



Rationale and design of the Medication adherence Improvement Support App For Engagement—Blood Pressure (MedISAFE-BP) trial

Kyle Morawski, MD,^a Roya Ghazinouri, PT, DPT, MS,^a Alexis Krumme, MS,^a Julianne McDonough, BS,^a Erin Durfee, BS,^b Leslie Oley, MS,^b Namita Mohta, MD,^a Jessie Juusola, PhD,^b and Niteesh K. Choudhry, MD, PhD^a
Boston, MA and Menlo Park, CA

Background Hypertension is a major contributor to the health and economic burden imposed by stroke, heart disease, and renal insufficiency. Antihypertensives can prevent many of the harmful effects of elevated blood pressure, but medication nonadherence is a known barrier to the effectiveness of these treatments. Smartphone-based applications that remind patients to take their medications, provide education, and allow for social interactions between individuals with similar health concerns have been widely advocated as a strategy to improve adherence but have not been subject to rigorous testing.

Methods/design The MedISAFE-BP study is a prospective, randomized control trial designed to evaluate the impact on blood pressure and medication adherence of an mhealth application (Medisafe). Four hundred thirteen patients with uncontrolled hypertension have been enrolled and randomized in a 1:1 fashion to usual care or to the use of the Medisafe mhealth platform. Patients will be followed up for 12 weeks and the trial's co-primary outcomes will be change in systolic blood pressure and self-reported medication adherence.

Discussion The MedISAFE-BP trial is the first study to rigorously evaluate an mhealth application's effect on blood pressure and medication adherence. The results will inform the potential effectiveness of this simple system in improving cardiovascular disease risk factors and clinical outcomes. (*Am Heart J* 2017;186:40-47.)

Background

Hypertension is a major contributor to the health and economic burden imposed by stroke, heart disease, and renal insufficiency. Worldwide, there are 9.4 million deaths each year that can be attributed to hypertension through its effect on cardiovascular disease,¹ and annual expenditures for hypertension have been estimated to be \$46 billion in the United States alone.² Antihypertensives can prevent many of the harmful effects of elevated blood pressure, but medication nonadherence is a known barrier to the effectiveness of these treatments.³⁻⁵ It has been estimated that >50% of those classified as resistant hypertension are actually “pseudoresistant,” with medication nonadherence being the cause of uncontrolled blood pressure.⁵

The rapid adoption of smartphone technologies⁶ makes this an attractive avenue to help address nonadherence by delivering reminders about medication administration, offering education about healthy behaviors, creating a support network for caregivers and family members, and monitoring biometric measurements. Previous studies have shown improvement in blood pressure when mobile health (mhealth) applications are used to self-monitor,^{7,8} facilitate communication between patients and providers,⁹ and/or deliver text messages,^{10,11} but all of these have used technologies in clinic-based settings within the context of established doctor-patient relationships. In contrast, most mhealth applications are used by patients without the active participation, or even knowledge, of their care providers. The impact of “stand-alone” mhealth tools to improve medication adherence has not been rigorously evaluated, especially with regard to its ability to influence clinically-relevant health outcomes.

Methods

Trial design

The MedISAFE-BP trial is a prospective, intent-to-treat randomized control trial that aims to evaluate the impact of the Medisafe mhealth platform on blood pressure control and self-reported medication adherence for patients with uncontrolled blood pressure. Patients will be followed up

From the ^aCenter for Healthcare Delivery Sciences (C4HDS) and Division of Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, and ^bEvidence Health, Menlo Park, CA. RCT No. NCT02727543

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Reprint requests: Niteesh K. Choudhry, MD, PhD, Brigham and Women's Hospital, Harvard Medical School, 1620 Tremont St, Suite 3030, Boston, MA 02120.

E-mail: nkchoudhry@bwh.harvard.edu

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Table 1. Inclusion/exclusion criteria

Inclusion	Exclusion
Age ≥ 18 and ≤ 75 y Self-reported blood pressure $\geq 140/90$ mmHg Self-reported use of 1-3 of the following antihypertensive medications (thiazide, CCB, β -blocker, ACE-I, ARB) Systolic blood pressure ≥ 140 mm Hg, but $\leq 180/120$ mmHg confirmed by home blood pressurecuff (see text for details)	Current use of a smartphone medication adherence application No ownership of a smartphone with compatible iOS or Android operating system Currently taking >3 antihypertensive medications (thiazide, CCB, β -blocker, ACE-I, ARB) by self-report Currently undergoing dialysis Currently receiving chemotherapy or radiation Does not understand English

Abbreviations: CCB, calcium-channel blocker; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

for 12 weeks. The study was approved by the Chesapeake institutional review board (Columbia, MD) and is registered with clinicaltrials.gov (NCT02727543). The trial protocol was designed and written by the academic investigators.

