providing feedback on the entered data. The feedback is driven by the values of the patient's data, the trend of any recently entered data and the physician's medication instructions for each patient. Entered data are captured in real-time in the web-based logbook. Patients may provide their PCPs with printed copies of their electronic logbooks and other information because Group Two physicians do not have access to the individual patient portal system. Patient action plans summarizing the patient-entered data and identifying possible self-management actions for improving their diabetes control are electronically sent to the patients every 2.5 months. Each patient is instructed that action plans also serve as a pre-visit summary for the patient's next office visit to their PCP.

*2.6.2.2. Group 3: intervention — patients and PCPs with access to the data.* Patients receive the coaching software system on the mobile phone, input patient data, and receive feedback and action plans as described for Group 2 (above). Their PCPs are provided access to a web portal where they may choose to review their patients' electronic logbooks — this is "raw" patient data that have not been analyzed.

*2.6.2.3. Group 4: intervention — patients and PCPs with access to patient's data which are analyzed based on treatment algorithms.* Patients receive the coaching software system on the phone and PCPs are provided access to a secure web portal where they can choose to see their patients' electronic logbooks. In addition, physicians are provided with data analysis reports as described in Section 2.6.2 (above). The study physician is reminded that all data analysis is based on patient-entered, unvalidated data. The physician has the option to use this information and remains responsible for all treatment decisions.

### *2.7. Adverse event reporting*

Adverse event monitoring data are collected by the following methods: (1) reports of participants or study personnel; (2) biweekly reviews of study data, checking for hospitalizations or death of study patients; and (3) questionnaires mailed every 6 months during the one-year intervention with the question, "Have you experienced any new and serious health problems since you enrolled in the Mobile Diabetes Intervention Study. If yes, please describe." Categories of possible serious adverse events (SAEs) and adverse events (AEs) are provided in the text of the questionnaire. For example, although severe hypoglycemia is infrequent and most people can manage their hypoglycemia such that there is minimal risk of incapacitation [26] hypoglycemia may be considered an AE. Hypoglycemia is defined in the mobile diabetes communication system as measured plasma glucose concentration $\leq$70 mg/dL and data are captured based on patient self-report. For severe hypoglycemia, the patient may not be able to treat without assistance and the mobile phone prompts the patient to call 911. Adverse events are categorized as serious (SAE) if they are life-threatening or fatal, require or prolong a hospitalization or result in a major disability. The SAEs and AEs are grouped as expected or unexpected. As the study intervention is a communication system and provides information similar to information requested in a regular physician office visit, serious adverse events as a result of the intervention are not expected. Adverse events are reported promptly to the principal investigator, UMB IRB and the DSMB.

## 3. Data collection and outcome measures

### *3.1. Study measures and data*

When they agree to participate, physicians are interviewed for demographic information and at the completion of the study intervention will be asked about their satisfaction with the communication intervention system. Study patient baseline and clinical measures (Time One [T1]) are recorded from medical charts, eligibility screening and telephone interviews; survey inquiries (Patient Health Questionnaire, symptoms, Diabetes Distress Scale, patient perception of provider's management of their diabetes) are made at baseline and at 12 months [T5]) or every 3 months (T2, T3, T4, T5) (diabetes stages of change, health care utilization) through the one-year study intervention.

#### *3.1.1. Physician and patient information*

Physician and patient characteristics are collected from self-reported interviews with trained study staff and medical chart reviews. Physician information collected at baseline includes physician demographics, years in practice, and practice descriptors. Patient information includes demographics, health history, diabetes health status, current medications, risk factors for complications of poorly controlled diabetes, and self-management and lifestyle activities (exercise, eating behavior, glucose monitoring).

