Effect of a Smartphone Application on Medication Adherence and Blood Pressure Control: The MedISAFE-BP Randomized Clinical Trial

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Initial protocol

Introduction

Hypertension is a major factor in health issues such as stroke, heart disease, and kidney disease. Worldwide there are 9.4 million deaths each year that can be attributed to hypertension and its effects through cardiovascular disease (1). It has been estimated that annual medical expenditures of $46 billion can be attributed to hypertension in the United States (2). Medications exist for the treatment of hypertension and can prevent the harmful effects of elevated blood pressure and its associated morbidities and mortalities, but medication adherence is a known barrier to effective treatment (3-5).

The rapid adoption of smartphone technologies (6) makes this an attractive avenue to influence health practices, primarily medication adherence and subsequent blood pressure control. Smartphone applications can deliver reminders about medication administration to encourage the proper timing and adherence to prescriptions, provide education about healthy behaviors in life, be a means for loved-ones to check in, create a network of patients to form a support system through social media, and monitor biometric measurements.

Previous studies have examined the impact on hypertension of a smartphone application paired with an on-call medical professional (1) or the effect of tele-monitoring (17, 19, 20) and found improvements in blood pressure. Other smartphone-based interventions have been performed in people with elevated cardiovascular risk, but have focused on text messages that are semi-personalized to the patient (18). The impact of a stand-alone smartphone application on blood pressure has not been tested in a rigorous manner, especially with regards to clinically meaningful outcomes of hypertension control. Medisafe was developed to address non-adherence, and provide alerts to patients when it is time to take their medications. Other features include the ability to allow a “Medfriend” to check in if a medication is not taken, weekly reports of medication adherence, and monitoring of biometric measurements (either directly into the application, or through synchronization with the smartphone’s health applications).

Objectives and Overall Study Design

The Medication adherence Improvement Support App For Engagement – Blood Pressure (MEDISAFE–BP) trial is a prospective, intent-to-treat randomized control trial that aims to evaluate the impact of the Medisafe smart application on blood pressure control and self-reported medication adherence for patients with uncontrolled blood pressure.

Patient Eligibility

Inclusion	*Exclusion*
• ≥ 18 and ≤ 75 years of age • Self-reported systolic blood pressure ≥ 140 mmHg • Self-reported active prescription of 1-3 of the following anti-HTN medications (thiazide, CCB, ß-blocker, ACE-I, ARB) • Systolic blood pressure ≥ 140 mmHg (+/- diastolic blood pressure ≥ 90 mmHg), but blood pressure ≤ 180/120 mmHg confirmed by home BP-cuff (see below)	• Current use of a smartphone medication adherence application • No ownership of a smartphone with iOS or compatible Android operating system • Currently taking > 3 anti-HTN medications (thiazide, CCB, ß-blocker, ACE-I, ARB) by self-report • Currently undergoing dialysis • Currently receiving chemotherapy or radiation • Does not understand English

Subject Recruitment and Randomization

Recruitment will be conducted by Evidation Health, which uses an online strategy to virtually announce, recruit, verify eligibility and enroll participants in clinical studies. Subjects will be recruited through various digital platforms such as online patient communities, social media, pertinent mobile applications, and targeted advertisements. As shown in Figure 1, potential study subjects will be evaluated for inclusion and exclusion criteria, will give informed consent, complete the baseline assessment, and then be sent a Bluetooth-enabled home blood pressure cuff to verify that they have uncontrolled blood pressure (systolic blood pressure $\geq$ 140 mmHg but overall blood pressure $\leq$ 180/120 mmHg). Patients will be provided with a study overview and blood pressure measurement guide that will outline how to set up the monitor and take an accurate measurement, as well as the standard insert for how to use the home monitor and its associated smartphone application. Blood pressure readings will be electronically transmitted to Evidation Health via an Application Program Interface (API) with the blood pressure monitor manufacturer. If patients are unable to activate the smartphone application associated with the blood pressure monitor, they may submit their blood pressure readings by taking a time-stamped photo of the blood pressure monitor display. Blood pressure will be calculated as the average of two measurements that are taken five minutes apart, which is in accordance with previous literature (14). Once their blood pressure readings have been confirmed as being elevated, patients will undergo randomization in a 1:1 ratio to intervention or control using simple randomization through a random number generated at the time of study enrollment.