Participants

Eligible participants were individuals between 18 and 75 years of age who self-identify as having inadequately controlled hypertension (defined as a systolic blood pressure ≥ 140 mmHg) and who are receiving treatment with at least 1, but not >3 , first-line antihypertension medications (defined as thiazide diuretics, calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, or β -blockers). Before randomization, each participant's blood pressure was verified using a Bluetooth-enabled home blood pressure cuff (UA-615BLE A&D Medical, San Jose, CA).

Individuals were excluded if they are already using a smartphone application to support medication adherence, did not own a smartphone, did not live in the United States with a valid mailing address, were undergoing hemodialysis or chemotherapy at the time of screening, or had hypertension that required immediate medical attention (defined as a systolic blood pressure >180 mmHg or a diastolic blood pressure >120 mmHg) (see Table 1).

Study enrollment began on April 25, 2016 and was completed on September 29, 2016. A total of 413 study participants were randomized (Figure 1). Follow-up of all trial participants will end by December 29, 2016.

Intervention

The Medisafe smartphone platform and application was developed to address nonadherence (Figure 2) and operates on either the iOS (version 6 or newer) or Android mobile system (version 4.4 or newer). It provides alerts to patients when it is time to take medication. Medisafe also allows patients to generate weekly reports of medication adherence, monitor biometric measurements (either directly into the application or through synchronization with the smartphone's non-Medisafe health devices), and designate a "Medfriend" of their choosing, who is granted access to

a patient's medication taking history, receives alerts when doses are missed, and can provide peer support. Medication lists can be entered manually, along with timing of administration as recommended by their doctor, or be auto-populated through a linkage with an existing record in those cases where this integration has been established. The University of Arkansas performed an independent evaluation of usability in all available medication adherence smartphone applications in 2015 and ranked Medisafe highest.¹²

