A Cluster-Randomized Effectiveness Trial of a Physician-Pharmacist Collaborative Model to Improve Blood Pressure Control

Barry L. Carter, PharmD; William Clarke, PhD; Gail Ardery, PhD; Cynthia A. Weber, PharmD; Paul A. James, MD; Mark Vander Weg, PhD; Elizabeth A. Chrischilles, PhD; Thomas Vaughn, PhD; Brent M. Egan, MD; on behalf of the Collaboration Among Pharmacists Physicians To Improve Outcomes Now (CAPTION) Trial Investigators*

Abstract—Numerous studies have demonstrated the value of team-based care to improve blood pressure (BP) control, but there is limited information on whether these models would be adopted in diverse populations. The purpose of this study was to evaluate whether a collaborative model between physicians and pharmacists can improve BP control in multiple primary care medical offices with diverse geographic and patient characteristics and whether long-term BP control can be sustained. This study is a randomized prospective trial in 27 primary care offices first stratified by the percentage of underrepresented minorities and the level of clinical pharmacy services within the office. Each office is then randomized to either a 9- or 24-month intervention or a control group. Patients will be enrolled in this study until 2012. The results of this study should provide information on whether this model can be implemented in large numbers of diverse offices, if it is effective in diverse populations, and whether BP control can be sustained long term.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00935077.

(Circ Cardiovasc Qual Outcomes. 2010;3:418-423.)

Key Words: hypertension ■ clinical trial ■ pharmacists ■ blood pressure

Blood pressure (BP) control and guideline adherence are low in the United States, with the lowest rates among racial minorities and people of lower socioeconomic status. The reasons for poor control include patient, physician, and structural factors, but suboptimal treatment regimens and clinical inertia are common causes.

The current debate on healthcare reform frequently notes the need to develop the medical home for the delivery of primary care. The physician-pharmacist collaborative model (PPCM) is consistent with the medical home in which the patient has an ongoing relationship with a personal physician who delegates responsibility to the pharmacist to assist with achieving BP control. Use of this model has achieved high BP control rates in 2 studies, primarily through resolving clinical inertia. In 1 study (n=179), patients from 2 intervention clinics achieved 89% BP control compared to 54% in 2 control clinics. The mean difference in systolic BP (SBP) was 8.7 mm Hg (95% CI, 4.4 to 12.9 mm Hg). In a second study, among 402 patients from 6 medical offices who achieved BP control, 62.9% were from intervention clinics compared to 29.9% in the control group (odds ratio, 3.2; 95% CI, 2.0 to 5.1; P<0.01). A systematic review of controlled trials of team-based care found significant improvements in BP control. Other trials were small efficacy studies, did not use a standardized research-measured BP, did not use intention-to-treat analysis, or included few patients from minority groups.

The present study is designed to determine whether PPCM will be adopted and implemented in diverse medical offices with large minority populations and whether BP control deteriorates after discontinuation of a 9-month intervention compared to a 24-month intervention. This effectiveness, or pragmatic trial, will evaluate variation and provider attitudes to adoption of PPCM following the Theory of Planned Behavior.

Methods

Study Design

We will conduct a 5-year prospective, cluster-randomized, multi-center clinical trial in 27 clinics from 13 states in the United States. All clinics employ clinical pharmacists, and 47% of the patients are underrepresented minorities. Clinics were stratified and then randomized to a 9-month PPCM arm (n=219), 24-month PPCM arm (n=219), or control group (n=219) that also includes a distracter.
intervention for asthma (Figure 1) (see online-only Data Supplement). A study coordinator in each clinic will enroll 24 subjects with hypertension who will be followed for 24 months (n = 648). In addition, we will perform a retrospective chart review for another 486 subjects (18 per clinic) with hypertension that will serve as an observational cohort (pure control). The purpose of the observational cohort is to determine whether the intervention diffuses into the rest of the practice, even for patients not enrolled in the trial.

The primary hypothesis for the study is that BP control at 9 months will be significantly greater in patients from clinics randomized to the 2 intervention groups compared to the control group. The secondary aims will compare mean BP among study arms and in minority groups and patients from lower socioeconomic groups and will evaluate the association between provider attitudes to deliver PPCM by mean BP and BP control rates.