#### *3.1.2. Diabetes behavior change/self efficacy*

The Diabetes Stages of Change (DStoC) is an 18-item stage of change interview measure created for this study and is based on the Transtheoretical Model (TTM) of Change, which has been used in developing interventions to promote health behavior change [27]. The interview questions focus on the decision making of the individual in five key areas: self-management blood glucose (SMBG), managing carbohydrates, portion control, medication adherence, and smoking. Study subjects are asked about self-management behavior either less than 6 months (action phase scored as "0") or more than 6 months (maintenance phase scored as "1"). If subjects score "0", then they are asked about their readiness to change a particular behavior and confidence in change based on a scale of one to ten, with "one" being " not at all ready" or "not at all confident" and "ten" being "extremely ready" or "extremely confident". For the "quit smoking" question, the traditional TTM algorithm is applied: Precontemplation (not considering in the next 6 months) contemplation (considering in the next 6 months) preparation (planning in the next 30 days and a recent quit attempt), action (quit less than 6 months), and maintenance (quit more than 6 months).

*3.1.3. Depression*

The Patient Health Questionnaire (PHQ) is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders [28]. For purposes of this study it is administered as part of the baseline and follow-up interviews. The PHQ-9 is the depression module, which scores each of the 9 DSM-IV criteria as "0" (not at all) to "3" (nearly every day). Total scores (severity score) range from 0 to 27. PHQ-9 scores of 1–4, 5–9, 10–14, 15–19, and ≥20 represent minimal symptoms, mild, moderate (minor), moderately severe (major), and severe depression, respectively [29].

*3.1.4. Diabetes symptoms*

The nine-item version of the Self-Completion Patient Outcome Instrument (Symptom measure) [30,31] assesses the following diabetes symptoms: cold hands and feet, numb hands and feet, polyuria, excessive hunger, abnormal thirst, shakiness, blurred vision, feeling faint, and feeling sleepy. Patients are asked, "In the past month, on how many days have you…." Ranked on a five point Likert scale from "never" (1) to "every day" (5) and summed, positive symptoms are defined as those experienced at least "several days" in the recent month (scored as ≥3 on individual items) [31]. The diabetes symptom instrument has been shown to have satisfactory internal consistency, test–retest reliability and has detected significant symptom improvements within 6 weeks in previous intervention studies. [30,32].

*3.1.5. Diabetes distress*

The Diabetes Distress Scale (DDS17) is a 17-item measure that uses a Likert scale with each item scored from 1 (a little distress) to 6 (serious distress) related to distress experienced during the previous month by persons with diabetes [33]. Based on five separate previous study samples, "the scale yielded 4 reliable subscales which target different types of distress related to diabetes: emotional burden (feeling overwhelmed), physician-related (concerns about access, trust, care), regimen-related distress (diet, physical activity, medications), and interpersonal distress (not receiving understanding and support from others)" [34]. Internal consistency was documented by coefficient $\alpha$ of 0.93 for the total scale, and 0.88 to 0.90 for the four subscales. A mean item score of ≥3 (moderate distress) is used to distinguish high from low distress for each item and for the mean of the 17 items [33,34].

*3.1.6. Patient perception of provider's management of their diabetes*

An investigator-created measure of patient perception of their provider's management of their diabetes (PPPM measure) asks 3 questions about advice given to patients about diet, exercise and testing daily blood sugar levels. Patient responses are yes/no.

*3.1.7. Health care utilization and claims data*

Study patients are interviewed by phone every 3 months and asked health services questions, "How many times in the last 3 months have you been hospitalized?….visited an emergency room?....visited a physician as an outpatient as a result of your diabetes? (this includes any physician, dermatologist, gynecologist, primary care, specialist)." Medication data (diabetes drug class, dose, medication changes) will be collected at baseline on medical chart reviews and from the intervention communication system.

Claims data will be provided by a third party insurer (CareFirst BCBS of Maryland) for those patients covered by the single insurer. Patient-specific encounter and cost data, including inpatient hospitalizations, emergency room visits, physician office visits, laboratory procedures, home health care, hospice, nursing home and medications are collected, for 1 year prior to the intervention and 1 year following study enrollment. Data will be aggregated on a calendar year, per person per month, basis for most outcomes.