Study procedures

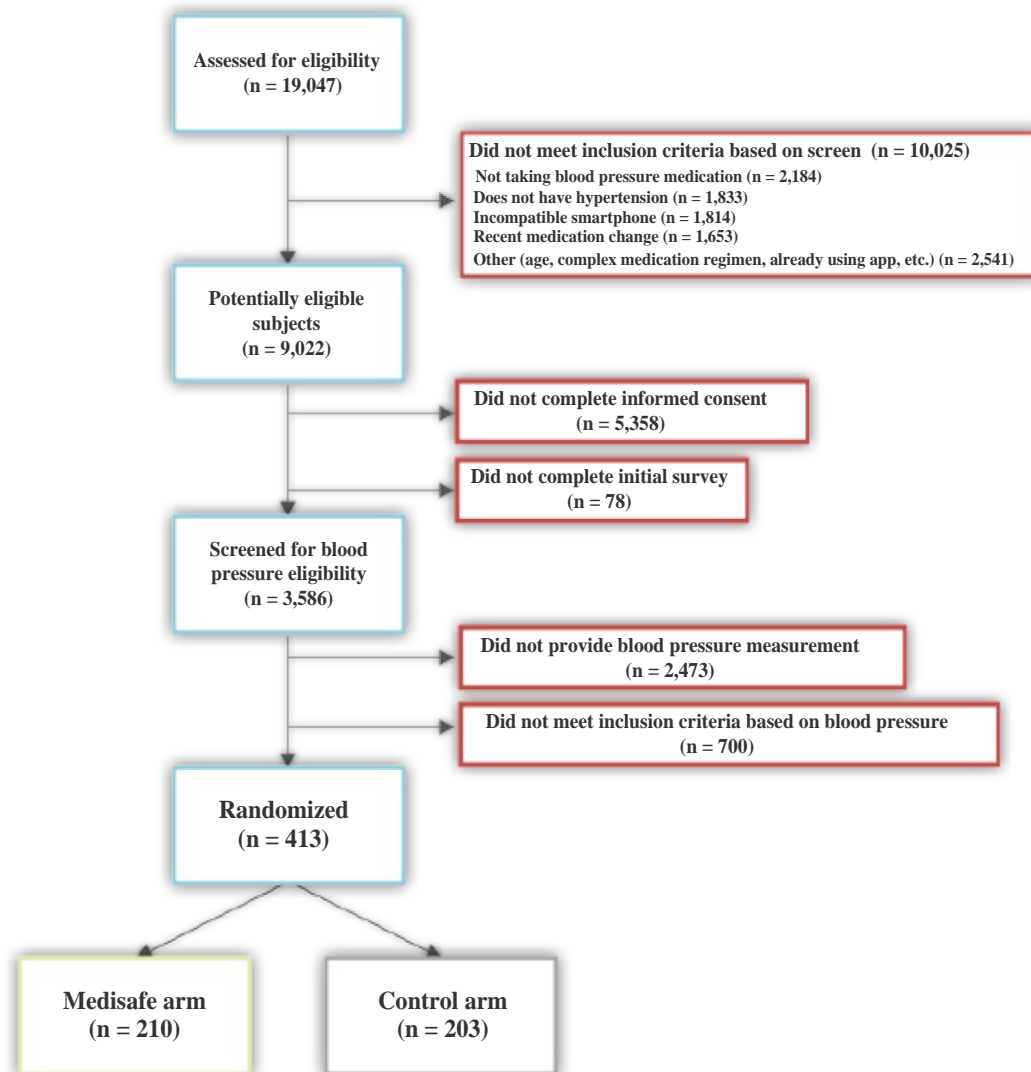
(a) Recruitment

Recruitment was being conducted by a Contract Research Organization, Evidation Health (Menlo Park, CA), which uses an online strategy to virtually announce, recruit, verify eligibility, enroll participants in clinical studies, and collect data from participants once enrolled. Participants were recruited through online patient communities, social media, pertinent mobile applications, and targeted advertisements.

(b) Screening and randomization

As shown in Figure 3, potential study participants were evaluated for inclusion and exclusion criteria, provided informed consent, and completed a baseline survey consisting of questions about demographics, cardiovascular comorbidities, use of cigarettes, and educational attainment.¹³ Baseline medication adherence was assessed with the Morisky 8-item adherence scale, which has been validated to accurately capture antihypertensive medication adherence by self-report.¹⁴ Baseline hypertension knowledge was assessed based on the methods of Oliveira et al.¹⁵ Participants were asked to complete the Consumer Health Activation Index as a marker for patient activation, as developed by Wolf et al (personal communication). After completing the baseline assessment, participants were sent a Bluetooth-enabled home blood pressure cuff to verify that they have uncontrolled

Figure 1



Consort diagram of enrolled study participants.

blood pressure (systolic ≥ 140 mmHg but $\leq 180/120$ mmHg). The cuff was sent by courier to allow the tracking of its receipt. Participants were provided with detailed instructions on how to accurately measure and transmit their blood pressure readings. In specific, the study participants were asked to provide 2 measurements that are taken 5 minutes apart, in accordance with professional society guidelines, and blood pressure was calculated as the average of these measurements.¹⁶ All submitted blood pressure measurements were transmitted and logged with a timestamp. Because of the pragmatic nature of this study, acceptable readings were considered as 2 measurements that were at least 3