Study Sites
The study will be conducted in National Interdisciplinary Primary Care Practice Based Research Network medical offices. Features of the medical offices were previously published and showed that 85.4% are located in family medicine residencies, 10.4% in internal medicine residencies, and 4.2% in faculty practices.12 Sixty-seven percent of the offices used electronic medical records when surveyed in 2006.12 The mean number of providers were 10 attending physicians, 23 resident physicians, 6 nurses, 5 medical assistants, 0.4 nurse practitioners, 0.4 physician assistants, 0.7 psychologists, 0.3 social workers, 0.4 dieticians, and 0.4 patient educators.

Clinical Pharmacists
Only 2 of the 27 offices have pharmacies. All 27 offices have clinical pharmacists (mean, 1.9 per clinic) who are faculty in the office and are employed primarily to provide education for physicians and patient care. They spend an average of 2 days per week (0.4 clinical full-time equivalents) in direct patient care and cover clinic hours an average of 75% of the time. Most have a PharmD degree (96%) and a postdoctoral residency or fellowship (78%), and 43% are board-certified pharmacotherapy specialists. Seventy percent of clinics have had clinical pharmacy services for >5 years.12

Patient revenue is used to cover pharmacist salaries in 22% of practices.

Patient Population
The mean racial/ethnic population of these clinics is 26% blacks and 21% Hispanics. We expect to recruit at least 40% of patients from these minority groups. Payers include Medicaid or government assistance (28%), Medicare (22%), private insurance (34%), no insurance (12%), and other (4%).10

Clinic Stratification
We used a validated survey instrument13 to score clinical pharmacy services based on the extent of direct patient care services provided in the medical office. Clinic scores fell into 2 distinct levels similar to previous findings.13,14 Clinics were stratified based on the pharmacy structure scores (low and high) and percentage of minority patients (<44% versus ≥44%).

Data and Safety Monitoring
A data and safety monitoring board was appointed following National Heart, Lung, and Blood Institute guidelines and includes internationally recognized experts in hypertension and team-based care models. The data and safety monitoring board will meet at least once a year to review the rate of patient recruitment, evaluate the safety of the study, and make recommendations to the investigators to improve the conduct of the study.

Intervention Training
Providers in clinics randomized to the intervention arms received training from 1 investigator (B.L.C.) on BP guidelines15,16 strategies to overcome clinical inertia and suggested methods of communication between physicians and pharmacists. Eight regional training sessions were conducted between September 2009 and January 2010 and were delivered to 1 pharmacist and 1 physician investigator from each medical office in train-the-trainer sessions. Separate training programs occurred for providers from clinics randomized to either the BP intervention or usual care (alternative asthma intervention). The trainers also included a physician-pharmacist team from 1
community-based family medicine program that successfully implemented the intervention model in a previous study. These individuals encouraged physicians to improve participation of providers; instilled confidence and enthusiasm; addressed strategies to overcome barriers to BP control; and discussed methods to effectively overcome clinical inertia, adverse drug reactions, and poor medication adherence.

One to 3 months after the train-the-trainer session, each physician-pharmacist pair delivered the same training program for all providers in their own clinic. Pharmacists in clinics randomized to the 9-month BP intervention will provide training sessions with their physicians twice a year for 2 years, whereas those randomized to the 24-month intervention will provide training sessions for 3 years.

Following the initial training sessions, 2 investigators will conduct a telephone conference with each physician-pharmacist pair to discuss questions or issues that the providers were not able to answer regarding the intervention. The investigators will continue to support all offices quarterly the first year, and twice a year in year 2 and year 3 (for clinics randomized to the long-term BP intervention).

**Study Coordinator Training**

A study coordinator (registered nurse, licensed practical nurse, or medical assistant) employed in each medical office will enroll patients, collect study data, and abstract medical records for the observational cohort. All coordinators completed human subjects education and were trained in Iowa City, Iowa, in December 2009 on the Web-based case report forms that will be used on the secure Web site operated by the study data coordinating center.

One investigator (A.A.) provided training and certification on proper BP measurement technique using an automated Omron HEM 907-XL device. Study monitors from the data coordinating center will make site visits to each medical office at least annually to evaluate data fidelity and will recertify each research nurse in BP measurement at each monitoring visit.

