A Pharmacist Intervention for Monitoring and Treating Hypertension Using Bidirectional Texting: PharmText BP

Linnea A. Polgreen, Ph.D[a,*], **Barry L. Carter, Pharm.D**[a,b], **Philip M. Polgreen, M.D**[c,d], **Peter M. Snyder, M.D**[c], **Daniel K. Sewell, Ph.D**[e], **Emine O. Bayman, Ph.D**[e,f], **Shelby L. Francis, Ph.D**[c], **Jacob E. Simmering, Ph.D**[c], **Christopher Parker, Pharm.D**[a], **Rachel Finkelstein, Pharm.D**[a]

[a]Department of Pharmacy Practice and Science, College of Pharmacy, United States

[b]Department of Family Medicine, Roy J. and Lucille A. Carver College of Medicine, United States

[c]Department of Internal Medicine, College of Medicine, United States

[d]Department of Epidemiology, College of Public Health, United States

[e]Department of Biostatistics, College of Public Health, United States

[f]Department of Anesthesia, College of Medicine, United States

Abstract

Background: New approaches are needed to better monitor blood pressure (BP) between physician visits, especially for patients in rural areas or for those who lack transportation. We have developed a custom-built bi-directional texting platform for home BP measurements that can then be managed by clinical pharmacists located remotely. The purpose of this study is to evaluate whether the BP texting approach combined with a pharmacist-based intervention improves BP management and to determine if the approach is cost effective.

Methods: This study is a randomized, prospective trial in four primary care offices that serve patients in rural areas. Subjects will receive standardized research BP measurements at baseline, 6 and 12 months. The primary outcome will be differences between the intervention and control group in mean systolic BP at 12 months. Secondary outcomes will include systolic BP at 6 months; diastolic BP at 6 and 12 months, number of medication changes and costs.

Conclusions: This study plans to enroll subjects through 2022, follow-up will be completed in 2023 and results will be available in 2024. This study will provide information on whether a combined approach using texting of home BP values and a pharmacist-based telehealth services can improve BP control.

Keywords

hypertension management; pharmacist management; blood pressure control

*Corresponding author at: College of Pharmacy, University of Iowa, Iowa City, Iowa, 52242, linnea-polgreen@uiowa.edu.

INTRODUCTION

More than 2,200 Americans die of Cardiovascular disease (CVD) every day, or 1 death every 39 seconds, and many are due to poor blood pressure (BP) control.[1] The prevalence of hypertension is 45.6%, approximately 108 million adult Americans.[2] The 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines lowered the goal BP to <130/80 mm Hg and these authors found BP was controlled in 46.6% of adults taking BP medications.[2] Rural Americans are a vulnerable population and have higher rates of uncontrolled hypertension, especially those with lower socioeconomic status and from minority groups.[3,4]

Clinical inertia has been identified as the primary cause for delays in achieving BP control for over 20 years.[5–7] Providers often discount office BP readings that may be falsely elevated due to measurement error and/or the clinical surroundings (e.g., white coat hypertension).[8–10] Patients are often seen only once or twice a year to assess their BP. Medications are frequently not intensified leading for calls to adopt home BP monitoring. [7,11,12] New approaches are needed for acquiring more BP readings to better monitor and titrate treatment between physician visits. These strategies increasingly become more important for patients in rural areas or those who lack transportation.

Home BP measurements can facilitate the timely diagnosis of hypertension (HTN) by reducing diagnostic uncertainty.[11,12] In fact, home measurements are better prognostic indicators of stroke and cardiovascular mortality than clinic measurements,[13–15] are more closely correlated with end-organ damage from HTN than clinic measurements,[16,17] are cost effective and well-tolerated by patients,[18] and generate BP readings that are at least as reproducible as clinic readings.[12,19]

Telemedicine and smart phone application-based approaches have been used to obtain home BP data but these strategies require more effort from healthcare workers and patients.[20–22] Workload is particularly intense if the interactions are required to be synchronous, when patients and providers need to find a common time to interact. Texting may be particularly attractive for patients with limited mobility and those who live in rural areas, farther from clinics,[23] and in areas where high-speed Internet availability is limited.[24] We have designed the present clinical trial to evaluate whether our scalable SMS approach combined with a pharmacist-based intervention improves BP management and determine if it is cost effective.