*3.1.8. Patient intervention satisfaction*

An investigator-created survey evaluates patient satisfaction with ability to use the mobile phone communication system and patient portal. Patients respond yes/no to 23 questions about how they use the phone and patient portal.

*3.1.9. Physician intervention acceptability*

This measure is a telephone interview survey based on the Centers for Medicare and Medicaid (CMS) IDEATel Demonstration Project findings [35]. The physician evaluation of the intervention will be administered at the end of the study intervention phase. It includes questions related to four concepts: acceptability of interactions and physician time using the communication technology software; impact on patients; impact on the physician's practice; and, communications issues, such as quality of feedback, method of communication, format of information.

*3.2. Primary outcome*

The primary outcome of the study is mean change in A1c comparing Group One and Group Four on baseline (T1) A1c versus A1c at 12 months (T5). For baseline A1c, medical chart reviews record most recent A1c. For patients without an A1c within the recent 4 months, a free A1c is offered to determine eligibility. A1c is measured using the same A1c test device by trained staff who are blind to patient group assignment. All tests are done using Clinical Laboratory Improvement Amendments (CLIA) quality control practices.

*3.3. Secondary outcomes*

*3.3.1. Changes in the A1c measures, patient clinical measures, diabetes symptoms, diabetes distress*

Secondary outcomes include change in A1c comparing all four groups on A1c at 3, 6, 9, and 12 months. Other secondary outcomes are changes in measures related to three diabetes complications (blood pressure, BMI, and lipid levels) from baseline (T1) to 12 months (T5), changes in diabetes symptoms (Symptom measure), and diabetes distress (Diabetes Distress Scale).

These outcomes are measured for the four study groups and are compared between control and active study treatment groups.

*3.3.2. Patient utilization of health care services, including hospitalizations, emergency room use, and physician office visits*

Patient utilization of health care services, (number of hospitalizations, number of emergency room visits, and number

of physician office visits) in the year post-randomization will be compared between those patients with PCPs randomly assigned to the interventions and those with PCPs randomly assigned to usual care.

*3.3.3. Costs of care, total and service specific [hospital, emergency room, physician]*

Secondary outcome analyses of cost of care will compare the change in costs of care (total and service specific [hospital, emergency room, physician]) for the year prior to study enrollment to costs incurred during the intervention across the study groups. Claims data for study patients who are members of CareFirst Blue Cross Blue Shield (BCBS) of Maryland will be analyzed.

*3.3.4. Changes in clinical measures related to diabetes complications*

Medical chart data on blood pressure, cholesterol, and weight collected at baseline and at the end of 12 months will be compared.

*3.3.5. Eye and foot exam completion*

The proportion of patients completing annual foot (defined as microfilament testing) and eye examinations in the year post-randomization among intervention and control study groups will be compared.

*3.3.6. Medication changes*

Comparison of medication changes made by PCPs across study groups, where change is defined as yes/no on any changes, defined as medication events, actions, and diabetic drug classes. Based on work in a previous pilot study this would include medication change action, including increasing the same medication (dosage), adding insulin, adding oral medication, adding second drug to existing oral agent, adding a combination oral drug (both new medications), or any medication action. Medication changes will be assessed at the 3, 6, 9, and 12 month intervals in comparison to baseline.

*3.3.7. Prevalence of depression or depressive symptoms*

We will determine the prevalence of depression among study participants (as measured by the PHQ-9) and compare change in depressive symptoms between baseline and at 12 months for study groups. Depression on the PHQ-9 will be categorized at a score of $\leq 4$ (minimal symptoms), 5–9 (mild), 10–14 (moderate 15–19 (moderately severe [major], and $\geq 20$ (severe depression) (29).

*3.3.8. Trajectories of self efficacy*

Trajectories of self efficacy will be measured using the Diabetes Stages of Change and compared over time among the study groups. Self efficacy data are collected at baseline, 3, 6, 9, and 12 months.

*3.3.9. Patient perception of provider's management of their diabetes*

We will compare patient perception of the PCPs management of their diabetes from baseline (T1) to 12 months (T5) for all study groups and compare control to intervention groups.

