Abstract

DESCRIPTION (provided by applicant): Many African-Americans and Latinos with diabetes do not achieve the recommended goals for normal blood sugar, blood pressure, or cholesterol level, placing them at high risk for complications. This study will evaluate the impact of a novel intervention designed to improve lifestyle behaviors and medication adherence, and intensify therapy to reach goals. The first component of the intervention includes a clinic-based pharmacist disease management program. The program includes detailed patient assessments, physician- approved treatment plans, patient education and support services to enhance medication adherence. In addition, this program includes intensification of medication therapy to improve blood sugar, blood pressure, and cholesterol levels to reach recommended goals. The second component of the intervention includes health promoters (HPs), or community-based lay health workers. Health promoters are commonly found in minority communities and provide assistance for neighbors overcoming language, cultural, and other barriers to conventional health care services. They may provide autonomy support and solve problems related to medication adherence barriers. Furthermore, health promoters may complement pharmacist activities by improving access to medications, assisting in continuity of care with providers, monitoring response to therapy, and reinforcing educational messages. The proposed study will determine whether the addition of health promoters to clinic based pharmacist service delivery improves care. The study will involve the recruitment of 300 African-American and Latino adults with uncontrolled diabetes through the University of Illinois Medical Center in Chicago and randomization to one of two groups: (1) pharmacist management (Pharm) for 12 months; or (2) pharmacist management with HP support (Pharm+HP) for 12 months. Cross-over will occur at 12 months such that the Pharm group will be intensified by the addition of HP support and HP support will be phased out from the Pharm+HP group to assess maintenance. The specific aims include: (1) To evaluate the effectiveness of Pharm+HP compared with Pharm alone on diabetes behaviors (including healthy eating, physical activity, and medication adherence), hemoglobin A1c, blood pressure, and LDL-cholesterol levels; (2) To evaluate the maintenance of improved diabetes behaviors as well as clinical outcomes by phasing out HP support from the Pharm+HP group after year 1; (3) To evaluate the intensification offered by adding an HP after one year of Pharm alone; and (4) To evaluate the cost and cost-effectiveness of Pharm+HP and Pharm alone. PUBLIC HEALTH RELEVANCE: This research evaluates a diabetes management intervention designed to improve medication adherence and intensify therapy to reach goals in blood sugar, blood pressure, and cholesterol levels. This study will determine the benefit and cost of adding community health promoters to pharmacist disease management services. If there is benefit, then this approach may help reduce the burden of diabetes and its related complications among minorities with diabetes.

Specific Aims

Of the 23 million adult Americans with diagnosed diabetes, 50% have a hemoglobin A1c level above 7.0%; 53% have a blood pressure above 130/80 mm Hg; and 65% have an LDL-cholesterol level above 100 mg/dl (goals set by the American Diabetes Association).[1] Inadequately controlled blood glucose, blood pressure, and cholesterol levels are concerning because they increase the risk of disease related-complications or death.[2] Effective interventions to improve these levels are critically needed to reduce the current burden of disease. Intervention is of particular importance for African-American and Latino populations, who are almost twice as likely to be affected by diabetes as non-Latino Whites and experience disproportionate rates of related complications.[3, 4]

Lifestyle modification is the cornerstone of diabetes therapy, augmented by medication to meet therapeutic goals. Most patients must maintain a high level of *adherence* to both lifestyle and prescribed medication to reach goals. This can be particularly difficult for ethnic/racial minority populations who often reside in environments with limited resources to support healthy lifestyles and have limited finances. Additional challenges to medication adherence include limited English proficiency, low health literacy, differing cultural beliefs and problems in the patient-provider relationship.[5] In addition to patient adherence, primary care providers (PCPs) must *appropriately intensify therapy* to achieve effective medication management.[6] Providers who do not adequately adjust therapy to treat chronic diseases contribute to "clinical inertia," which results in a lower likelihood of achieving therapeutic goals regardless of patients' adherence.[7, 8] In summary, effective interventions must address patient adherence to lifestyle modification and medication in addition to providers' intensification of medication therapy.

Clinic-based pharmacists are health professionals housed within primary care settings who collaborate with other providers to provide diabetes education, intensify medication therapy, and address patient adherence barriers.[9, 10] Although studies conducted to date suggest that pharmacists are effective in improving glycemic control and blood pressure, minority patients have benefitted less than non-Latino Whites.[11] Underserved minority groups often experience complex physical, psychological, social, behavioral, and economic barriers to adherence that challenge pharmacist care. New models of care designed to support healthy lifestyles and focus on medication management are needed. Additionally, clinic-based pharmacists need assistance in reaching and addressing the unique needs of racial/ethnic minorities with uncontrolled diabetes.