RATIONALE AND OBJECTIVES

We developed a custom-built bi-directional SMS-based (short message service, or texting) mobile health platform called What's your BP? (WyBP).[25] WyBP is inexpensive (i.e., does not require investment in ambulatory blood pressure monitoring equipment and software, smartphone technology, or WiFi), acceptable to a broad range of patients (including the elderly and medically underserved populations), scalable to subject volume observed in large clinical settings, and easily integrated into typical clinic workflows. We demonstrated a high rate of adherence in two pilot studies, indicating that patients were willing and able to take home BP measurements and send them to our research team via SMS.[25,26] However,

these additional home measurements did not lead to an increased rate of treatment changes, nor did they improve patients' BP control.

We have pioneered physician-pharmacist collaborative management (PPCM) as a strategy for team-based care that has been shown to decrease clinical inertia and improve BP control. [27–32] In this model, pharmacists embedded within the medical office perform BP management. The pharmacists are able to assess patients' needs and give recommendations to physicians regarding treatment changes, providing patients with timely therapy adjustments.[29,31] We have demonstrated that these strategies are cost-effective[33,34] but many medical offices do not have the resources to hire onsite clinical pharmacists. Additionally, there was a great deal of variability in effectiveness of implementation of these on-site clinical pharmacy services which may have been complicated by inability or unwillingness of patients to make frequent clinic visits.[35]

To address some of these barriers, we developed a "virtual", remote clinical pharmacy service conducted primarily by telephone with patients.[36,37] Pharmacists monitor patients remotely and transmit recommendations to busy clinicians directly via the electronic medical record (EMR). In our recent study of remote pharmacists providing telehealth services, 95% of the pharmacists' recommended changes in therapy were accepted by physicians.[37]

Our prior work demonstrated that texting is an efficient method for obtaining home BP measurements; clinic-based pharmacist-assisted interventions can improve BP; and that providers routinely accept remote pharmacists' recommendations. We have theorized that combining our texting platform with home BP monitoring may allow our remote pharmacist team to focus on improving BP management by improving access and avoiding the common and costly need to play "phone tag" with patients. However, we do not know if the combination of texting and the use of remote pharmacists will lead to better BP control, especially in a rural population. Furthermore, the intervention may be clinically successful but prove too costly to implement outside research settings. Thus, further research is needed to address these gaps in our knowledge.

The objective of this study is to evaluate whether our scalable SMS approach combined with a pharmacist-based intervention improves BP management and if it is cost effective. In order to accomplish these objectives, we have established the following specific aims and hypotheses:

Aim 1: Determine if our intervention leads to decreases in BP.

1.1 Hypothesis: Mean systolic BP in the pharmacist-intervention group will be significantly lower than mean systolic BP in the control group at 12 months (primary outcome).

1.2 Hypothesis: Mean systolic BP in the pharmacist-intervention group will be significantly lower than mean systolic BP in the control group at 6 months (secondary outcome).

1.2 Hypothesis: Mean diastolic BP in the pharmacist-intervention group will be significantly lower than mean diastolic BP in the control group at 6 and 12 months (secondary outcomes).

Aim 2: Determine if our intervention leads to intensification of therapy.

2.1 Hypothesis: Subjects in the pharmacist-intervention group will have more treatment changes, on average, than those in the control group.

Aim 3: Determine the cost effectiveness of the intervention.

3.1 Hypothesis: The intervention will be cost effective when compared to the control group.

Subject Inclusion/Exclusion Criteria—Subjects who are English or Spanish speaking males and females, 21 – 100 years of age will be eligible for the study. Each subject must have a clinic measured BP of   145 mm Hg systolic BP or   95 mm Hg diastolic BP at two previous clinic visits or one previous clinic visit and on the day of enrollment. Previous clinic visit BPs must be within the past 18 months and measured at least 2 weeks apart from each other. Subjects must live in a zip code that is scored as a 4–10 on the Rural-Urban Commuting Area (RUCA) Codes.

Subjects will be excluded if they are currently pregnant or planning to become pregnant in the next year, have an upper arm circumference over 50 cm (20 in), are prisoners or they are unable to provide own informed consent.

Study Design—The PharmText BP study was funded by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) in September 2019. The study is a prospective, randomized controlled trial conducted in primary care medical offices in Iowa.

The study will last 5 years and involve recruitment of 420 subjects from 4 clinics within 35 miles of University of Iowa Hospitals and Clinics. All subjects will live in areas that are considered rural by Rural-Urban Commuting Area Codes. The study aims to enroll at least 125 subjects (30%) who represent minority populations.