**Pharmacist Intervention**

The suggested PPCM model will specify recommended visit frequency and activities. However, because this is an effectiveness study, strict adherence to the model and intervention schedule will not be required. Instead, we will encourage the use of the model and the time required to complete various steps in the study visit.

The therapeutic strategies will be based on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, and the BP goal will be <140/90 mm Hg for patients with uncomplicated hypertension and <130/80 mm Hg for patients with diabetes or chronic kidney disease. The study has been designed to minimize selection bias. Potential patients will be identified from a list generated from each clinic and then randomized for inclusion by the data coordinating center. Study coordinators will receive the ordered lists and then review the medical records in this order and invite a patient to participate if the study criteria are met. The study coordinator will continue this process until 24 patients are consented and enrolled. We will record the reasons patients declined, did not meet criteria, or dropped from the study in order to evaluate the generalizability of the selected subjects to the entire population.

If a potential subject only speaks Spanish, we will use bilingual coordinators or translators within the office to explain the study and assist with obtaining informed consent. The consent form and scripts have been translated into Spanish. All patient questionnaires are scripted to ensure consistent administration.

The study coordinator will measure BP in the sitting position after appropriate rest and at baseline, 6, 9, 12, 18, and 24 months. The study coordinator will collect the following at baseline: height, weight, and pulse; the duration of hypertension; presence of other cardiovascular risk factors, symptoms, and adverse drug reactions; medication adherence; sociodemographics; comorbidities; current medications and dose, how the patient actually took the medication; and an evaluation of medication adherence using validated instruments. The timing of collection of these variables are shown in Table 1.

Patients enrolled in the control group will receive usual care from their physicians. Patients in intervention clinics will be referred to the pharmacist-pharmacist pair.

Study monitors from the data coordinating center will perform site visits to compare the completeness of the case report forms with the medical records and the Web-based database. Each site will be visited at least once a year to evaluate data fidelity.

**Observational Cohort (Pure Control Group)**

The purpose of the retrospective observational cohort will be to evaluate whether the effect of the intervention using our previous methods diffuses throughout the practice for patients not actively enrolled in the study. Once 24 patients have been enrolled into the prospective interventional study at a given site, the study coordinator will identify another 18 patients who meet the same inclusion criteria. Qualification in the retrospective observational...
We will evaluate and control for self-reported adherence at baseline, 9, and 24 months using a recently published strategy. We will use a symptom survey from our previous studies and evaluate symptoms among the 3 study arms at baseline, 9, and 24 months.

Costs will be assigned to each BP medication at baseline, 9, and 24 months. All clinic visits (including pharmacist), telephone follow-up, emergency department visits, hospitalizations, and laboratory procedures will have costs assigned, and the 3 groups will be Compared using methodologies previously described. Incremental costs as a function of differences in BP will be calculated at baseline, 9, and 24 months. These findings will be expressed as dollars per incremental reduction in BP (mm Hg). We will compare the costs associated with this intervention to that of other studies that have estimated the value of controlled BP to society.

Formative evaluations will be conducted with physicians, pharmacists, study coordinators, and office administrators once the study has been completed. A detailed description of the formative evaluations appears in the online supplement.

### Data Analysis

The primary end point is BP control at 9 months among study arms. Secondary end points will include (1) BP control and mean BP differences among groups at 12, 18, and 24 months; (2) between-group comparison of BP control and mean BP in patients from underrepresented minorities, education level, and household income; (3) medication intensification; (4) provider-level variables as predictors of mean BP and BP control; and (5) pharmacist-level variables (billing and collections) as predictors of mean BP and BP control. A separate analysis for items 1 to 5 will be conducted across the 3 arms for patients in the observational cohort.