*3.3.10. Patient and physician satisfaction with the intervention*

We will compare the satisfaction with the intervention among the three active intervention groups. Data about satisfaction will be collected at 12 months only.

### 3.4. Statistical methods

*3.4.1. Statistical analysis plan*

Patient data will be analyzed according to original treatment group assignment. All tests are two-sided with a type I error of 5%. As described in Section 2.6, the interventions are tiered. Our primary goal is to examine whether the most information-intensive multi-component intervention (Group 4) is better than usual care (Group 1). However, because the Group 4 intervention has multiple sources of information, it may include components that provide no incremental benefit to diabetes management beyond the implementation of a subset of components. Thus, the secondary analysis including all three interventions will provide evidence about whether the specific components in Group 4 that are not in Groups 2 and 3, relate to better diabetes management and whether the simpler interventions in Groups 2 and 3 are better than usual care.

*3.4.1.1. Primary study analysis.* The primary study analysis will compare the mean 12-month A1c (operationalized as absolute A1c % change) among patients with diabetes whose PCPs were assigned to the usual care group (Group One) to the mean 12-month A1c (%) among patients with diabetes whose PCPs were assigned to the Group Four intervention group, taking baseline A1c and correlation within practice into account with a generalized effects mixed model to compare two means. The fixed effects in the model are treatment group indicators, time indicators, and interactions between treatment group and time. There is a random intercept that accounts for within-person correlation (over time) and within-PCP correlation.

*3.4.1.2. Secondary study analyses.* Secondary analyses will test the null hypotheses of no difference between the control group and Group Four with and without adjustment for baseline covariates that may be associated with outcomes, such as demographic variables (age, gender, race), baseline comorbidities (hypertension, hyperlipidemia, microvascular complications, and coronary artery disease), baseline PHQ-9, A1c, number of medications, clinical measures (blood pressure, lipid levels, BMI), diabetes health status (diabetes duration, diabetes self-management) and physician variables (age, gender, race) and PCP-level characteristics (location and practice size). Hypoglycemic events will be reported as the proportion (percentage) of patients affected and the event rates (e.g., episodes per patient-year or 100 patient-years) [36].

The secondary analysis models include the same fixed and random effects as the primary analysis model. In addition, the models will include a subset of covariates that are imbalanced at baseline. To identify the covariates to be included in the model, we will first fit separate models including each covariate, one at a time. The final model will include those covariates such that their inclusion changes the estimates treatment effect by at least 10%. As suggested in the CONSORT statement, decisions about covariates will not be based on *p*-values [37,38]. A large number of covariates will be evaluated. Therefore the final model will be limited such that there are at least 20 patients per covariate category. Thus the covariates that produce the largest change in estimated treatment effect will be included.

In addition, we will perform tertiary analyses testing the null hypotheses that Groups 2 and 3 are equal to Group 1 versus the alternative that at least one of Group 2 or 3 is different from Group 1. We will also test the null hypothesis that Groups 2 and 3 are equal to Group 4 versus the alternative that at least one of Group 2 or 3 is different from Group 4. The first test examines whether the intervention in Groups 2 and 3 is better than usual care, and the latter test examines whether the most information-intensive intervention (Group 4), is better than less-intensive interventions. Differences of each intervention group from the control group will be reported with 95% confidence intervals. The purpose of these analyses is to obtain preliminary estimates regarding the incremental benefits of the intervention components [39]. This model is used to account for correlation of repeated A1c measures and correlation of patients with the same PCP (i.e., patient-level and PCP-level random intercepts). Changes in clinical measures related to three intermediate outcomes (blood pressure, BMI, lipid levels) from baseline to 12 months for the four study groups will be compared using ANCOVA models.

To compare self efficacy (Diabetes Stages of Change) over time among the study groups, mean differences between groups will be analyzed. We will also compare the study groups with respect to patient utilization of health care services, using a Poisson mixed-effects regression model with random intercept to account for within-PCP clustering. Unadjusted *p*-values will be reported for the test of the null hypothesis of equal health care utilization between Group One and Group Four, the test comparing Groups 2 and 3 with Group 1, and the test comparing Groups 2 and 3 with Group 4.