Informed Consent

Informed consent will be attained from subjects prior to enrollment using an eConsent process. Patients will be told that a study is being conducted for evaluation of blood pressure, and focused on strategies to optimize treatment using technology. They will also be informed of how their personal

information will be secured and that all analysis will be conducted on de-identified data. Because Medisafe is a free application and notification may lead to use of this technology in the control arm, patients will not be told about Medisafe before randomization. After randomization patients in the intervention arm will be provided with information and instructions to download Medisafe. During the informed consent process, there will be a contact form as well as a phone number and email available to patients for any questions or to withdraw from the study.

Study Procedures

Prior to randomization, patients will be asked to complete a baseline assessment. This will consist of baseline demographics including cardiovascular comorbidities, use of cigarettes, and education level (15). The Morisky 8-item adherence scale will also be collected, which has been validated to accurately capture anti-hypertensive medication adherence by self-report (8). Baseline hypertension knowledge will also be assessed in accordance with Oliveira et. al (16). Subjects will also be asked to complete the Consumer Health Activation Index (CHAI) as a marker for patient activation, as developed by Wolf et al. Blood pressure monitors will then be mailed after the patients complete the baseline assessment.

Patients assigned to the intervention arm will be emailed with instructions to download the Medisafe application. Through an integration with Medisafe, Evidation Health will confirm that the application has been downloaded and launched at least once within two days from randomization. Patients who do not download and launch the application at least once within two days will be contacted by email two more times and provided the instructions for download until they launch the application. If they still do not launch the application, they will be contacted twice via telephone, then one final time by email. If after three reminder e-mails and two phone calls the participant still does not launch the

application, they will not be contacted further about downloading the application, but they will remain in the intent-to-treat analysis group.

Patients assigned to the control arm will not receive any intervention.

At two time points, four and eight weeks after randomization, all subjects assigned to intervention and control will be e-mailed and asked to measure their blood pressure using the Bluetooth-enabled blood pressure cuff and its associated smartphone application (all blood pressures will be done via two measurements, taken at least five minutes apart, and averaged (7)). If there is no blood pressure measurement received within 2 days after the intended upload date, there will be two reminder e-mails sent until a blood pressure measurement is received. If there is still no blood pressure measurement received, two phone calls will be made to the study participant, followed by one final email reminder. If they are unable to be reached by three reminder e-mails and two phone calls, they will not be contacted again for that blood pressure measurement, but will be contacted to obtain the next assessment (either 8-week blood pressure measurement or study exit assessment) and will remain in the intent-to-treat analysis group.

At 12 weeks, all subjects will be asked to complete an exit questionnaire consisting of Morisky 8-item medication adherence scale (8), hypertension knowledge questionnaire (16), and a CHAI. They will also be asked to take their final blood pressure measurement. The same protocol described above of three reminder e-mails and two phone calls will be followed, with one additional reminder email (for a sequence of 2 reminder emails, 2 phone calls, 2 reminder emails), should there be a delay in answering the questionnaire or taking the blood pressure measurement. Subjects who do not complete the exit questionnaire or take their final blood pressure measurement will be lost to follow-up. After completing the study, subjects will be given the option to keep the blood pressure cuff or donate it to an organization that recycles digital health and wellness products for underserved populations.

Subjects may choose to take blood pressure measurements using the Bluetooth-enabled blood pressure cuff more often than the four readings required in the study. That data will also be transmitted to Evidation Health via the API and stored in the study database.

Throughout the study, subject data including blood pressure measurements and survey data will be reviewed to ensure data quality and consistency. Patients may be contacted by phone or email to address suspicious or unusual data submissions.

All study subjects will be provided compensation for their time to participate in the study, staged in four intervals throughout the study (i.e., after randomization, after submitting blood pressure measurement at 4 and 8 weeks after enrollment respectively, and after completion of final blood pressure measurement and exit questionnaire). Maximum total compensation per study subject will not exceed $150.

Data Security and Confidentiality

All identifiable information about patients, their medical conditions, and other study data will be secured by Evidation Health in accordance with all local and state laws, regulations and Human Subjects Committee policies regarding collection and distribution of patient information. Evidation Health will use a HIPAA compliant survey system to collect the participant information and consent. Participant information received from smartphone applications will be transmitted using Transport Layer Security (TLS).

Data will only be stored electronically. All PHI and PII will be stored only on a single secured server in the Amazon EC2 cloud designed exclusively for this purpose. The server will be protected by two-factor authentication (requiring a password and a code generated on a separate device that changes every 60 seconds). All communication with the server will be encrypted using TLS. Only Evidation

Health's VP of Engineering and Head of Operations will have access to server. Data will be encrypted at rest.