Sample size calculations assumed that there will be 1:1:1 randomization to 2 intervention arms and 1 control arm and that the primary comparison is that of the BP control rate in the 2 intervention arms combined with the BP control rate in the control arm. Effect sizes of 25% versus 60% at 6 months were determined from our previous study. Sample sizes were computed to ensure that there would be a sufficient number of minority group patients for a 5%-level test (alpha) of proportions to achieve 90% power to detect a difference of 60% in the combined intervention arms versus 35% in the control arm using the method described by Donner and Klar. The method computes a sample size for independent observations then inflates the sample size 15% to account for the correlation among patients in the same clinic. Briefly, the sample size calculations inflate the number of subjects needed for independent samples by a multiplier factor to account for the correlation among subjects in the same clinic. The required sample size is \( n = m^* (1 + (n-1)c)* \), where \( m \) is the sample size computed assuming independent samples, \( n \) is the number of subjects in each clinic, \( x \) is an estimate of the dependence among subjects in the same clinic, and \( n^* \) is the sample size adjusted to take into account the correlation among subjects in a clinic. For continuous responses (SBP and DBP), likelihood-based mixed models with random patient effects will be fit in SAS Proc Mixed to incorporate all available data from baseline through 9 months in an intention-to-treat analysis. For BP control, a generalized estimating equation model using the binomial distribution and the logit link was fit in SAS Proc Genmod, accommodating the correlations across patients. This analysis accounts for the correlation among subjects from the same clinical center. The model will contain a term for treatment assignment (PPCM versus control), baseline SBP, baseline DBP, and age. The analysis will provide an estimate and 95% CI for the odds ratio of achieving BP control in the combined intervention arms compared to the control arm adjusted for any differences in baseline BP and age. These calculations suggested that we would need to enroll 648 subjects in 27 clinics. The primary comparison between the 3 groups at 9 months will have a minimal detectable difference in BP control of 35% versus 50% with an alpha of 5% and 90% power and 35% versus 48% with 80% power. We assumed for approximately 40% of subjects in the minority group that the minimal detectable difference for either of the 2 minority subgroups (black, Hispanic) would be 35% versus 60% with 90% power and 35% versus 58% with 80% power. The model will contain a term for treatment assignment (intervention...
versus control), baseline BP, and age. If a patient’s BP control status is missing at 9 months, that subject will be considered to have uncontrolled BP. We will perform a sensitivity analysis to determine the potential dependence of the results of the primary analysis on the missing values, which will include using multiple methods to impute the missing values to determine the effect of the choice of imputation method on the results. Methods will include worst case (patients with missing BP not controlled in the intervention group, but patients with missing data have controlled BP in the control group), best case (missing assumed controlled in the intervention group and assumed not controlled in the control group), random assignment of outcome, and use of regression methods to predict the outcome for each subject with a missing value based on his or her baseline values of known predictors of BP. Because randomization is by center, there may be differences among the treatment groups with respect to other potential predictors of outcomes, including patient-, physician-, or clinic-specific factors. Although the primary analysis will include only baseline BP and age, we will explore the effects of other potential covariates in a separate secondary analysis, including sex, race, education, insurance status, household income, marital status, smoking status, alcohol intake, body mass index, number of coexisting conditions at baseline, number of baseline antihypertensive medications, baseline medication adherence, and total number of clinic visits. We will first determine whether there are significant (clinical or statistical) differences among the treatment groups with respect to any of these potential covariates. Second, we will repeat the generalized estimating equation analysis but with the additional covariates identified in the previous step. To avoid multicollinearity, we will first fit univariate models to identify covariates that appear to have some influence on the effect of the treatment and then include those covariates whose univariate probability values are ≤0.2 in multivariate models. These analyses will provide estimates of the effect size for the intervention adjusted for differences among the treatment groups with respect to important potential confounders.

Discussion

The Collaboration Among Pharmacists Physicians To Improve Outcomes Now (CAPTION) trial will be the first study of team-based care to be conducted in a national practice-based research network. The study is designed to address several aspects of the National Institutes of Health Roadmap and the National Heart, Lung, and Blood Institute strategic plan. This study will implement a proven team-based care strategy to improve the use of BP guidelines and BP control, thus translating basic and clinical research to the community. The National Institutes of Health has a strong desire to implement models that work, overcome provider and health system barriers, and sustain the effect of interventions so that they can eventually be scaled up for broader use. The CAPTION trial is designed to address these goals and to determine how to implement and sustain the team-based intervention in a very diverse group of clinics and patients. If this model yields a 10 mm Hg difference in SBP and can be implemented broadly in US clinics that currently use clinical pharmacists, there would be 20% fewer coronary deaths and 25% fewer stroke deaths.29 The current healthcare reform debate has focused on the medical home as 1 strategy to improve care,3 1 component of which is team-based care. The CAPTION trial will help to determine how effective team-based care may be for controlling BP in diverse medical offices and for underrepresented minorities.