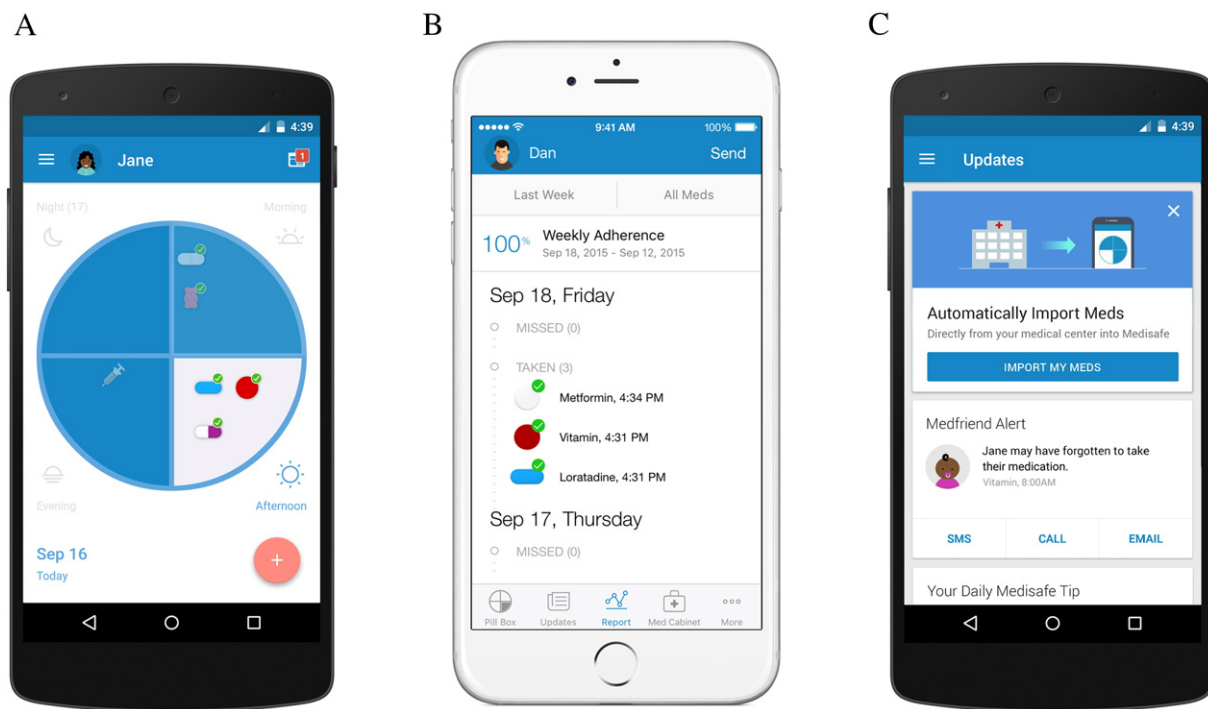
minutes apart, but not >30 minutes apart.

Once their blood pressure readings were confirmed as being elevated, participants underwent randomization in a 1:1 ratio to intervention or control using simple randomization with a random number generator.

(c) Treatment arms

Participants assigned to the intervention arm were e-mailed instructions on how to download the Medisafe application. Participants who did not download the application and have 1 login within 2 days of randomization were contacted by e-mail up to 2 times and were provided with the instructions for downloading the application. If

Figure 2



Smartphone application. **A**, The home screen of the Medisafe application for a hypothetical patient. **B**, A weekly report describing the percentage of time pills was missed. **C**, A demonstration on how medications can be automatically imported and the use of the Medfriend Alert system.

they still did not login, they were contacted twice via telephone, then 1 final time by e-mail. If after these attempts, a participant still did not login, they are not contacted further but they were followed up for outcomes and analyzed in the intent-to-treat analysis.

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

(d) Follow-up assessments

Blood pressure measurements are being collected 4, 8, and 12 weeks after randomization. At each of these periods, participants in both treatment groups are contacted and asked to check their blood pressure using the Bluetooth-enabled blood pressure cuff that they were provided at enrollment. Blood pressure is assessed as the average of 2 measurements, taken at least 5 minutes apart.¹⁶ If no blood pressure measurement is received within 2 days after the intended upload date, there are 2 reminder e-mails sent until a blood pressure measurement is received. If there is still no blood pressure measurement received, 2 phone calls are made to the study participant, followed by 1 final e-mail reminder. If they are unable to be reached

after 3 reminder e-mails and 2 phone calls, they are not contacted again for that assessment, but are contacted to obtain the next scheduled blood pressure reading.

At 12 weeks, all participants are asked to complete an exit questionnaire consisting of Morisky 8-item medication adherence scale,¹⁴ hypertension knowledge questionnaire,¹⁵ and the Consumer Health Activation Index. Participants who do not complete the exit questionnaire or take their final blood pressure measurement are characterized as lost to follow-up after the same e-mail and phone call schedule described previously. After completing the study, participants are 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. Participants may choose to take blood pressure measurements using the Bluetooth-enabled blood pressure cuff more often than the required in the study. Those data will also be stored in the study database. Throughout the study, participant data including blood pressure measurements and survey data are reviewed by study personnel blinded to treatment assignment to ensure data quality and consistency. Patients may be

Table II. Outcomes

Outcome	Description
Primary	(1) Change in blood pressure from baseline to 12 wk after randomization (2) Self-reported medication adherence
Secondary	Change in number of participants with well-controlled blood pressure (<140/90 mmHg)

contacted by phone or e-mail to address suspicious or unusual data submissions that are suggestive of device malfunctioning or misuse.