De-identified data will be stored on a separate password-secured server with data at rest encryption. Only Evidation Health's Head of Operations and Data Science and Data Engineering teams have access to this server. Only de-identified data will be transferred to the Center for Healthcare Delivery Science (C4HDS) at Brigham Women's Hospital. Questionnaire data and other de-identified data will only be linked to PHI and PII through a unique study-generated identifier. This identifier will be generated via a secure cryptographic hash that cannot be reverse-engineered.

Outcomes

The study's co-primary outcomes will be a change in systolic blood pressure from randomization to three months later and self-reported medication adherence (see Table 1). The secondary outcome will be change in number of subjects who have well controlled blood pressure (<140/90 mmHg).

Analytic Plan

The Center for Healthcare Delivery Science (C4HDS) at Brigham Women's Hospital will conduct all analysis on de-identified data. We will report baseline patient characteristics and evaluate differences in the two groups to identify any potentially unmatched covariates despite randomization. We will plot changes in blood pressure over time.

Analyses will be performed by an intent-to-treat basis, where subjects will be analyzed in the groups they are assigned to during randomization. We will use linear regression to assess the impact of Medisafe on the study's 2 primary outcomes (change in systolic blood pressure and self-reported adherence) between the two study groups, 3 months after randomization. Our primary models will adjust

for unbalanced covariates between the two groups. Only the initial and 12-week blood pressure readings will be included in the primary analysis.

In secondary analyses, we will determine the number of patients that had their hypertension controlled (i.e., <140/90mmHg) during the study period in both arms, and calculate an odds ratio using multivariate logistic regression in order to control for potentially unmatched baseline covariates. We will also repeat our analyses with longitudinal modeling methods that incorporate blood pressure readings at 4, 8, and 12 weeks after randomization. If there are additional blood pressure readings from patients who took their blood pressure more often than required, we will include this data in exploratory longitudinal modeling analyses.

In supplemental analyses, we will evaluate whether the impact of Medisafe differed for subjects who interacted with Medisafe frequently (defined as being in the upper median of use for the Medisafe application based on frequency of user sessions during the study period) as compared to subjects who interacted with Medisafe less frequently. We will perform this analysis by including categorical variables for high and low use in our outcome model, whereby control subjects are indicating by null values for both of these indicators. We will also evaluate effect modification by hypertension knowledge (16) recorded at baseline.

Sample Size

With a change in systolic blood pressure of 5mmHg, which has previously been shown to be clinically significant (12,13), a standard deviation of 17mmHg, a power of 80%, and an alpha of 0.05 there would need to be 312 patients enrolled. With allowance for 20% loss to follow-up, the study will seek to enroll 390 patients total to have an 80% power with an alpha of 5%. With a standard deviation of 1.6 (8) and a sample size of 390 patients, we will be able to detect a 0.5 Morisky score difference between the groups with a power of 87%.

Risks Associated with the Intervention

Since the intervention under investigation is not aimed at altering a patient's treatment, but rather to promote adherence to treatments that they have already been prescribed, the risk will be minimal. There is a possible risk of patients receiving escalating anti-hypertensive medications from their treatment team due to non-adherence, and with the better adherence through Medisafe reminders there could be medication induced hypotension. During the informed consent process and on the blood pressure measurement guidance sheet there will be recommendations to reach out to their treatment team if they ever have a blood pressure > 180/120 mmHg or < 90/50 mmHg. The informed consent will also clearly state that no component of the study, including the home blood pressure cuff use and study personnel, is a replacement for care from a health care professional.

The likelihood that a study participant has a blood pressure reading > 180/120 mmHg or < 90/50 mmHg during the study is very low, since this is a low-risk patient population. Inclusion criteria is limited to patients with stage I or II hypertension, and patients with an initial blood pressure reading > 180/120 mmHg will be excluded. Patients taking more than three anti-hypertensive medications will also be excluded. Additionally, patients will be notified during the informed consent process that their blood pressure readings will not be monitored by the research team, and that they should reach out to their treatment team if their blood pressure is ever very high or very low.

Final protocol

Introduction

Hypertension is a major factor in health issues such as stroke, heart disease, and kidney disease. Worldwide there are 9.4 million deaths each year that can be attributed to hypertension and its effects through cardiovascular disease (1). It has been estimated that annual medical expenditures of $46 billion can be attributed to hypertension in the United States (2). Medications exist for the treatment of hypertension and can prevent the harmful effects of elevated blood pressure and its associated morbidities and mortalities, but medication adherence is a known barrier to effective treatment (3-5).

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The study's co-primary outcomes will be a change in blood pressure from randomization to three months later and self-reported medication adherence (see Table 1). The secondary outcome will be change in number of subjects who have well controlled blood pressure (<140/90 mmHg).