To further assess health services, we will compare the change in costs of care (total and service specific [hospital, emergency room, physician]) for the year prior to study enrollment to costs incurred during the intervention across the study groups. For CareFirst BCBS members, claims data will be analyzed. Cost changes will be expressed in dollars per hospitalization or other services (emergency room and physician use), and differences in changes will be calculated by dividing the difference in cost between each intervention group and the control group (from baseline to 12 months) by the difference in number of hospitalizations and other services (from baseline to 12 months) between each intervention group and the control group. We will use the method of calculating the variance of a ratio for clustered data described in Korn and Graubard [40] to calculate a pair-wise *t*-test (Group One versus Group Four) and two *F* tests for the comparison of Groups 2 and 3 with Group 1 and the comparison of Groups 2 and 3 with Group 4 while accounting for correlation among patients within the same PCP.

We will compare receipt of annual eye exam and annual foot exam between treatment and control study groups using a logistic mixed-effects regression model with random intercept to account for within-PCP correlation.

We will compare medication changes made by PCPs across study groups, where change is defined as yes/no on any medication change action, including increasing the same medication (dosage), adding insulin, adding oral medication, adding second drug to existing oral agent, adding a combination oral drug (both new medications), or any medication action. We will perform an analysis comparing 1) the overall number of changes between groups and 2) the number of increases and/or additions for each of the categories as defined in the previous statement using Poisson mixed-effects regression. If some medication actions occur too rarely during follow-up to produce stable analysis results, we will combine similar actions. Differences in changes in medication will be compared between the study groups using generalized linear mixed-effects models to account for within-PCP clustering of patients and within-patient clustering of observations over time. Longitudinal analyses rather than time-to-event analyses will be performed for medication change status because medication initiation and intensification are not absorbing states and can recur.

To assess patients' mental health we will determine the prevalence of depression among study participants (as measured by the PHQ-9) and compare change in depressive symptoms between baseline and at 12 months for study groups. For categorical depression status, we will use multinomial logistic mixed-effects regression to account for within-PCP clustering of patients and within-patient clustering of observations over time.

We will compare the satisfaction with the intervention among Groups Two, Three, and Four at 12 months using ANOVA.

### *3.4.2. Sample size calculation*

To perform the primary analysis using methods for comparison of two means with allowance for cluster randomization and baseline A1c (mixed-effects models) under the intention-to-treat paradigm, we determined a sample size for the primary analysis of 75 for the usual care group (Group One) and 75 for tailored patient–physician combined with patient data analyzed (Group Four) (Table One), for a total of $n = 150$ patients in the two main study groups. If there is a 10% loss to follow-up, then the effective sample sizes are 67 patients for both groups.

Assuming within practice correlation between 0.10 and 0.75, and within-patient correlation of 0.50, this sample will provide no less than 79% power to detect an effect size of 0.5 standard deviations (SD) between Group Four and Group One in a mixed-effects ANCOVA model with random intercepts and 5% type I error. A recent study by Shea et al. [18] reported an SD in the control group of 1.58 for A1c (%) at baseline and 1.40 A1c (%) at 12 months. Conservatively assuming that the SDs at both baseline and 12 months are 1.58 A1c (%), and that the correlation between the two measures is 0.5, then the SD for the change from baseline is assumed to equal 1.58 A1c (%). Therefore, a moderate effect (0.5 SD) corresponds to differences in changes of A1c of 0.79 % (0.5 times 1.58).

Given that 75 patients in Groups 1 and 4 were needed to have sufficient power to detect differences of 0.5 SD for primary analyses, the sample sizes for Groups 2 and 3 to be used in secondary analyses were limited by remaining available resources. Assuming within practice correlation between 0.10 and 0.75, and within-patient correlation of 0.50, a sample size of 55 patients in each of Groups 2 and 3 will provide no less than 60% power to detect differences of 0.5 SD and no less than 80% power to detect differences of 0.6 SD when comparing Groups 2 and 3 with Group 1 and when comparing Groups 2 and 3 with Group 4.