Outcomes

The study's co-primary outcomes are change in (a) systolic blood pressure and (b) self-reported medication adherence from randomization to 12 weeks later (see Table II). The secondary outcome is change in proportion of participants who have well-controlled blood pressure (<140/90 mmHg).

Statistical considerations

(a) Analytic plan

We will report the means and frequencies of prerandomization variables separately for intervention and control subject, and between-group differences will be evaluated using *t*tests and χ^2 tests and their nonparametric analogs, as appropriate. We will then plot changes in blood pressure for each of the study groups over time.

Analyses will be performed on an intention-to-treat basis, where participants will be analyzed in the groups to which they are assigned at randomization. We will use linear regression to assess the impact of the smartphone application on the study's co-primary outcomes, change in blood pressure, and self-reported adherence from baseline to 12 weeks. We will perform crude and adjusted analysis as a sensitivity analysis for any unmatched covariates despite randomization.

We will evaluate for rates of missing data between the 2 study arms to ensure it is nondifferential. We will use multiple imputation with 5 imputations for data entries that are unavailable. All analyses will be performed with these imputations, and then data will be combined using standard procedures.¹⁷ This approach has been used previously¹⁸ and minimizes both false-positive and false-negative conclusions.¹⁹ As a sensitivity analysis, we will analyze only those participants for whom we have complete outcome data.

In a secondary analysis, we will use multivariable logistic regression to determine the proportion of patients who had their hypertension controlled (ie, <140/90 mmHg). We will 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 these data in exploratory analyses.

In subgroup analyses, we will evaluate whether the impact of the smartphone application differed for participants who interacted with it frequently (defined as being in the upper median based on number of days with use of the application during the study period) and less frequently. We will perform this analysis by including categorical variables for high and low use in our outcome model, whereby control subjects are indicated by null values for both of these indicators. We will also evaluate effect modification by hypertension knowledge¹⁵ recorded at baseline.

(b) Sample size

Our planned enrollment was 390 patients; however, ultimate enrollment in the study was 413. This provides us with at least 80% power to detect a 5-mmHg change in systolic blood pressure, with an α of .05, even with a 20% loss to follow-up or anSD of up to 17. A decrease in systolic blood pressure by 5 mm Hg correlates with clinically-meaningful reductions in coronary heart disease and stroke.²⁰⁻²² This sample size also provides 87% power detect a 0.5 Morisky score difference between the groups assuming anSD of 1.6¹⁴ and an α of .05.

Funding

This study is supported by a grant from Medisafe, Inc. The authors are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the manuscript and its final contents.

Limitations

There are several limitations to this trial. The intervention lasts for 12 weeks; therefore, we will be unable to determine the effect of the smartphone application on longer-term outcomes, including stroke or myocardial infarction. However, previous evidence supports the

notion that short-term adherence is predictive of long-term adherence,²³ and therefore, results of this trial may signal longer-term effects for health improvement.

Although the trial aims to be pragmatic with minimal inclusion and exclusion criteria, because patients are primarily recruited through online and virtual methods, the results may not be generalizable to other patient populations. However, the use of mobile technology, especially as it pertains to informing medical conditions, is increasing and may soon be present in >50% of the population.²⁴ In addition, we exclude those with extremely high blood pressure, for which immediate medical attention is recommended, and therefore, this intervention may not be applicable to populations with blood pressures greater than 180 mmHg systolic or 120 mmHg diastolic. Many patients with this level of blood pressure elevation require careful medical supervision, and therefore, reliance on a stand-alone smartphone application may not be prudent.

Performing this trial through online and virtual methods also potentially increases the rate of drop-off during the recruitment process. Previous hypertension trials have had variable proportions of patients enrolled that begin the screening process. The recent SPRINT trial performed recruitment in the clinical setting and ultimately enrolled 64% of those approached for screening,²⁵⁻²⁷ whereas the SHEP trial used community advertisements, referrals from clinicians, and site enrollment and enrolled 1.06% of those screened.^{23,24} We anticipate that between 2% and 5% of participants screened will ultimately enroll in our trial. Because this drop-off is before randomization, and our analysis will be done in an intent-to-treat manner, this will not compromise the internal validity of the trial, but may have implications for the generalizability of our results.