Analytic Plan

The Center for Healthcare Delivery Science (C4HDS) at Brigham Women's Hospital will conduct all analysis on de-identified data. Analyses will be performed by an intent-to-treat basis, where subjects will be analyzed in the groups they are assigned to during randomization.

We will begin by comparing the baseline patient characteristics in each of the arms using t-tests, chi-square tests or their non-parametric analogues, as appropriate. We will evaluate for rates of missing data between the two study arms to ensure that it is non-differential.

We will use linear regression to assess the impact of Medisafe on the study's 2 primary outcomes (change in blood pressure and self-reported adherence) between the two study groups. Our null

hypothesis will be that there is no difference in the change in blood pressure between the two groups after 12 weeks.

Our primary models will adjust for unbalanced covariates between the two groups (i.e. age, gender, ethnicity, BMI, comorbidities, number of antihypertensive medications, total number of medications, education, exercise level, cell phone use) should any exist using a p-value threshold of 0.05 and will impute missing outcome data where 12 week outcome data is unavailable. Imputation will be performed using the PROC MI command in SAS and will include the covariates defined above as well is intermediate outcomes (i.e. blood pressure at weeks 4 and 8). Multiple imputation with 5 imputations will be used and the imputed values will be inspected to ensure in-range values. After imputation, analyses will be conducted on the imputed data set and the results will be combined using the standard rules from Rubin et al. In sensitivity analyses, we will analyze only those subjects for whom we have complete outcome data (i.e. a complete case analysis).

In secondary analyses, we will determine the number of patients that had their hypertension controlled (i.e., <140/90mmHg) during the study period in both arms, and calculate an odds ratio using multivariate logistic regression with covariates indicated above. In supplemental analyses, we will repeat our analyses with longitudinal modeling methods that incorporate blood pressure readings at 4, 8, and 12 weeks after randomization. This will be done using generalized estimating equations to account for correlations between repeated blood pressure readings for any individual subjects. If there are additional blood pressure readings from patients who took their blood pressure more often than required, the longitudinal models will be re-run to include these additional values.

In subgroup analyses, we will evaluate whether the impact of Medisafe differed for subjects who interacted with Medisafe frequently (defined as being in the upper median of use for the Medisafe application based on number of days logged in during the study period) as compared to subjects who interacted with Medisafe less frequently. We will perform this analysis by including categorical variables for high and low use in our outcome model, whereby control subjects are indicating by null values for

both indicators. We will also evaluate effect modification by hypertension knowledge (16) recorded at baseline.

Sample Size

With a change in blood pressure of 5mmHg, which has previously been shown to be clinically significant (12,13), a standard deviation of 1~~6~~7mmHg, a power of 80%, and an alpha of 0.05 there would need to be 312 patients enrolled. With allowance for 20% loss to follow-up, the study will seek to enroll 390 patients total to have an 80% power with an alpha of 5%. With a standard deviation of 1.6 (8) and a sample size of 390 patients, we will be able to detect a 0.5 Morisky score difference between the groups with a power of 87%.

Risks Associated with the Intervention

Since the intervention under investigation is not aimed at altering a patient's treatment, but rather to promote adherence to treatments that they have already been prescribed, the risk will be minimal. There is a possible risk of patients receiving escalating anti-hypertensive medications from their treatment team due to non-adherence, and with the better adherence through Medisafe reminders there could be medication induced hypotension. During the informed consent process and on the blood pressure measurement guidance sheet there will be recommendations to reach out to their treatment team if they ever have a blood pressure > 180/120 mmHg or < 90/50 mmHg. The informed consent will also clearly state that no component of the study, including the home blood pressure cuff use and study personnel, is a replacement for care from a health care professional.

The likelihood that a study participant has a blood pressure reading > 180/120 mmHg or < 90/50 mmHg during the study is very low, since this is a low-risk patient population. Inclusion criteria is limited

418 to patients with stage I or II hypertension, and patients with an initial blood pressure reading > 180/120
419 mmHg will be excluded. Patients taking more than three anti-hypertensive medications will also be
420 excluded. Additionally, patients will be notified during the informed consent process that their blood
421 pressure readings will not be monitored by the research team, and that they should reach out to their
422 treatment team if their blood pressure is ever very high or very low.