## 4. Discussion

This four-arm randomized clinical trial compares usual diabetes care to three treatment interventions that use wireless mobile phones and secure individualized patient/physician portals to communicate patient information and treatment options for patients managed by community primary care physicians to improve diabetes management. The primary analysis is to compare the mean 12-month A1c (operationalized as A1c % change) among patients with diabetes whose PCPs were assigned to the usual care group to the mean 12-month A1c % change among patients with diabetes whose PCPs were assigned to the Group Four intervention group.

The importance of glucose control in diabetes has been evaluated in several large clinical trials. Previous studies provide evidence that persons with Type 2 diabetes (diabetes) have an age-adjusted prevalence of coronary heart disease twice as high as those without diabetes, and the high incidence of macrovascular complications, such as strokes and amputations, are a major cause of illness and mortality [41–44]. Microvascular complications, including retinopathy, neuropathy, and kidney disease also account for a huge burden of morbidity and mortality [41,44] among patients with Type 2 diabetes. These studies provide evidence that multiple modifiable risk factors for complications in patients with diabetes (including hyperglycemia, hypertension, and hyperlipidemia) increase the risk of poor outcomes.

During the past 20 years, randomized clinical trials for diabetes and its complications (UKPDS, HOT, DCCT, ACCORD, ADVANCE) focusing intensified interventions on single risk factors, such as blood glucose control, lowering blood pressure and cholesterol, demonstrate benefits in preventing or managing microvascular complications [45–47]. It is important to note that during the initial recruitment for our study, the National Heart, Lung, and Blood Institute (NHLBI) , which sponsors the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Trial decided to stop the intensive blood glucose control intervention in ACCORD due to excess mortality [48]. Researchers from the ACCORD trial enrolled and randomized 10,000 patients with diabetes and vascular disease or multiple cardiovascular risk factors to an intensive treatment program targeting normal blood glucose values and an A1c less than 6% or a standard treatment program with an A1c between 7% and 7.9%. The study evaluated the effects of intensively targeting blood glucose control among adults with established diabetes, high blood glucose levels, and pre-existing heart disease or at least two cardiovascular disease risk factors in addition to diabetes. ACCORD examined the application of multiple medications at the same time, which is a routine occurrence in clinical care, but less often found in trials.

Another recent randomized study of long-term intensified interventions (drugs and modifying lifestyle behavior) showed reduced risk of cardiovascular and microvascular events [49,50]. Prior to the recent ACCORD trial results, these studies and subsequent studies provided the basis for the American Diabetes Association's (ADA) [25] and American Association of Clinical Endocrinologists' (AACE) [51] clinical guidelines recommending that most people with Type 2 diabetes reach and maintain an A1c of less than 7%. The guidelines also state that treatment should be individualized. The ongoing RCT we describe here, evaluates a diabetes coaching software system using mobile phones and a web-based platform to deliver individualized behavior support and treatment recommendations based on evidence-based guidelines.

The intervention described in the current RCT is based on the conceptual framework of behavioral change. There is increasing evidence that good self-care is related to improved diabetes outcomes [52–56]. Disease management programs and guidelines for managing diabetes and other chronic diseases have been evaluated for more than 25 years [57]. Weingarten's review found that provider education, feedback to patients, and reminders were associated with improvements in provider adherence to guidelines and with clinically significant improvements in patient outcomes [58]. Norris found strong evidence for improvements in provider monitoring and screening and effectiveness when delivered in conjunction with additional educational, reminder, or support interventions [59]. Studies by Lorig concluded that an intervention designed to address multiple chronic diseases and comorbidities was effective in changing behavior compared to usual care [60,61].