To assess study outcomes, we are measuring blood pressure several times over the course of the 12-week trial. This interaction has the potential to increase hypertension awareness and to potentially improve medication adherence itself, or cause healthier lifestyle behaviors that would lower blood pressure. Home use of blood pressure cuffs has been shown to decrease systolic blood pressure by 2.5 mmHg systolic and diastolic blood pressure by 1.8 mmHg.⁷ It is reassuring that any bias this would introduce would be nondifferential between the 2 study arms.

Finally, we are monitoring blood pressure with ambulatory blood pressure monitors, whereas previous hypertension trials had blood pressures measured in clinic. Although this approach, which minimizes the “white-coat effect” of artificially elevated blood pressure in a medical clinic²⁸ and is advocated by the American Heart Association for blood pressure monitoring,²⁹ we are not able to verify the accuracy of the blood pressure readings that we receive. We are using Food and Drug Administration–approved blood pressure cuffs and information will be transmitted automatically in an attempt to

remove any manual entry, or self-reporting, bias that may occur with blood pressure measurements.

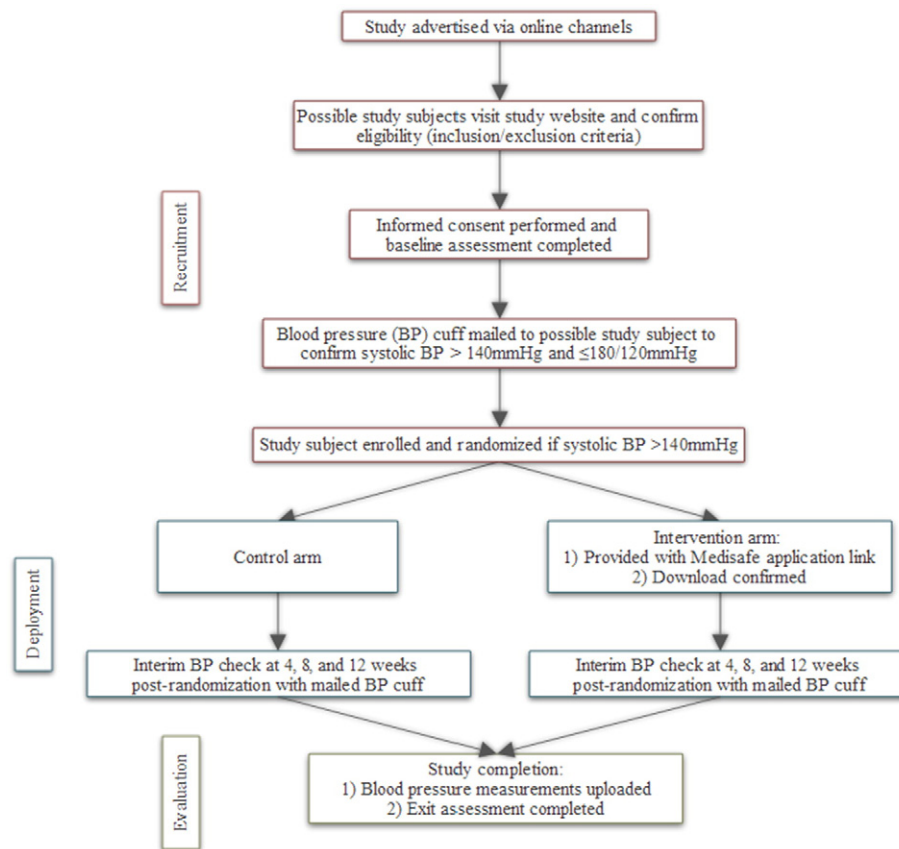
Discussion

Although there could be as many as 1.7 billion mhealth users globally by 2018,²⁴ very few mhealth applications have been adequately tested. Given the near ubiquity of smartphones and other mobile devices, there is great potential for this technology to increase engagement in the time between clinic visits, and to promote healthier lifestyle choices. An especially attractive target is hypertension in which there are no daily symptoms, but can have significant morbidity if left untreated. A 2012 review identified 147 unique smartphone applications available to target medication adherence, but effectiveness data were lacking.³⁰ In the years since, the number of adherence apps has increased substantially but the evidence base supporting their impact on health care quality remains extremely limited.