Conclusions

The CAPTION study will have patients enrolled through 2012. The results of this study should provide information on barriers and facilitators to implementing this PPCM to improve BP control and on whether the intervention is effective in underrepresented minorities.

Appendix

Site investigators for the CAPTION study: Renu Singh, PharmD, Marie Williams, MA, and Carlos Rojas, MD, Fourth & Lewis Family Medicine, San Diego, Calif; Grace Kuo, PharmD, MPH, Nathan Painter, PharmD, Alita Newsome, MA, and Dustin Lillie, MD, Scripps Ranch Family Medicine, San Diego, Calif; Eric Jackson, PharmD, Alan Cementina, MD, and Evelyn Pianko, MA, Family Medicine Center at Asylum Hill, Hartford, Conn; John Guns, PharmD, Steven Smith, PharmD, Delores Buffington, RN, and Karen Hall, MD, University of Florida Family Practice, Gainesville, Fla; Eduardo Gonzalez, MD, Kevin Sneed, PharmD, H. James Brownlee Jr, MD, and Kymia Love Jackson, BBA, University of South Florida Department of Family Medicine, Tampa, Fla; Mark Jones, PharmD, Katherine M. Brash, LPN, and Andrew Andresen, MD, Genesis Family Medical Center, Davenport, Iowa; Coralynn Trewet, PharmD, Mary Frockhol, BS, CHES, and Larry Severidt, MD, Broadlawns Family Health Center, Des Moines, Iowa; James Hoepps, PharmD, Pam Trenkamp, RN, CCRP, and Jim Pook, MD, Northeast Iowa Family Practice Center, Waterloo, Iowa; Brandon Mickelsen, DO, Rex Force, PharmD, John Holmes, PharmD, and Mary Macdonald, LPN, Pocatello Family Medicine Clinic, Pocatello, Idaho; Jennifer Goldman-Lexine, PharmD, Sandy Coughano, MA, and Greg Sawin, MD, Tufts University Family Medicine, Malden, Mass; Angela Wissinkewski, PharmD, Meredith Snyder, BA, MPH, and Jeanette Figueroa, MD, Jefferson Family Medicine Clinic, Buffalo, NY; Timothy Ives, PharmD, Betty Bryant-Shilliday, PharmD, and Robb Malone, PharmD, University of North Carolina Enhanced Care Clinic, Chapel Hill, NC; Phillip Rodgers, PharmD, Tracie Rotheroth-Christian, PharmD, Lynn Bowby, MD, and Angela Braswell, LPN, Duke University Medical Center, Durham, NC; Rebecca Edwards, PharmD, Geraldine Zurek, MEd, CCRP, and David Townsend, MD, Northwest Area Health Education Center, Wake Forest University, Winston-Salem, NC; Patricia Klatt, PharmD, Roberta Farrah, PharmD, Sandra Saudereisen, MD, and M. Maggie Folan, PhD, University of Pittsburgh Medical Center, St Margaret Family Medicine, Pittsburg, PA; Kelly Ragucci, PharmD, Sarah Shrader, PharmD, Allison McCutcheon, MPH, and Eric Matheson, MD, MS, Medical University of South Carolina, Department of Family Medicine Clinic, Charleston, SC; Lori Dickerson, PharmD, Allison McCutcheon, MPH, and Peter Cerek, MD, MS, Trident Family Medicine, Charleston, SC; Adrienne Z. Akes, PharmD, I.S. Simon, MD, and Lynda Lowe, RN, Spartanburg Family Medicine, Spartanburg, SC; Eric MacLaughlin, PharmD, Debbie Hermes, LPN, and Rodney Young, MD, Texas Tech Center for Community and Family Medicine, Amarillo, Tex; Debra Lopez, PharmD, Patricia Kaplan, MA, and Terrell Benold, MD, Blackstock Family Practice, Austin, Tex; Jen Sias, PharmD, Ulysses Urquidi, MD, and Jose Rodriguez, CPHT, CCRP, Texas Tech Community Partnership Clinics, El Paso, Tex; Margie Perez-Padilla, PharmD, and Jose Luna Jr, MD, University of Texas, Centro San Vicente, El Paso, Tex; Julie Adkison, PharmD, Michael Crouch, MD, and Dianna Torres, MA, Mission Family Practice, Mission, Tex; Land, Tex; Oralia Bazaldua, PharmD, John Tovar, PharmD, Bryan Bayles, PhD, Ramin Poursani, MD, and Mark Nadeau, MS, University of Texas Health Science Center, San Antonio, Tex; Carrie Stoltenberg, RPh, Jody Pankow, BSN, RN, and Louis Sanner, MD, Northeast Family Practice, Madison, Wis; Connie Kraus, PharmD, Anna Legreid Dopp, PharmD, Terri Carufel-Wert, RN, and Beth Potter, MD, Wingra Family Medical Center, Madison, Wis; and Elizabeth Musil, PharmD, Victoria Mertins, RN, and Jesse DeGroat, MD, Wheaton Franciscan Medical Group, Racine, Wis.