Preliminary data from our research group supports the role of community-based health promoters partnering with clinic-based pharmacists in improving clinical outcomes in minorities with diabetes.[12] **Based on this approach, we propose a randomized, controlled trial to evaluate the effectiveness and cost of providing the health promoter/pharmacist team for African-Americans and Latinos with uncontrolled type 2 diabetes.** We will recruit 300 patients through the University of Illinois Medical Center (UIMC) ambulatory network and randomize them to either: (1) pharmacist management (*Pharm*); or (2) pharmacist management with *health promoter (HP)* support (*Pharm+HP*). After one year, the *Pharm* group will be augmented by the addition of *HP* support and maintenance will be assessed by phasing out *HP* support from the *Pharm+HP* group (crossover design). **The specific aims and hypotheses (H) to be tested include:**

Aim 1: To evaluate the **effectiveness** of *Pharm+HP* compared with *Pharm* alone on diabetes behaviors (including healthy eating, physical activity, and medication adherence), hemoglobin A1c, blood pressure, and LDL-cholesterol levels among African-American and Latino adults with uncontrolled type 2 diabetes.

H_1: Hemoglobin A1c, blood pressure, and LDL-cholesterol levels will be lower and diabetes behaviors improved in patients receiving *Pharm+HP* compared with those receiving *Pharm* alone.

Aim 2: To evaluate the **maintenance** of improved diabetes behaviors as well as clinical outcomes by phasing out *HP* support from the *Pharm+HP* group after year 1.

H_2: Diabetes behaviors and clinical outcomes will not change one year after phase out of *HP* support.

Aim 3: To evaluate the **intensification** offered by adding an *HP* after one year of *Pharm* alone.

H_3: Diabetes behaviors and clinical outcomes will be improved by adding *HP* support after receiving one year of *Pharm* alone.

Aim 4: To evaluate the **cost and cost-effectiveness** of *Pharm+HP* and *Pharm* alone.

A. Significance - National Health and Nutrition Examination Survey (NHANES) data from 2001-2002 found that among adults with diabetes, 50% had a hemoglobin A1c ("A1c") level above 7.0%; 53% had a blood pressure above 130/80 mm Hg; and 65% had an LDL-cholesterol level above 100 mg/dl (goals set by the American Diabetes Association, ADA).[1] While time-trend analyses through 2006 show improvement in blood sugar, blood pressure, and cholesterol control in non-Latino Whites (likely due to improved management), no significant improvements were evident in racial/ethnic minorities.[13] In fact, gaps in blood sugar control between Latino and non-Latino White adults has widened.[13] Observational studies and meta-analyses have also shown worse control by African-American and Latino populations.[14-18] These differences in intermediate factors may contribute to higher complication rates in minority groups such as renal disease, coronary artery disease, amputations, and mortality.[15, 19, 20] Improvement in minority diabetes management is a priority for research.[21]

The Lifestyle Modification and Medication Adherence Problem: Urban minorities face complex physical, economic, and socio-cultural barriers to healthy eating and physical activity.[22] Examples barriers include an abundance of fast-food restaurants, limited access to fresh vegetables, and high levels of neighborhood crime. Similarly, medication adherence is lower among minority populations due to barriers such as cost, lack of social support, ineffective doctor-patient communication, lack of trust in the physician, and concerns about side effects and dependency.[12, 23-28] As individuals may experience no symptoms prior to the development of complications, there is often a lack of interest in taking preventive medications long-term.[29] Collectively, these factors likely contribute to disparities in diabetes control and must be addressed in effective interventions. While many investigations evaluate lifestyle change in diabetes self-management, there is an urgent need for medication adherence interventions. Systematic reviews of informational, behavioral and social interventions to improve medication adherence found few studies improved clinical outcomes, sample sizes were small, and minorities (especially Latinos) were underrepresented.[30, 31] Our study will be among the few medication adherence studies designed and powered to detect change in glycemic control in a diverse population.

The Clinical Inertia Problem: "Clinical inertia" occurs when PCPs fail to appropriately intensify therapy in patients despite recognizing elevations in blood glucose, blood pressure, or cholesterol.[32] This contributes to a lower likelihood of achieving therapeutic goals. Clinical inertia is related to PCPs having limited time available and patients presenting with concerns that compete for attention. In addition, PCPs are often not trained in the complex array of psychosocial or environmental factors impacting adherence which must be addressed prior to intensification of medication.[33] Additional frequent and comprehensive monitoring, evaluation, and intervention are necessary to improve adherence and overcome inertia. Our proposed study includes an intensive, team-based approach including pharmacists to assist in therapy intensification with PCP approval.