Although there have been several trials evaluating the impact of short message service text messaging on chronic disease management,^{10,31,32} the randomized trial of an mhealth application for patients with hypertension relied heavily on nurse health coaches to provide treatment recommendations.⁹ In this study, Moore et al evaluated the use of CollaboRhythm, an interface that allows tracking of medications and pairs a patient with a coach to offer recommendations and reminders. After 12 weeks, those in the intervention arm decreased their blood pressure by 10 mmHg more than the control group. There was also a trend for a greater proportion in the intervention becoming well controlled; however, this did not reach statistical significance. The only published observational study of a “hypertension management app”—created by the study investigators—was a preimplementation/postimplementation study that found a statistically significant increase in self-reported medication adherence after 4 weeks using the modified Morisky scale.³³ As such, MedISAFE-BP trial is, to our knowledge, the first randomized trial to evaluate the effect of a stand-alone mhealth platform to increase medication adherence and improve blood pressure control.

In chronic conditions other than hypertension, there is some evidence of benefit for smartphone applications. Bricker et al³⁴ evaluated 2 stand-alone smartphone applications for smoking cessation and found a nonsignificant 2.7 times higher odds of quitting at 2 months with the use of SmartQuit vs National Cancer Institute's QuitGuide application, although there was no control group in this study. Kirwan et al³⁵ randomized 72 individuals with type 1 diabetes to control or the use of “Glucose Buddy,” the most downloaded diabetes management application on iOS. They found a statistically significant decrease in HbA_{1c} of 1.1%, although the baseline HbA_{1c} and other characteristics of the patients in the 2 treatment arms were not well balanced at baseline

Figure 3



Study flowsheet.

and, as part of the intervention, patients received personalized text messages from a certified diabetes educator. In contrast 2 trials of smartphone applications for patients with obesity found no impact on weight loss, even with the use of personal coaching.^{36,37}

In conclusion, MedISAFE-BP will evaluate the effectiveness of the stand-alone mhealth application with respect to its clinical impact on blood pressure control. It will inform whether this strategy can improve preventive strategies for cardiovascular morbidity.

References

1. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2224-60.
2. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation* 2015;131(4):e29-322.
3. Burnier M, Wuerzner G. Ambulatory blood pressure and adherence monitoring: diagnosing pseudoresistant hypertension. *Semin Nephrol* 2014;34(5):498-505.
4. Ghebaza MA, Senoussaoui Y, Tani MK, et al. Impact of patient knowledge of hypertension complications on adherence to antihypertensive therapy. *Curr Hypertens Rev* 2014;10(1):41-8.
5. Oliveira-Filho AD, de Costa FA, Neves SJF, et al. Pseudoresistant hypertension due to poor medication adherence. *Int J Cardiol* 2014;172(2):e309-10.
6. Smith A. U.S. smartphone use in 2015 [Internet]. Pew Research Center: Internet, Science & Tech. [cited 2016 Jun 13]. Available from: <http://www.pewinternet.org/2015/04/01/us-smartphone-use-in-2015/2015>.
7. Glynn LG, Murphy AW, Smith SM, et al. Interventions used to improve control of blood pressure in patients with hypertension. *Cochrane Database Syst Rev* 2010;3:CD005182.
8. Plante TB, Urrea B, MacFarlane ZT, et al. Validation of the instant blood pressure smartphone app [Internet]. *JAMA Intern Med* 2016. [cited 2016 Apr 5]; Available from: <http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2016.0157>.
9. Moore JO, Marshall MA, Inch B, et al. Technology-supported apprenticeship in the management of hypertension: a randomized controlled trial. *JCOM* 2014;21(3). [Internet. [cited 2016 Mar 22];