Acknowledgments

We thank the Executive Committee of the National Interdisciplinary Primary Care Practice-Based Research Network who assisted with the development of this network and the study design: John Guns,
Sources of Funding
This study is supported by the National Heart, Lung, and Blood Institute, RO1 HL091841. Drs Carter and Chrysiches are supported by the Agency for Healthcare Research and Quality Centers for Education and Research on Therapeutics Cooperative Agreement #SU18HS016094. Drs Carter, Vander Weg, and Vaughn are supported by the Center for Research in Implementation in Innovative Strategies in Practice, Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development Service (HFP 04–149).

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

Disclosures
None.

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_Circ Cardiovasc Qual Outcomes_. 2010;3:418-423
doi: 10.1161/CIRCOUTCOMES.109.908038
_Circulation: Cardiovascular Quality and Outcomes_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circoutcomes.ahajournals.org/content/3/4/418

Data Supplement (unedited) at:
http://circoutcomes.ahajournals.org/content/suppl/2010/08/14/3.4.418.DC1

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Supplemental Material
Appendix:

**Asthma Intervention in Control Clinics (Usual Care for Patients with Hypertension).**

Coordinators from clinics randomized to the control group in the CAPTION trial will recruit patients with hypertension in the control group as well as patients with asthma so that the pharmacists in these offices can provide the intervention to patients with asthma. The intervention for patients with asthma will follow previously published interventions for asthma.¹⁻⁷

While the study coordinators will enroll patients with hypertension into both the BP control group and the observational cohort in control sites, we will institute an alternative asthma PPCM model only in the control clinics. While the results of the asthma management are not primary outcomes, we expect an impact from the intervention and our structured trial will be one of the largest to examine PPCM for this condition. A literature search revealed that most asthma studies were conducted in community pharmacies.¹⁻⁴ The few studies that used the PPCM model for asthma within a clinic setting have yielded mixed results in outcomes. However, Pauley et al found that a PPCM program for asthma management resulted in significantly fewer emergency department visits during the study period compared to two similar time periods prior to study initiation.² The true benefit derived from PPCM for asthma is unknown. The aim of this sub-study is to determine if patients who receive PPCM for asthma can achieve improved asthma control at 9 months compared to the 9 month time period prior to study enrollment. Our primary hypothesis is that there will be a
reduction in ED visits during the 9-month study period and the 9 month period after the intervention (time between 9 and 18 month visits) compared to the 9-month time period prior to enrollment into the study. Secondary hypothesis will evaluate if the Asthma Quality of Life Questionnaire and Asthma Control Test scores will be improved at 9 and 18 month time periods compared to baseline.

**Inclusion criteria:** males or females 12 years of age or older with a diagnosis of persistent asthma who are cared for in sites randomized to the control group (Note: consent for those under the age of 18 years will require the consent of the parent/guardian and the patient).

**Exclusion criteria:** 1) hypertension which would qualify them for the BP control group 2) history of severe, life-threatening asthma evidenced by a history of loss of consciousness, ICU admissions or mechanical ventilation due to asthma; 3) diagnosis of chronic obstructive pulmonary disease; 4) previous involvement in a multidisciplinary asthma management clinic; 5) pregnancy; 6) poor prognosis with a life expectancy estimated less than 2 years; 7) residence in a nursing home or diagnosis of dementia, or 8) inability to give informed consent or impaired cognitive function (defined as ≥ 3 errors on the 10-item Pfeiffer Short Portable Mental Status Questionnaire, administered during study intake).