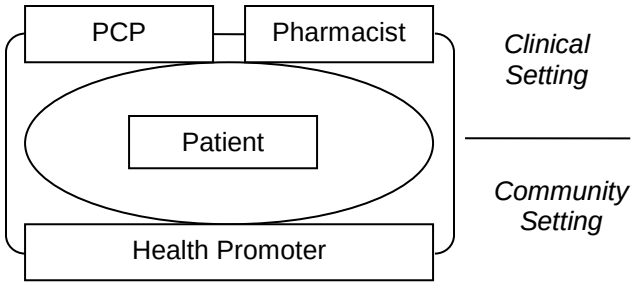
Current Team-Based Approaches to Diabetes Management: Given the increasing prevalence of diabetes and the lack of patients reaching recommended therapeutic goals, novel models of team-based care are emerging that include nurses, case managers, pharmacists, and community-based peer health promoters (HPs).[12, 34-36] Team management plays a significant role in the *patient-centered medical home* approach, which has been endorsed widely by major national health plans, most Fortune 500 companies, consumer organizations and labor unions, the American Medical Association, and other specialty societies.[37, 38] Medical homes involve health professional teams working collaboratively with PCPs to provide high levels of care, access, communication, care coordination and integration.[37] In addition, they promote patient engagement, work with family members, establish goals of care, and focus on preventing chronic disease complications.

Recent evidence supports the role of pharmacists in diabetes management to improve glycemic control as they offer expertise in medication management with the ability to collaboratively intensify therapy.[39-41] However, few studies of pharmacy-based models of care have focused upon low income, minority populations who are most in need of intervention. Alternatively, HP interventions have focused largely upon low income minority groups, addressing their unique psychosocial and environmental challenges in diabetes self-care. Studies using HPs have shown less consistent results in terms of improvement in glycemic control and included fewer randomized clinic trials.[34, 36, 42-44] Following up on our pilot work, this will be the first study to evaluate the impact of HPs as a complement to pharmacist management in a randomized controlled trial. Health care systems routinely provide pharmacist services, but not those of community HPs. Yet, the pharmacist plus HP team intervention may represent a significant and feasible strategy to improve minority diabetes management.

B. Innovation - Our proposed study evaluates an innovative, integrated approach to chronic disease self-management in minorities with poorly controlled diabetes. The approach is comprised of clinic-based pharmacists and community-based HPs collaborating on a PCP- directed team to address patient and provider

level factors. We recently demonstrated feasibility of this new approach in a pilot study (see Appendix IX).[12] The intervention targets patient-level factors (i.e., lack of adherence to lifestyle modification and medications) and provider-level factors (i.e., clinical inertia) that contribute to poor clinical outcomes in diabetes (Figure 1). Importantly, the proposed study design and analytic approach will allow us to discern the differential and combined impact of adherence to lifestyle changes, medication, and intensification on clinical outcomes. The study will determine the specific mechanisms by which any improvement occurs through mediation models that include autonomy related concepts reflected in our theoretical conceptual framework. Furthermore, we plan to evaluate the maintenance of behavioral change after phasing out of HP support. This addresses an issue that is infrequently studied. Finally, an innovative aspect of the proposed study is the inclusion of cost and cost-effectiveness analyses. While research suggests that diabetes self-management programs are cost-effective (when cost savings due to complication reduction are considered),[45] there is limited data available on health care utilization and cost associated with HP implementation in diabetes care.[46] This study will be a major contribution to this area.

Figure 1: Intervention Model



The study design includes clinic-based pharmacists. We chose to study pharmacists because the strongest empirical support for improved diabetes medication management currently lies in PCP-directed collaborative teams with pharmacists. In fact, collaborative medication therapy management by pharmacists has been approved in 46 states in the U.S. since 2008 for diabetes and dyslipidemia.[47, 48] This supports the need for further study of pharmacists in team management as part of a patient-centered medical home.

To complement pharmacist efforts in reaching minority populations, we include HPs. Despite the endorsement of peer HPs by the American Association of Diabetes Educators (AADE) and American Public Health Association (APHA), they remain controversial in the U.S. healthcare system.[49-51] Criticisms of HPs focus upon the lack of formal evaluation studies supporting their effectiveness on clinical endpoints and weak connections between HPs and providers. We plan to provide stronger evidence on the use of HPs in the context of the conventional health care system by connecting them with clinic-based pharmacists.

C. Approach - Our research group has experience working with pharmacists and community HPs to improve lifestyle behaviors and medication management among minority populations with diabetes. We have access to extensive HP training and educational materials targeting African Americans and Latinos for study use and are a member of the *Global Network of Peer Support Organizations* (developed by *Peers for Progress*, a program of the American Academy of Family Physicians Foundation promoting global exchange of knowledge and program models about peer support services).