Research assistants (RA) employed by the study team will review the EMR for patients who are scheduled to visit each of the participating clinics. They will screen the record for the past 18 months to ensure that the eligibility criteria are met and that no exclusionary criteria exist. All subjects will have an initial screening/enrollment/baseline visit conducted by a RA, followed by a second visit at 6 months, and a final visit at 12 months with a RA. Each in-person visit will include research BP measurements (Omron HEM 907-XL), interviews, and medical record review. The LifeSource, UA-789AC Automatic BP Monitor with an extra large cuff will be used for obese subjects. Each research BP will be measured following standardized research technique.[32] Subjects are asked to refrain from smoking for 20 minutes prior to the BP measurement. The arm circumference will be measured and the appropriate cuff will be selected. Cuffs will be placed over a bare arm and subjects will be seated in a chair, with back supported, legs uncrossed with feet flat on the floor. The arm

will be placed on a desk at heart level with palm facing upward. Subjects will remain seated for at least 5 minutes prior to the BP measurement. The RA will palpate the brachial artery in the antecubital fossa and place the arrow of the cuff over the pulsation, ½ to 1 inch above the inner side of the elbow joint. The first BP measurement is determined but not used since the first reading is frequently higher than subsequent readings. Two more BP measurements are made 1 minute apart and these readings are averaged for the outcome measurement. If the 2nd and 3rd values are more than 4 mmHg apart, a 4th value is taken and the two nearest values are averaged.

In addition to the in-person visits, all subjects will be provided with a home BP cuff (Omron 5 Series), enrolled in our bi-directional text-messaging platform, WyBP, and asked to submit 7 morning and 7 evening BP measurements via text message following the baseline visit. Text message prompts asking for these BP measurements will stop after the 14 measurements have been submitted, or after 15 days, whichever occurs first. Following the home BP measurements, subjects will be randomized to either the pharmacist intervention arm or the texting-only control arm using a randomized block design with variable block sizes. Randomization will be stratified according to clinic. The methods for assigning subjects is described below. A timeline for the study procedures is provided in Table 1.

Once a potential subject has been identified, the RA will notify the appropriate medical staff that the patient is eligible for the study. If the medical staff confirms that the BP study is appropriate for the patient, they will inform the patient about the study during the appointment and ask for permission for the RA to explain the study further. If the patient is interested in learning more, the RA will either meet with the patient in the examination room or move the patient to a research-dedicated room, whichever has a lesser impact on clinic flow for that day. The screening questions will be reviewed again with the patient to ensure accuracy. If all eligibility criteria are confirmed and they wish to participate, the RA will describe the study, give the patient time to read the consent form, and answer any questions that the patient may have. If the patient agrees to participate, they will sign written informed consent.

Baseline Data Collection: After the consent form has been signed, the RA will continue with the other baseline activities. Together, the RA and subject will complete the demographic information that is collected and populate the study Data REDCap form.

Trained RAs will measure the subject's BP and document it on the Baseline Data REDCap form. Each research BP will be measured following standardized research technique.[32]

The RA will record all BP medications (and dosage) that the subject is taking at the baseline appointment in the REDCap BP Medication Form. This REDCap form is linked to the Master Drug Data Base Clinical Drugs BioPortal Ontology Service so that when a RA begins typing a medication name, an appropriate spelling of the drug and all of the available dosages will automatically populate. This will substantially reduce data entry mistakes. If a subject is taking more than one BP medication, the REDcap form will allow them to create multiple entries. The RA will use the updated Drug Codes for Antihypertensive Agents form

used in the CAPTION trial to help them determine which of the patient's medications are appropriate to record.[32]

The subject will then be enrolled in WyBP so that they can send home-BP measurements via text message. The RA will then educate the subject about the proper methods to measure BP using standardized technique as recommended by the American Heart Association.[11,38] The RA will then provide each subject with a BP device for their home use. All subjects will be asked to text their BP values for the first 14 days prior to randomization. These texted values will be obtained in both groups to establish a baseline and ensure that both the control and intervention groups receive at least some education about their BP. Once the subject has completed the baseline visit, they will be mailed $50.

Randomization and Subject Assignment: The biostatistician created randomization lists for each clinic site that were uploaded to a website created by our software developer (unblinded). Subjects are randomized in a 1:1 ratio and no stratification will be used. When the 14 day BP texting period has ended, a study pharmacist will log into this website using a unique username and password. They will input the Record ID and clinic site name for the subject they will then determine if the subject was randomized to the control or intervention group. The website will inform the pharmacist of group assignment and they will record that in the REDCap form. The website will store a log with a date and time stamp of which pharmacist randomized each subject to ensure that pharmacists do not intentionally or unintentionally alter the biostatistician's randomization in any way. This strategy should ensure that a relatively equal number of intervention and control subjects are enrolled at each clinic.