**Patient recruitment (Asthma):** Patients will be recruited by the study coordinator using the same procedures as above for patients with hypertension. The intervention model is very similar to that used for BP control. The clinical pharmacist will conduct a patient interview at baseline. The pharmacist and physician will decide upon short-term and long-term goals. Clinical pharmacists will provide patients with
asthma information and training in asthma management skills, self-monitoring education (symptoms or peak flow), and a written plan for daily treatment and self-management of exacerbations or symptom episodes. The pharmacist will develop an assessment of the patient’s medication regimen. Suggestions will be made to the physician regarding potential improvement of the current regimen in accordance with the National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Clinical pharmacists will assess asthma severity and asthma control and make recommendations to the physician for monitoring and adjusting therapy.

We will encourage the use of the intervention but then measure the extent to which each patient actually received the intended PPCM. The suggested PPCM model is designed to include structured face-to-face visits with the pharmacist at baseline and 2, 4, 6 and 8 months. Optional visits at 1, 3, 5, 7, and 9 months and a telephone call at 2 weeks will be possible for patients with continued poor asthma control. Each patient will be followed for 9 months. The pharmacist will assess medication delivery technique at each visit. Medication therapy will be reviewed, with special attention given to frequency of β-agonist use. At each visit the Asthma Control Test questionnaire will be given. An asthma action plan will be given to the patients and it will be reviewed and adjusted as needed.

**Data Collection and Analysis:** The study coordinator will collect the following data by patient-report at baseline and 9 month visits: demographic data, list of asthma medications, clinic visits, hospitalizations and/or ED visits for breathing difficulties in past 9 months, non-ED visits for breathing difficulties in past 9 months, courses of oral
corticosteroids in past 9 months and days of missed work or school in past 9 months. Adherence to long-term maintenance medication will be assessed using patient self-report. The nurse will administer the Asthma Quality of Life Questionnaire. At the 9 and 18 month data-collection visits the study coordinator will administer the same questionnaires/surveys as at baseline and will also administer the Asthma Control Test which was previously completed at pharmacist visits. Since this intervention is secondary to the BP study, lacks a control group and is an alternate intervention, we will only collect descriptive statistics and no sample size or power calculations have been done. We estimate that 100-150 patients may be enrolled in this group so before-after comparisons in disease control should be possible.

We will use Poisson regression methods to compare total number of ED visits across the three groups. We will use Generalized Estimating Equation (GEE) methods with a appropriate Poisson link function to account for the repeated measures across the three time periods. QOL scales will be compared across the three time periods using appropriate linear mixed models while accounting for repeated measures across time. Asthma control test scores will be compared across the three time periods using appropriate linear mixed models to compare mean scores across the three time periods while accounting for repeated measures across time.

Formative Evaluations:

We will evaluate provider experiences regarding adoption of the intervention model using formative evaluations that will examine: 1) frequency and content of recommendations made by pharmacists to physicians and patients; 2) the effect of the recommendation on BP control; 3) physicians’ acceptance of PPCM; 4) pharmacist
acceptance of the intervention; and 5) patient acceptance of the intervention.

Medication intensity scores will be assigned using approaches from other studies and our own research and correlated with BP control. Lastly, study coordinator interviews and case report forms will be used to determine if recommendations for medication changes were implemented by the physician and patient.

Recommendations by the pharmacist will be succinctly summarized for physicians using a format similar to that used in our prior trials. Pharmacologic recommendations will be further categorized into: 1) medication additions; 2) medication elimination; and 3) changes in dosing of existing medications.

We will conduct semi-structured interviews with the physician leader, pharmacists and other key informants at each clinic at baseline regarding organizational characteristics that might support or inhibit adoption and sustainability of PPCM, as well as the use of PPCM for patients not in the study at baseline and at the end of the study. Each clinic will determine what organizational changes they deem appropriate and implement them. Some of these changes may be developed for broader application within the clinic.