Preliminary Study 1: Pharmacist and Health Promoter to Improve Diabetes Medication Management: (Funded by the UIC Institute for Health Research and Policy; Co-PIs – Drs. Gerber and Sharp; see Appendix IX). The proposed project builds directly upon our pilot study that evaluated the feasibility of a pharmacist/HP team to improve medication adherence and intensify therapy.[12] Clinical staff at UIMC referred Latino patients with uncontrolled diabetes (A1c ≥ 8.0%) and nine patients completed the study. A bilingual, bicultural HP reviewed detailed needs assessments and worked with patients at home, clinic visits, and via telephone calls. The promoter identified lifestyle modification goals with patients, adherence barriers, regimen, psychosocial issues, and access to care. The clinic-based pharmacists worked with the patient and HP to provide strategies to improve medication adherence and collaborated with the PCPs to intensify therapy between clinic visits. With assistance from the HP, the pharmacist was better able to reconcile medication lists, monitor response to medications, and work with the physician to guide adjustments in therapy. Success with this approach required: (1) frequent communication between the HP and participant; and (2) easy access for the HP to communicate with clinic-based pharmacists. Mean A1c declined from 9.6% to 9.0% over six months, with greater improvement among those with more HP contact. The current project expands this research to include African American patients while implementing a refined strategy of intensive pharmacist/HP involvement in addressing barriers to medication adherence and intensifying therapy.

Preliminary Study 2: Implementing Culturally Appropriate Diabetes Education Programs for African-Americans and Latinos: (Funded by AHRQ; PI – Dr. Gerber; Co-I: Dr. Berbaum). We conducted a multicenter, randomized, controlled trial, "Diabetes Education Multimedia for Vulnerable Populations."[52] We developed 19 bilingual computer multimedia lessons on diabetes self-management targeting Latino and African-American

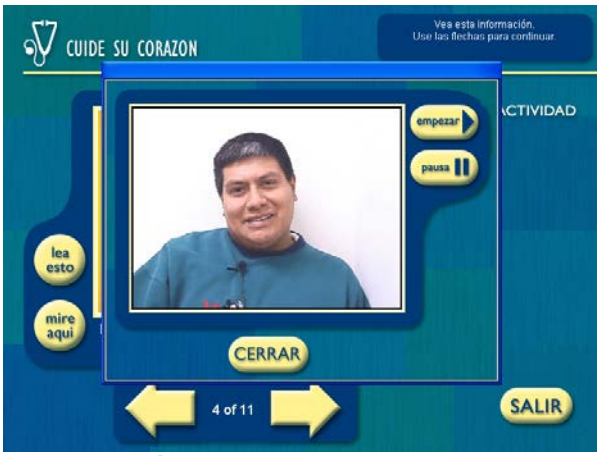


Figure 2: Screen Capture "Living Well with Diabetes"

populations (Figure 2). To create the program, the research team video recorded over 160 African-American and Latino individuals with diabetes for testimonials related to diabetes self-care, emphasizing barriers to care, challenges, and personalized solutions they or family members had encountered. A study of 255 individuals with diabetes found that waiting room use of the multimedia program improved diabetes self-efficacy and perceived susceptibility to complications, with the greatest impact observed among users with low health literacy.[52] In subgroup analysis including subjects with low health literacy and poor glycemic control, there was a significantly greater improvement in A1c (2.1% versus 0.3% decline; p=.036). More recently, we conducted another randomized, controlled study of 100 low-income, minority patients at the Cook County Fantus Clinic. We found greater intensification in oral medication therapy for diabetes among participants exposed to the multimedia program prior to physician encounters with a greater reduction in A1c over three months (manuscript in preparation). The program remains in use in primary care clinics and health fairs[53] and by HPs in the community. Lesson content includes an introduction to diabetes, blood glucose management, oral medications and insulin, nutrition and physical activity, depression and stress, oral hygiene, and the prevention of complications (including eye, foot, cardiovascular, and kidney diseases). The Canadian Diabetes Association named the multimedia program as a "Best Practice" in 2008. The program will be available for HPs in the proposed study to use via portable tablet computers in providing lifestyle education, addressing beliefs toward medication and disease management, and promoting skills in taking medication (e.g., insulin injections).