The Control Group: Once the research pharmacist is informed of the subject's group assignment, they will contact the subjects. For subjects randomized to the control group, the pharmacist will discuss their home BP measurements and only provide general education on hypertension. If the BP values are elevated on home monitoring, the pharmacist will advise the subject to make an appointment with their physician to address BP elevations. This will be the only pharmacist contact for the control group. While the 14-day baseline BP texting and the one-time pharmacist education may improve BP in the control group, we expect that the effect will be modest when compared to the intervention group.

The Intervention Group: Subjects randomized to the intervention group will receive a second set of subscriptions so that they can send their BP values for 3 days of each month for the remaining 11 months of study participation. These subscriptions will be created by our software developer (unblinded). He will check REDCap once per week to see which new subjects have been randomized to the intervention group. Then, he will create subscriptions for them to send 3 days of BPs each month beginning on the date that the subject was enrolled (i.e., if a subject was enrolled on August 15, they will submit their first day of BPs on the 15th, 16th, and 17th of each month throughout follow up). This strategy will allow the pharmacists to see a variety of BPs from different days of the week.

Two pharmacists who are certified hypertension clinicians designated by the American Society of Hypertension will provide the interventions. Pharmacists will provide telephone,

text message, and email support for intervention subjects and communicate with physicians via the electronic medical record (EMR). The pharmacists will have access to the intervention subjects' EMRs, all information collected by the research interns, and the home BP values that are submitted via text message. Pharmacists will employ a patient-centered approach to improve subject's BP by providing support, education, and recommendations for treatment intensification, as necessary. They will communicate with subjects via phone, text message, or email, based on subject preferences. They will not follow a specific protocol, but will base treatment decisions on current BP guidelines.[39] They may schedule more home BP measurements than the 3 days per month specified as the minimum in the research protocol.

The pharmacists will review the home BP values with the intervention subjects. If the home BP values are controlled, the pharmacist will continue to monitor home BP values. However, if the pharmacist identifies issues such as poor medication adherence, inability to afford medications or other issues, they will work with the subject and physician to optimize therapy, recommend lifestyle changes and/or reduce cost. If the pharmacist suspects white coat hypertension in which BP is only elevated in the clinic, they will make a recommendation to the physician to refer the subject to the University of Iowa ambulatory blood pressure service. Recommendations to physicians will primarily be made through the EMR to quickly improve BP control. Pharmacists will also recommend laboratory testing if indicated (e.g., serum potassium or creatinine).

If BP values are elevated, the pharmacist will assess medication adherence, ability to pay for medications and whether the regimen is optimal to control BP based on subject demographics and co-existing conditions. The pharmacist will communicate recommendations for lifestyle and other changes directly to the subject. If medication changes are needed, the pharmacist will communicate to the physician through the electronic medical record. The pharmacist may recommend increased medication dose, addition of a medication, discontinuation of a medication, or modification of the regimen to optimize therapy, improve convenience (e.g., fixed-dose combinations) or reduce cost.

All subjects in the intervention group will continue to have access to a study pharmacist for the entire 12 months of follow up. Additionally, they will be asked to continue measuring and texting BP values (1 morning, 1 evening) for 3 days each month throughout the 12-month follow up. The pharmacists will typically contact the subjects every 2 weeks while BP is not controlled. Once BP is controlled, they will continue monitoring the subject's records and home BPs and make contact at least every 2 months to support adherence and reassess BP control. All data obtained by the pharmacists will be recorded in REDCap forms.

6-Month Research Visit Procedures: All subjects will be asked to return to the clinic where they enrolled for a 6-Month appointment with a RA. To allow for flexibility with scheduling, 6-Month appointments will be allowed to occur anytime within a window between 5 months and 7 months after the enrollment date. This BP value will be the outcome research BP value. If a subject is not able to make it to the clinic during this window, but does want to come in after the 7 month date, this will be allowed and all data

will be collected, however, it will not be counted in the 6-month outcome and the 6-month outcome will be considered missing. In this case, a note will be placed in the subject's record and these data may not be used in analyses.

At the 6-Month appointment, the RA will collect the research BP values, any BP medications that the subject is currently taking, the last 3 BP values that were recorded by the subject's home BP cuff, and test the home BP cuff for accuracy. If the home BP cuff appears to be measuring inaccurately, it will be replaced. The subject will be sent another $50 compensation check. All of the procedures outlined at baseline will be followed again.