- Available from: http://www.turner-white.com/pdf/jcom_mar14_hypertension.pdf.
10. Chow CK, Redfern J, Hillis GS, et al. Effect of lifestyle-focused text messaging on risk factor modification in patients with coronary heart disease: a randomized clinical trial. *JAMA* 2015;314(12):1255.
 11. Thakkar J, Kurup R, Laba T-L, et al. Mobile telephone text messaging for medication adherence in chronic disease: a meta-analysis. *JAMA Intern Med* 2016;176(3):340.
 12. Heldenbrand SD, Dayer L, Renna C, et al. Navigating the flooded adherence app marketplace: rating the quality of medication adherence apps. *ResearchGate [Internet]*; 2015. [cited 2016 Jun 17. Available from: https://www.researchgate.net/publication/276204576_Navigating_the_Flooded_Adherence:App_Marketplace:Rating_the_Quality_of_Medication_Adherence:Apps].
 13. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment To Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288(23):2981-97.
 14. Morisky DE, Ang A, Krousel-Wood M, et al. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens Greenwich Conn* 2008;10(5):348-54.
 15. Oliveria SA, Chen RS, McCarthy BD, et al. Hypertension knowledge, awareness, and attitudes in a hypertensive population. *J Gen Intern Med* 2005;20(3):219-25.
 16. Siu AL. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statementscreening for high blood pressure in adults. *Ann Intern Med* 2015;163(10):778-86.
 17. Rubin DB. *Multiple imputation for nonresponse in surveys*. New York: Wiley. 1987. [258 p. *Wiley series in probability and mathematical statistics*].
 18. Asch DA, Troxel AB, Stewart WF, et al. Effect of financial incentives to physicians, patients, or both on lipid levels: a randomized clinical trial. *JAMA* 2015;314(18):1926-35.
 19. Li P, Stuart EA, Allison DB. Multiple imputation: a flexible tool for handling missing data. *JAMA* 2015;314(18):1966-7.
 20. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1997;336(16):1117-24.
 21. Harsha DW, Bray GA. Weight loss and blood pressure control (Pro). *Hypertension* 2008;51(6):1420-5.
 22. Crim MT, Yoon SSS, Ortiz E, et al. National surveillance definitions for hypertension prevalence and control among adults. *Circ Cardiovasc Qual Outcomes* 2012;5(3):343-51.
 23. Franklin JM, Shrank WH, Lii J, et al. Observing versus predicting: initial patterns of filling predict long-term adherence more accurately than high-dimensional modeling techniques. *Health Serv Res* 2016;51(1):220-39.
 24. Kumar N, Khunger M, Gupta A, et al. A content analysis of smartphone-based applications for hypertension management. *J Am Soc Hypertens* 2015;9(2):130-6.
 25. Group TSR. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;373(22):2103-16.
 26. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP)*JAMA* 1991;265(24):3255-64.
 27. Vogt TM, Ireland CC, Black D, et al. Recruitment of elderly volunteers for a multicenter clinical trial: the SHEP pilot study. *Control Clin Trials* 1986;7(2):118-33.
 28. Ghuman N, Campbell P, White WB. Role of ambulatory and home blood pressure recording in clinical practice. *Curr Cardiol Rep* 2009;11(6):414-21.
 29. Pickering TG, Miller NH, Ogedegbe G, et al. Call to action on use and reimbursement for home blood pressure monitoring: executive summary. A joint scientific statement from the American Heart Association, American Society of Hypertension, and Preventive Cardiovascular Nurses Association. *Hypertension* 2008;52(1):1-9.
 30. Dayer L, Heldenbrand S, Anderson P, et al. Smartphone medication adherence apps: potential benefits to patients and providers. *J Am Pharm Assoc* 2013;53(2):172-81.
 31. Bobrow K, Farmer AJ, Springer D, et al. Mobile phone text messages to support treatment adherence in adults with high blood pressure (StAR): a single-blind, randomized trial. *Circulation* 2016. [CIRCULATIONAHA.115.017530].
 32. Pfaeffli Dale L, Whittaker R, Jiang Y, et al. Text message and internet support for coronary heart disease self-management: results from the Text4Heart randomized controlled trial. *J Med Internet Res* 2015;17(10):e237.
 33. Kang H, Park H-A. A mobile app for hypertension management based on clinical practice guidelines: development and deployment. *JMIR MHealth UHealth* 2016;4(1):e12.
 34. Bricker JB, Mull KE, Kientz JA, et al. Randomized, controlled pilot trial of a smartphone app for smoking cessation using acceptance and commitment therapy. *Drug Alcohol Depend* 2014;143:87-94.
 35. Kirwan M, Vandelanotte C, Fenning A, et al. diabetes self-management smartphone application for adults with type 1 diabetes: randomized controlled trial. *J Med Internet Res* 2013;15(11). [Internet. [cited 2016 Jun 14]; Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3841374/>].
 36. Laing BY, Mangione CM, Tseng C-H, et al. Effectiveness of a smartphone application for weight loss compared with usual care in overweight primary care patients: a randomized, controlled trial. *Ann Intern Med* 2014;161(10 Suppl):S5-12.
 37. Svetkey LP, Batch BC, Lin P-H, et al. Cell phone intervention for you (CITY): a randomized, controlled trial of behavioral weight loss intervention for young adults using mobile technology. *Obesity* 2015;23(11):2133-41.