Preliminary Study 3: Experience with Community Health Promoters: (Funded by the CDC; PI- Dr. Aida Giachello, Co-I – Dr. Castillo; see letter of support). The UIC Midwest Latino Health Research Training and Policy Center (MLHRC) developed the Diabetes Empowerment Education Program (DEEP) to educate HPs in the delivery of diabetes education to community residents (see Appendix I). To date, 486 HPs in Chicago, the U.S.-Mexico border, and 20 other states in the U.S. have completed DEEP training. Under the CDC - Racial and Ethnic Approaches to Community Health (REACH) 2010 Initiative, the MLHRC implemented the training of trainers and educational curriculum components of DEEP among the Hispanic and African-American communities of Southeast Chicago. The Chicago Southeast Diabetes Community Action Coalition engaged HPs in addressing health literacy among patients with type 2 diabetes. In 2007, the MLHRC completed a pilot study to evaluate the feasibility and effectiveness of the diabetes education program delivered by HPs to 70 community residents. After the 10-week program, participants showed a significant reduction in numerous diabetes-related behaviors and clinical outcomes including A1c (unpublished data). The MLHRC continues to train HPs with funding through the Center of Excellence in the Elimination of Disparities (CEED). Dr. Castillo is the CEED Master Trainer and Director of Training and will lead the HP training for the proposed study.

C.1. Conceptual Framework: Our intervention is informed by the motivational framework of *Self-Determination Theory (SDT*) and *Problem Solving Theory*.[54, 55] The SDT posits that people make healthier choices when they become autonomous self-regulators and obtain a sense of perceived competence.[54] These gains are fostered by having access to experiences that convey autonomy and competence support (Figure 3). *Autonomous self-regulation* is important in the initiation of behaviors, and reflects the feeling that one is willing to make healthy food choices and take medications without outside intervention or coercion. *Perceived competence* is the sense that one is capable and physically able to attain a desired goal. SDT hypothesizes that long term diabetes self-care is most probable when patients genuinely feel that eating healthy and taking their medications will benefit them and when they feel that they have the knowledge and skills to effectively take their medications. A person develops autonomous self-regulation and perceived competence by receiving autonomy support. An individual can provide support by asking questions, listening, providing encouragement, and acknowledging the

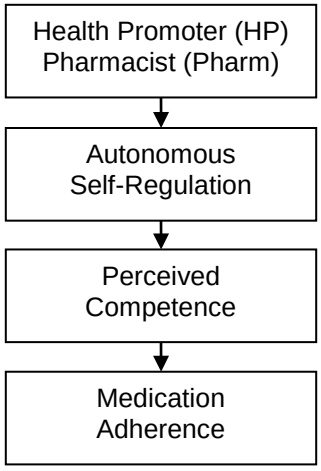


Fig. 3: Conceptual Framework

individual's beliefs. Finally, autonomous support includes the provision of health information, education, and skill building in a patient-centered format that minimizes power differentials (see Table 2 for examples).

Problem Solving Theory is directed at guiding patients towards more effective maneuvering of individual barriers to diabetes self-management.[55, 56] These barriers are often context specific and exist within patients' home or community as well as the clinical setting. The pharmacists and HPs will support patients' problem-solving skills building with the goal of overcoming identified barriers and improving autonomy. By aligning themselves with their patients, pharmacists and HPs increase motivation and potentially strengthen their relationship with their clients.[56, 57]

In the proposed study, the HPs and pharmacists have the opportunity to provide autonomy and problem solving support to promote diabetes self-care. We anticipate that pharmacists will improve perceived competence by reconciling medications, providing education, and problem-solving that will reinforce autonomy support. However, we anticipate that autonomous self-regulation will be significantly augmented by the addition of HPs who have a greater understanding of the participant's context and culture allowing them to share perspectives. We hypothesize that this will result in improved lifestyle and medication adherence. Furthermore, improved adherence may reduce clinical uncertainty and increase the opportunity for therapy intensification, resulting in even better disease control.[33, 58] Through these mechanisms, we hypothesize that the pharmacist plus health promoter group will experience greater improvements in clinical outcomes relative to the pharmacist only comparison group.

C.2. Study Design: The proposed study is a randomized, controlled trial with crossover after one year (Figure 4). Three hundred African-American and Latino patients with uncontrolled type 2 diabetes will be randomized to receive either: pharmacist services (*Pharm*) or pharmacist services with HP support (*Pharm+HP*). After one year, groups will crossover. The *Pharm* group will be intensified by adding HP support, and maintenance will be evaluated in the *Pharm+HP* group by phasing out HP support. Outcomes evaluated at 0, 6-, 12- and 24-months include diabetes behaviors including medication adherence, A1c, blood pressure, and LDL-cholesterol levels. Budget limitations prevent data collection at 18 months. The study design will achieve the specific aims as follows:

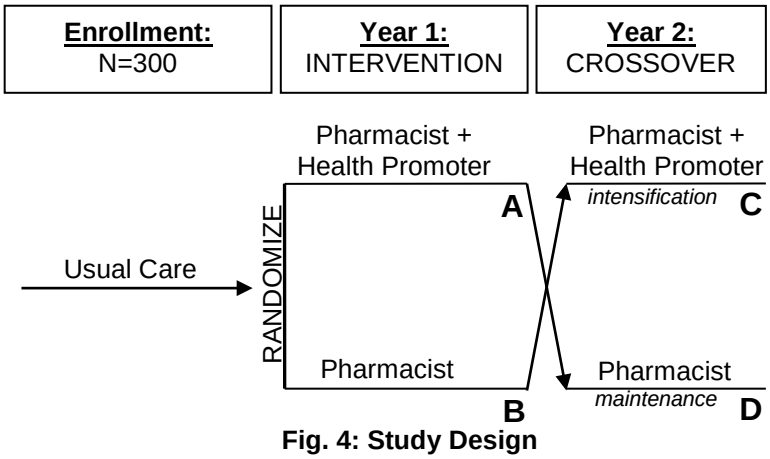


Fig. 4: Study Design

- **Aim 1**: To evaluate the **effectiveness** of *Pharm+HP* compared with *Pharm* at year 1 (main effect comparison of cell means **A**-**B** in Year 1, and interaction comparison of cell means (**C**-**B**)-(**D**-**A**))
- **Aim 2**: To evaluate the **maintenance** of behaviors and clinical outcomes by phasing out HP support in the *Pharm+HP* group after year 1 (comparison of cell means **D**-**A**)
- **Aim 3**: To evaluate the **intensification** offered by adding *HP* after one year of *Pharm* alone (comparison of cell means **C**-**B**)
- **Aim 4**: To evaluate the **cost and cost-effectiveness** of *Pharm+HP* compared with *Pharm* alone by developing and applying a cost-effectiveness model, evaluating net costs and net effectiveness of the two study groups

C.3. Recruitment: The University of Illinois Medical Center (UIMC) includes both inpatient and outpatient facilities serving a diverse population in Chicago. During fiscal year 2009, there were approximately 8,000 unique African American or Latino individuals who received care for diabetes in the outpatient setting. The UIMC has 13 off-site ambulatory centers staffed by Family Practice and Internal Medicine PCPs (see letters of support by Dr. Duperval, Mile Square and Ms. Margaret Kryda, UIMC Ambulatory Network). We anticipate including between 6-8 clinical sites for participation. All sites share access to the electronic medical record (EMR), Cerner Powerchart.

The referral/recruitment process will be individualized for each ambulatory site as determined by the project coordinator and clinical staff. The research assistant (RA) will work from a physician approved list of potential research patients with diabetes and A1c ≥ 8 identified from patient registries. On-site RAs will receive additional referrals from staff or patients interested in being screened for the study. Individuals deemed eligible (see Appendix II) will be scheduled for an appointment at the UIC Clinical Interface Core facility to complete

written consent, HIPAA authorization, and baseline data collection. The RA will inform patients that the research is being conducted to improve medication management in diabetes care and to find out if pharmacists and HPs help people reach goals of therapy. The RA will discuss the study protocol in detail as part of consent procedures and use the "teach back" method to ensure participant comprehension. Table 1 shows the inclusion and exclusion criteria for participants. Subjects must take at least one oral medication for diabetes or hypertension for adherence measurement using the Medication Event Monitoring Systems (MEMS).

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Self-identified as Latino/Hispanic or African-American	• Unable to verbalize comprehension of study or impaired decision making (e.g., dementia)
• Verbal fluency in English or Spanish	• Lives outside Chicago communities of recruitment (3+ mo./yr)
• Age 21 or above	• Household member already participating in same study
• History of type 2 diabetes (> 1 yr.)	• Plans to move from the Chicago area within the next year
• Latest A1c ≥ 8.0% (within 1 yr.)	• Pregnant or trying to get pregnancy
• Receives primary care at UIMC (> 1 yr.)	
• Taking at least one oral medication for diabetes or hypertension	

C.4. Randomization: Randomization to receive either *Pharm* or *Pharm+HP* for the first year will be completed after consent and completion of all baseline data collection. A random sequence of 300 subject assignments will be used. Blocked randomization (with varying block sizes)[59] within each clinical site will balance the proportion of participants in each of the two study groups by geographic location of participant home (for HP assignments). The project coordinator will determine assignment group for research assistants and will log the subject information into a secured computer.