12-Month Research Visit Procedures: All subjects will be asked to return to the clinic for a 12-Month appointment with a RA. To allow for flexibility with scheduling, 12-Month appointments will be allowed to occur anytime between 11 months and 13 months after the enrollment date. If a subject is not able to make it to the clinic during this window, these data will be missing.

At the 12-Month appointment, the RA will collect the research BP values, any BP medications that the subject is currently taking, a 12-Month Exit Survey asking for the subject's feedback about the study, and send another $50 compensation check. All of the procedures outlined at baseline will be followed again. Subjects will also be asked about any hospitalizations or emergency room visits that occurred over the 12-month follow up period, especially those that occurred outside of the University of Iowa system.

Additionally, the research team will conduct a 12-Month Medical Record Review for each subject. This chart review will occur separately from the 12-Month visit and will not require any effort on the part of the subject. A member of the research team will screen the subject's medical record for all clinic/quick care visits (documenting reason), any emergency room visits (documenting reason), and any hospitalizations (documenting reason and length of stay). These data will be recorded on the REDCap forms.

Study Outcomes—The study will have one primary outcome and five secondary outcome measures for the three specific aims. The primary outcome is the mean difference in systolic BP (SBP) 12 months between the control and the intervention group. The secondary outcomes are mean differences SBP at 6 months and the mean difference in diastolic BP (DBP) at 6 and12 months, the number of medication changes as a measure of treatment intensification, and the additional cost of the intervention.

Aim 1: Determine if our intervention leads to decreases in SBP.

Our working hypothesis is that there will be lower mean SBP among the pharmacist-intervention group than among controls. The primary outcome measure for Aim 1 will be the difference in mean SBP between the control and intervention groups at 12 months.

Aim 2: Determine if our intervention leads to intensification of therapy.

Our working hypothesis is that there will be a greater number of medication changes in the intervention group compared to the control group. We will count the number of medication

changes (dose increased, dose decreased, drug stopped, drug started) during the 12 months following the start of the intervention. Each modification will be counted as one change. The total number of medication changes will be the primary outcome measure for Aim 2. In addition, we will determine the number of pharmacist recommendations that were accepted by physicians. These are process measures: we found in our previous studies that BP improvement was primarily related to medication changes. We are assuming that changes are a sign of close monitoring. Indeed, we have used this measure previously. However, we realize that not all medication changes are equal, and thus we will record both medication trends and final treatment for each subject.

Aim 3: Determine the cost effectiveness of the intervention.

Our working hypothesis is that our intervention will be cost effective when compared to the control group. In addition, we will compare these results to previous pharmacist interventions. Because much pharmacist time is spent on non-direct subject care activities, we are convinced that our bi-directional texting approach will be both labor and cost saving. We will compute the incremental cost effectiveness ratio (ICER) using the total costs of doctor visits, pharmacist time, medications and medication changes during the 12 months of the trial.[33] The ICER will be the difference between the control and intervention groups in average total cost divided by the difference in average decrease of SBP and DBP. The ICER will be expressed in the dollars per mmHg reduction in BP and will be the primary outcome in this Aim.

Statistical Design and Power

Aim 1 Analysis: The analysis will be done on an intent-to-treat basis regardless of the number of reported BP readings or the number of pharmacist interactions with the subject. Our primary outcome will be a comparison of mean SBP values at 12 months. We will use linear mixed effects models (LMMs) with BP as the outcome. We will explore the timing of the change by also evaluating BP at 6 months. To test the intervention, we will include time (baseline, 6 month, 12 month) as a fixed effect factor and its interaction with treatment arm. We will use random effects for clinic and physician nested within clinic to account for practice heterogeneity between clinics and providers. Temporal correlation will be accounted for by using an autoregressive error structure. This model will also be estimated for DBP.

Second, transition to control for subjects who had uncontrolled BP at their baseline visit will be modeled using a generalized linear mixed effects model (GLMM) based on the Bernoulli distribution with a logistic link. We will test the intervention by including a fixed-effects term for the treatment assignment (intervention versus control). As before, we will include random effects for provider nested within clinic.

Third, we will assess the duration of the change by modeling the odds of having controlled BP at 12 months among those uncontrolled at baseline but controlled at 6 months using a GLMM similar to that described above. All three models will contain any covariates (e.g., age, sex) that were not sufficiently addressed through randomization. In all analyses, the

random effects incorporated into the final model will be chosen via Akaike Information Criterion with correction for small sample sizes (AICc).