Relevant research includes studies of telehealth and electronic communication used to provide health information, assessment, treatment, and disease management to persons with chronic conditions, specifically diabetes. Although telehealth has grown rapidly there is a substantial gap between the demand for this health care delivery mode and the scientific evidence supporting its efficacy and cost-effectiveness [62–65]. Mair's review of 32 studies of patient satisfaction with live teleconsultation with providers identified methodological deficiencies (small sample sizes, inconsistent study measures) that limited exploration of the role of communication between providers and patients [66].

Several studies evaluate the effectiveness of electronic communication interventions for diabetes [67–73]. Shea and Starren describe the Centers for Medicare and Medicaid (CMS) demonstration study of Informatics for Diabetes Education and Telemedicine (IDEATel) project which randomized 1500 diabetic Medicare beneficiaries to test the feasibility, acceptability, and effectiveness of a telemedicine intervention [74]. However, in the CMS study, there is no comparison to diabetes usual care received by Medicare beneficiaries [18]. In other diabetes electronic communication intervention studies, only one was randomized but the intervention was short duration [68]; Albisser's study of Health Maintenance Organization members (HMO) [69] did not include a usual care control group, although the study treatment evaluates tiered interventions of education, self-management and computer-assisted self-care; and other studies use automatic telephone or internet messaging for special populations, such as Veterans and managed care patients for short term benefits [70,71]. Consequently, while much is promised by electronic communications and telehealth interventions, the evidence on achieving effectiveness in improved clinical outcomes, patient satisfaction, and cost is inconclusive.

We chose several indicators of diabetes management as secondary outcomes in addition to change in A1c. As a measure of long-term blood glucose control, lowering A1c is a

common outcome for diabetes management research. Although, low A1c does not mean that diabetes is being well-managed, well-managed diabetes will be characterized by A1c at normal or close to normal levels. Equally (or more) important for many patients are indicators relevant to every day life; symptoms of poor control, such as blurred vision or pain, taking control of their chronic disease, and having choices in food or exercise.

We plan to be cautious in generalizing our findings for several reasons. The interventions take place through community physician practices and are implemented through electronic communications. Physicians in the community have different experiences with and access to resources, including access to specialists, clinical practice guidelines, experience or use of electronic communication in practice. We have attempted to address these differences by identifying a broad range of community physicians available to participate in the study and by randomization at the practice level. We recognize as previous studies have documented, "recruitment to a clinical trial, independent of any therapeutic intervention" (p. 2989) may result in improved glucose control for the study control group, especially for those with poor control at the beginning of the study [75]. To a certain extent the study involves physicians who are early adopters of electronic communications, even if varying in sophistication in the use of the technology. The patient population in the study may also be distinctive because private health care insurance coverage and access to the internet (either at work or home) were required. Some age, gender and ethnic groups have a growing but lesser access to the internet [76].

## 5. Conclusion

Diabetes is a significant public health problem resulting in substantial morbidity and mortality. Diabetes affects 24 million persons in the U.S. The medical complications associated with diabetes are costly, but treatment is available. Glucose, lipid, and blood pressure control, in addition to lifestyle behavior change (weight and stress management, smoking cessation, and exercise) can improve outcomes associated with diabetes [46,47,77–81]. Recent studies of persons with diabetes suggest improved patient compliance with guidelines for treating diabetes coupled with improved lifestyle and behavior changes when care is provided through electronic communication and telehealth systems [18,82–84].

Mobile phones are ubiquitous—more than 2.7 billion people globally own mobile phones [5]. In the United States alone, the market has skyrocketed from 34 million users in 1995 to 230 million in 2006. [85]. This widespread distribution of mobile phones, across socioeconomic, gender, and age groups, combined with their unique ability to process and communicate data in real-time, make them an ideal platform to create simple, effective, and real-time diabetes management programs that can be promulgated en masse [5].

Few previous studies of electronic communication interventions for diabetes are randomized, include a control group, and involve more than one treatment group to evaluate multiple components of the intervention. Our evaluation of a mobile diabetes management system in the community where the majority of diabetes care is provided, exemplifies translational research. If successful, diabetes self-management and use of electronic communication between patients and their providers could be used to improve care for many persons with diabetes.

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