C.5. Pharmacist Intervention Component: Participants in both *Pharm* and *Pharm+HP* groups will all receive the pharmacist intervention component. This component includes medication and disease management services through patient encounters, medication intensification, communication with PCPs, and EMR documentation. All participating clinical sites will have pharmacists available to deliver this component. All participating pharmacists have faculty appointments in the UIC Department of Pharmacy Practice.

Medication/Disease Management: Pharmacists will provide medication and disease management services to patients following a Pharmacist Management Protocol (see Appendix III). In providing care, pharmacist disease management services are comparable to other disease management programs and include comprehensive needs assessments, proactive health promotion, patient-centric goals and education, interventions to encourage behavioral change, and PCP support and feedback.[60] The clinic pharmacist will review current medication use, identify therapeutic goals, formulate an approved plan of care, and document the plan in the EMR for PCP approval. Pharmacists will educate and encourage lifestyle changes based upon ADA nutrition and physical activity guidelines.[61, 62] However, all patients recruited into this study will also require medication to control their diabetes. The PCP and pharmacist will decide on the algorithm/approach to intensify therapy and how medication changes may be made (using algorithms based on national guidelines)[63-65]. The intention is to establish optimal communication with minimal PCP burden (a similar approach to our pilot study). Individual goals will be identified for each participant for A1c, blood pressure, and LDL-cholesterol (e.g., A1c $\leq$ 7%). Of note, recent studies such as the ACCORD trial raised concerns of aggressive glycemic control increasing mortality without reducing major cardiovascular events.[66] However, other trials found no increase in mortality in intensively treated patients.[67, 68] In the proposed study, PCPs and pharmacists will adopt the ADA approach to individualized care, where the general goal for non-pregnant adults is A1c less than 7%. They may decide upon less stringent goals for those with a history of severe hypoglycemia, limited life expectancy, advanced micro- or macrovascular disease, or extensive comorbid conditions.[69]

Patient Encounters: Initially, the pharmacist will meet with patients to reconcile medications and discuss therapeutic goals. Next, the pharmacist will administer the Pharmacist Intake Form (see Appendix IV) to assess common barriers to medication adherence including memory, beliefs, cost, medication burden, physical disabilities, and social barriers. Following the initial visit, encounters may occur in person at the clinic or by phone every two weeks. Duration between encounters may increase based on individual preference and when subjects reach goals (with maximum of three months). The pharmacist activities will include an evaluation of adherence, medication reconciliation, and review of home glucose and/or blood pressure monitoring log data. Pharmacist education will target medication (name and purpose of medications; time, strength, and method of administration); drug interactions and side effects; goals of therapy; basic lifestyle modifications; and use of pillbox, low-literacy medication lists, or other adherence aids (Table 2).

Table 2: Problem Solving Strategies and Autonomy Support Targeting 5 Dimensions of Adherence[70]		
	Problem Solving/Addressing Barriers	**Autonomy Support Examples**
Social and Economic	Use visual aids and medication charts. Enlist family, friend, or other support in transportation or obtaining/taking medications.	Ask participants to identify sources of social support. Provide options for community resources. Ask participants about health beliefs and values, including alternative and complementary medicine use.
Health Care System	Review information on contacting pharmacist and physician's office, and other medical staff. Determine alternative means of transportation and community resources. Encourage interpreter use if indicated.	Work with participants to outline goals for clinical visits (e.g., bring medication list or bottles). Support participants in scheduling clinic visits at days/times and acceptable frequencies such that they are more likely to be able to attend.
Chronic Condition Related	Assess use of medications when patient feeling well (without symptoms). Review when and why medications are taken. Present cuing (e.g., pair with behavior such as teeth brushing) and monitoring strategies (calendar to track medications taken).	Validate patients' feelings about medications and help them identify benefits. Teach patient skills for effectively talking with the PCP and pharmacist about medication concerns. Support participants' self-initiation of change. Provide relevant information concerning lifestyle change or medication use.
Therapy Related	Work with provider or pharmacist on simplifying medication therapy. Review insulin injection technique and promote self-injection skills. Review glucose meter results.	Discuss various lifestyle and alternative medication and treatment options/choices. Discuss possible benefits and side effects of lifestyle change and medication use. Provide choices to simplify medication therapy or integrate therapies into lifestyle. Ask participants how they would like to monitor their diabetes.
Patient Related	Assess physical (e.g., visual hearing, or cognitive impairment), psychological, and behavioral (e.g., motivation, attitudes toward therapy, fear, stress) factors. Use adaptive technologies (audio glucose meter, or computer multimedia for reinforcement).	Elicit thoughts and feelings about medication use and lifestyle change. Minimize use of controlling language and use collaborative approach.