Power: Based on prior work with the CAPTION trial, we expect a mean difference of 5.7 mmHg between the groups with an expected pooled standard deviation of 17.9 with equal sized groups.[32] We will evaluate the two independent samples with a t-test with two-sided type I error rate of 5%. In order to have 85% power to detect a difference of 5.7 mmHg or larger decrease in SBP with a standard deviation of 17.9 mmHg, we would need 180 subjects per arm or 360 subjects total.

In preliminary work in the CAPTION trial, 13.4% of control subjects dropped out or were lost to follow-up. 14.0% of subjects dropped out of the intervention arm during the first 9 months. In order to retain power after 14% drop-out rates over 12 months, we will recruit 420 patients total. One planned interim analysis will be performed after the outcome data is received from the first 210 patients. The interim monitoring method of Lan and Demets will be used with the O'Brien Fleming spending function for the interim analyses. The sample size calculation is performed taking into account one interim analysis.

Aim 2 Analysis: The analysis will be done on an intent-to-treat basis regardless of the number of reported BPs or the number of pharmacist interactions with the subject. The outcome for this analysis will be the number of medication changes over 12 months in the control and intervention groups. We will use a GLMM based on the Poisson distribution with a log link function, and as in Aim 1 we will incorporate random effects for clinic and physician nested within clinic to account for practice heterogeneity between clinics and providers. As the observed treatment effects in those clusters are likely to be non-independent, we will include both random intercept and random treatment effect for the intervention factor. The random effects incorporated into the final model will be chosen via AICc.

Power: Based on existing work, we expect an average of 4.9 medication changes in the intervention group (SD = 5.1) and an average of 1.1 medication changes in the control group (SD = 1.6). We would expect a difference of 3.8 changes per year with a pooled standard deviation of 3.8 (effect size of 1). Under these assumptions, with the sample size of 180 patients per group after 14% drop-out rate, the power of the two independent samples t-test with a two-sided type I error rate of 0.05 will be more than 95%.

Aim 3 Analysis: The analysis will be performed on an intent-to-treat basis regardless of the number of reported BP measurements or the number of pharmacist interactions with the subject. The perspective of this cost analysis is society in general. For each subject encounter, pharmacists will record the number of minutes spent in the following activities: medical record review, consultation, subject assessment, ordering medications, medical education, lifestyle education, BP measurement education, making recommendations, and documentation in the medical record. Pharmacist costs will be estimated by multiplying the time spent by their compensation rate. Costs for clinic visits will be obtained from the university. Utilization measures will be converted to costs per subject using the Medicare fee schedule for visits. Pharmacist and physician salaries will be obtained from the Bureau of

Labor Statistics.[33] The average wholesale drug cost for prescription medications will be obtained from Lexicomp Online (https://online.lexi.com). Generic prices will be used when available. The drug cost per prescription for each subject will be calculated by multiplying the average wholesale price (AWP) by frequency and dose.

We assume that subjects in the intervention and control groups will have similar characteristics. However, if there are significant differences between the subjects in these groups, costs will be predicted using a multivariate generalized linear model with a gamma family and a log link to control for these differences.

We will determine the cost of the intervention by subtracting the average total cost (pharmacist, clinic, and drugs) for the intervention group from the average total costs for the control group. The ICER is calculated as the cost differential from the intervention divided by the outcome differential from the intervention. Our outcome for this analysis will be average decrease in SBP, and the outcome differential will be the average decrease in SBP for the control group minus the average decrease in SBP for the intervention group. The result of this analysis will be an ICER, which gives the additional cost of the intervention per mm Hg of SBP decrease.

We will conduct at least two sensitivity analyses. Because the drug costs (average wholesale prices) from Lexicomp often overstate the actual prices paid by insurance companies and subjects, we will adjust our drug costs and re-estimate our cost-effectiveness analysis. Specifically, the Kaiser Family Foundation estimates that average wholesale prices are, on average 17% higher than weighted acquisition costs for brand-name drugs, and 80% higher than generic drugs. In addition, pharmacist time can be represented by either wages per hour, or the amount that pharmacists can bill Medicare for each activity. We will consider both ways to measure the value of pharmacists' time.

Summary—This study will evaluate an accessible, inexpensive, team-based, m-health approach to aid in the treatment of patients with a disease that affects 72 million Americans, especially from rural areas. The successful completion of our proposed aims will provide a more effective approach to help monitor and titrate treatment for hypertension. Finally, our results can help inform other team-based, m-health work by determining how to integrate remote home health monitoring data into clinical decision-making to improve outcomes using team-based care.