423

Summary of changes to protocol

Date of submission	Description of modification	Rationale for modification
	Changes in inclusion criteria as follows. Initial: • ≥ 18 and ≤ 75 years of age • Self-reported systolic blood pressure ≥140 mmHg • Systolic blood pressure ≥ 140 mmHg (+/- diastolic blood pressure ≥ 90 mmHg), but blood pressure ≤ 180/120 mmHg confirmed by home BP-cuff Final: • ≥ 18 years of age • Self-reported blood pressure ≥ 140/90 mmHg • Blood pressure ≥ 140/90 mmHg, but ≤ 180/120 mmHg confirmed by home BP-cuff	Removed restriction to individuals ≤ 75 years of age and clarifying poorly-controlled BP as being defined based on both systolic and diastolic BP
	Addition to exclusion criteria of current use of an automated home blood pressure cuff	Required patients to not currently be using home blood pressure monitors to standardize outcome evaluation
	Change in primary outcome as follows. Initial: • Change in systolic blood pressure from randomization to three months later Final: • Change in blood pressure from randomization to three months later	To reflect the updated inclusion/exclusion criteria

For a description of changes to the analytic plan, see sections below.

Initial analytic plan

Analytic Plan

The Center for Healthcare Delivery Science (C4HDS) at Brigham Women's Hospital will conduct all analysis on de-identified data. We will report baseline patient characteristics and evaluate differences in the two groups to identify any potentially unmatched covariates despite randomization. We will plot changes in blood pressure over time.

Analyses will be performed by an intent-to-treat basis, where subjects will be analyzed in the groups they are assigned to during randomization. We will use linear regression to assess the impact of Medisafe on the study's 2 primary outcomes (change in systolic blood pressure and self-reported adherence) between the two study groups, 3 months after randomization. Our primary models will adjust for unbalanced covariates between the two groups. Only the initial and 12-week blood pressure readings will be included in the primary analysis.

In secondary analyses, we will determine the number of patients that had their hypertension controlled (i.e., <140/90mmHg) during the study period in both arms, and calculate an odds ratio using multivariate logistic regression in order to control for potentially unmatched baseline covariates. We will also repeat our analyses with longitudinal modeling methods that incorporate blood pressure readings at 4, 8, and 12 weeks after randomization. If there are additional blood pressure readings from patients who took their blood pressure more often than required, we will include this data in exploratory longitudinal modeling analyses.

In supplemental analyses, we will evaluate whether the impact of Medisafe differed for subjects who interacted with Medisafe frequently (defined as being in the upper median of use for the Medisafe application based on frequency of user sessions during the study period) as compared to subjects who interacted with Medisafe less frequently. We will perform this analysis by including categorical variables for high and low use in our outcome model, whereby control subjects are indicating by null values for

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We will use linear regression to assess the impact of Medisafe on the study's 2 primary outcomes (change in blood pressure and self-reported adherence) between the two study groups. Our null hypothesis will be that there is no difference in the change in blood pressure between the two groups after 12 weeks.

Our primary models will adjust for unbalanced covariates between the two groups (i.e. age, gender, ethnicity, BMI, comorbidities, number of antihypertensive medications, total number of medications, education, exercise level, cell phone use) should any exist using a p-value threshold of 0.05 and will impute missing outcome data where 12 week outcome data is unavailable. Imputation will be performed using the PROC MI command in SAS and will include the covariates defined above as well is intermediate outcomes (i.e. blood pressure at weeks 4 and 8). Multiple imputation with 5 imputations will be used and the imputed values will be inspected to ensure in-range values. After imputation, analyses will be conducted on the imputed data set and the results will be combined using the standard rules from Rubin et al. In sensitivity analyses, we will analyze only those subjects for whom we have complete outcome data (i.e. a complete case analysis).

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In subgroup analyses, we will evaluate whether the impact of Medisafe differed for subjects who interacted with Medisafe frequently (defined as being in the upper median of use for the Medisafe application based on number of days logged in during the study period) as compared to subjects who interacted with Medisafe less frequently. We will perform this analysis by including categorical variables for high and low use in our outcome model, whereby control subjects are indicating by null values for both indicators. We will also evaluate effect modification by hypertension knowledge (16) recorded at baseline.

Sample Size

With a change in blood pressure of 5mmHg, which has previously been shown to be clinically significant (12,13), a standard deviation of 17~~6~~mmHg, a power of 80%, and an alpha of 0.05 there would need to be 312 patients enrolled. With allowance for 20% loss to follow-up, the study will seek to enroll 390 patients total to have an 80% power with an alpha of 5%. With a standard deviation of 1.6 (8) and a sample size of 390 patients, we will be able to detect a 0.5 Morisky score difference between the groups with a power of 87%.

Summary of changes to analytic plan

More concrete analysis methods for evaluating baseline patient characteristics as well as a list of potentially unmatched covariates are now provided which was not included in the original plan. Missing 12-week outcome data is also addressed in the final plan, specifically performing multiple imputation via the PROC MI function in SAS.