Acknowledgments

References

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics––2011 update: a report from the American Heart Association. Circulation. 2011;123:e18–e209. [PubMed: 21160056]

2. Muntner P, Carey RM, Gidding S, et al. Potential U.S. Population Impact of the 2017 ACC/AHA High Blood Pressure Guideline. J Am Coll Cardiol. 2018;71:109–118. [PubMed: 29146532]

3. Bale B Optimizing hypertension management in underserved rural populations. J Natl Med Assoc. 2010;102:10–17. [PubMed: 20158131]

4. Mainous AG 3rd, King DE, Garr DR, Pearson WS. Race, rural residence, and control of diabetes and hypertension. Ann Fam Med. 2004;2:563–568. [PubMed: 15576542]

5. Rose AJ, Berlowitz DR, Orner MB, Kressin NR. Understanding Uncontrolled Hypertension: Is It the Patient or the Provider? J Clin Hypertens. 2007;9:937–943.

6. Oliveria SA, Lapuerta P, McCarthy BD, L'Italien GJ, Berlowitz DR, Asch SM. Physician-related barriers to the effective management of uncontrolled hypertension. Arch Intern Med. 2002;162:413–420. [PubMed: 11863473]

7. Hyman DJ, Pavlik VN. Characteristics of patients with uncontrolled hypertension in the United States. N Engl J Med. 2001;345:479–486. [PubMed: 11519501]

8. Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension? JAMA. 1988;259:225–228. [PubMed: 3336140]

9. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Porcellati C. Prognostic significance of the white coat effect. Hypertension. 1997;29:1218–1224. [PubMed: 9180621]

10. Mancia G, Bertinieri G, Grassi G, et al. Effects of blood-pressure measurement by the doctor on patient's blood pressure and heart rate. Lancet. 1983;2:695–698. [PubMed: 6136837]

11. Pickering TG, White WB. ASH Position Paper: Home and ambulatory blood pressure monitoring. When and how to use self (home) and ambulatory blood pressure monitoring. J Clin Hypertens. 2008;10:850–855.

12. Pickering TG, Miller NH, Ogedegbe G, et al. Call to action on use and reimbursement for home blood pressure monitoring: a joint scientific statement from the American Heart Association, American Society Of Hypertension, and Preventive Cardiovascular Nurses Association. Hypertension. 2008;52:10–29. [PubMed: 18497370]

13. Ohkubo T, Imai Y, Tsuji I, et al. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. J Hypertens. 1998;16:971–975. [PubMed: 9794737]

14. Bobrie G, Genes N, Vaur L, et al. Is "isolated home" hypertension as opposed to "isolated office" hypertension a sign of greater cardiovascular risk? Arch Intern Med. 2001;161:2205–2211. [PubMed: 11575977]

15. Asayama K, Ohkubo T, Kikuya M, et al. Use of 2003 European Society of Hypertension-European Society of Cardiology guidelines for predicting stroke using self-measured blood pressure at home: the Ohasama study. Eur Heart J. 2005;26:2026–2031. [PubMed: 15917279]

16. Mule G, Caimi G, Cottone S, et al. Value of home blood pressures as predictor of target organ damage in mild arterial hypertension. J Cardiovasc Risk. 2002;9:123–129. [PubMed: 12006920]

17. Tsunoda S, Kawano Y, Horio T, Okuda N, Takishita S. Relationship between home blood pressure and longitudinal changes in target organ damage in treated hypertensive patients. Hypertens Res. 2002;25:167–173. [PubMed: 12047030]

18. McManus RJ, Mant J, Roalfe A, et al. Targets and self monitoring in hypertension: randomised controlled trial and cost effectiveness analysis. BMJ. 2005;331:493. [PubMed: 16115830]

19. Mallick S, Kanthety R, Rahman M. Home blood pressure monitoring in clinical practice: a review. Am J Med. 2009;122:803–810. [PubMed: 19699371]

20. Reed SD, Li Y, Oddone EZ, et al. Economic evaluation of home blood pressure monitoring with or without telephonic behavioral self-management in patients with hypertension. Am J Hypertens. 2010;23:142–148. [PubMed: 19927132]

21. Stuckey M, Fulkerson R, Read E, et al. Remote monitoring technologies for the prevention of metabolic syndrome: the Diabetes and Technology for Increased Activity (DaTA) study. J Diabetes Sci Technol. 2011;5:936–944. [PubMed: 21880237]

22. Zheng H, Nugent C, McCullagh P, et al. Smart self management: assistive technology to support people with chronic disease. J Telemed Telecare. 2010;16:224–227. [PubMed: 20511581]

23. de Jongh T, Gurol-Urganci I, Vodopivec-Jamsek V, Car J, Atun R. Mobile phone messaging for facilitating self-management of long-term illnesses. Cochrane Database Syst Rev. 2012;12:CD007459. [PubMed: 23235644]

24. Franklin VL, Waller A, Pagliari C, Greene SA. A randomized controlled trial of Sweet Talk, a text-messaging system to support young people with diabetes. Diabet Med. 2006;23:1332–1338. [PubMed: 17116184]

25. Polgreen LA, Anthony C, Carr L, et al. The effect of automated text messaging and goal setting on pedometer adherence and physical activity in patients with diabetes: A randomized controlled trial. PLoS One. 2018;13:e0195797. [PubMed: 29718931]

26. Anthony CA, Polgreen LA, Chounramany J, et al. Outpatient blood pressure monitoring using bi-directional text messaging. J Am Soc Hypertens. 2015; 9:375–81. [PubMed: 25771023]

27. Carter BL, Bergus GR, Dawson JD, et al. A Cluster Randomized Trial to Evaluate Physician/Pharmacist Collaboration to Improve Blood Pressure Control. J Clin Hypertens. 2008;10:260–271.

28. Carter BL, Zillich AJ, Elliott WJ. How pharmacists can assist physicians with controlling blood pressure. J Clin Hypertens. 2003;5:31–37.

29. Von Muenster SJ, Carter BL, Weber CA, et al. Description of pharmacist interventions during physician-pharmacist co-management of hypertension. Pharm World Sci. 2008;30:128–135. [PubMed: 17710561]

30. Carter BL, Clarke W, Ardery G, et al. A cluster-randomized effectiveness trial of a physician-pharmacist collaborative model to improve blood pressure control. Circ Cardiovasc Qual Outcomes. 2010;3:418–423. [PubMed: 20647575]

31. Carter BL, Ardery G, Dawson JD, et al. Physician and pharmacist collaboration to improve blood pressure control. Arch Intern Med. 2009;169:1996–2002. [PubMed: 19933962]

32. Carter BL, Coffey CS, Ardery G, et al. Cluster-randomized trial of a physician/pharmacist collaborative model to improve blood pressure control. Circ Cardiovasc Qual Outcomes. 2015;8:235–243. [PubMed: 25805647]

33. Polgreen LA, Han J, Carter BL, et al. Cost-Effectiveness of a Physician-Pharmacist Collaboration Intervention to Improve Blood Pressure Control. Hypertension. 2015;66:1145–1151. [PubMed: 26527048]

34. Kulchaitanaroaj P, Brooks JM, Ardery G, Newman D, Carter BL. Incremental costs associated with physician and pharmacist collaboration to improve blood pressure control. Pharmacotherapy. 2012;32:772–780. [PubMed: 23307525]

35. Carter BL. Primary Care Physician-Pharmacist Collaborative Care Model: Strategies for Implementation. Pharmacotherapy. 2016;36:363–373. [PubMed: 26931738]

36. Carter BL, Levy BT, Gryzlak B, et al. A centralized cardiovascular risk service to improve guideline adherence in private primary care offices. Contemp Clin Trials. 2015;43:25–32. [PubMed: 25952471]

37. Carter BL, Levy B, Gryzlak B, et al. Cluster-Randomized Trial to Evaluate a Centralized Clinical Pharmacy Service in Private Family Medicine Offices. Circ Cardiovasc Qual Outcomes. 2018;11:e004188. [PubMed: 29884657]

38. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension. 2005;45:142–161. [PubMed: 15611362]

39. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018;138:e484–e594. [PubMed: 30354654]

Table 1:

Study Procedures Timeline

Time	Activity	Control Group	Intervention Group
Day 0	Screening Consent Baseline Appointment	X	X
Day 1 – Days 7–15	Home BP measured and returned via text message	X	X
Days 7–15 – Day 18	Subjects randomized; Pharmacists review home BP values, contact subjects	X	X
Day 18 – 6 Months	Subjects text home BP values 3 days per month Pharmacists monitor BP, adjust treatment as needed		X
6 Months	Subjects return to clinic for appointment	X	X
6 Months – 12 Months	Subjects text home BP values 3 days per month Pharmacists monitor BP, adjust treatment as needed		X
12 Months	Subjects return to clinic for appointment	X	X