Medication Intensification: Pharmacists will adjust therapy according to the plan of care under PCP guidance and notify PCPs of agreed upon modifications via forwarded progress notes in the EMR. Side effects identified by the HP or pharmacist will be conveyed to the PCP immediately and if the PCP is not available, the covering clinic physician will be contacted per Pharmacist Management Protocol. Laboratory assessments including electrolytes and renal function will be completed per medication titration protocol. For hypoglycemia, pharmacists routinely monitor hypoglycemic events, address prevention and review treatment. This includes three steps: (1) addressing hypoglycemia with every patient contact; (2) applying principles of aggressive therapy (education, empowerment, frequent glucose self-monitoring, flexible medication regimen, individualized goals, professional guidance); and (3) considering risk factors for hypoglycemia.[71]

Communication with PCPs and EMR Documentation: PCPs and clinic-based pharmacists are located in the same clinic to facilitate communication. The pharmacists have direct access to the PCP and routinely communicate in person, by telephone, and by EMR messaging depending on urgency. The pharmacist may adjust the medication regimen and provider refills in accordance to the PCP-directed care plan and response to therapy (to optimize blood glucose, blood pressure, and cholesterol levels). All adjustments, refills, and testing are completed under guidance of the participants' providers and updated in the EMR medication list. Pharmacists have access to participants' full EMRs and can review flowsheet and other chart data including blood test results, clinical progress notes, problem and medications lists, drug allergies, hospitalization records, and emergency room reports. Pharmacists will forward all electronic progress notes to the PCP EMR "Inbox" after each encounter. Progress notes include a detailed list of medications, estimated adherence levels, and home glucose/blood pressure monitoring log information. However, for urgent medical reasons, the PCP or covering provider will be contacted. If, for any reason, the PCP feels that the patient should not remain in the study, the provider can inform the Co-PIs to disenroll the participant.

C.6. Health Promoter Intervention Component: Participants randomized to *Pharm+HP* will receive the HP component in Year 1, while participants randomized to *Pharm* will receive it in Year 2. This component includes patient encounters, medication and lifestyle adherence support and communication with pharmacists. Each clinical site will work with 1-2 HPs who are each responsible for 10-20 participants.

Hiring: Dr. Castillo (Co-I) and Dr. Cynthia Barnes-Boyd will facilitate HP recruitment through their extensive community connections which include access to numerous experienced HPs and organizations that work with HPs (see letters of support). Dr. Barnes-Boyd currently directs the UIC Neighborhoods Initiative and the Healthy City Collaborative of UIC's Great Cities Institute. Potential candidates will be identified through

advertisements, announcements, and organization meetings targeting these contacts. MLHRC will hire ten HPs (peer/lay health workers) who have: (1) U.S. citizenship; (2) a vehicle for transportation; (3) a minimum two years community HP experience; (4) a high school or GED education; and (5) excellent communication skills. HPs will be either African-American or Latino, and represent the communities being served. Identification and training of alternate HPs will be on-going to prepare for HP attrition.

Training: All HPs will receive standardized training/re-training via two educational curricula: (1) the *Diabetes Education Empowerment Program* (DEEP; see Appendix I), developed by the MLHRC; and (2) Dr. Bodenheimer's *Training Curriculum for Health Coaches* (see Appendix V). DEEP uses an empowerment/autonomy framework which is consistent with our self-determination model. In addition, it includes adult learning methodologies and interactive group exercises with role-playing. The DEEP program is aimed at increasing patients' knowledge, skills, and autonomy related to diabetes management and control. The training addresses physical activity, nutrition, psychosocial support, medication use, and the health care team interaction. Dr. Castillo and MLHRC staff will lead the DEEP training program sessions. Drs. Gerber and Sharp (co-PIs) will conduct additional training on navigating the health care system and motivational coaching based on the standardized *Training Curriculum for Health Coaches*, developed by a consultant, Dr. Thomas Bodenheimer. The curriculum includes six 1-hour sessions on the collaborative paradigm (*ask* instead of *tell*), action plans, problem solving, cardiovascular disease and medication management. Following training, we will assess HP competencies in counseling and diabetes-related clinical skills. Drs. Sharp and Castillo will utilize the Behavior Change Counseling Index (BECCI)[72] to assess the ability of each HP in collaboratively discussing behavior change in three mock encounters. The BECCI shows adequate reliability (Cronbach's Alpha 0.63) and good inter-rater reliability (0.79 - 0.93).[72] To evaluate clinical skills, the HPs will demonstrate reliable measurement of blood sugar, blood pressure, and pulse, and administration of insulin. They will not administer insulin to patients, but will be able to provide assistance to patients on self-injection technique. HPs will also observe and shadow pharmacists' interactions with patients in the UIMC Medication Therapy Management (MTM) Clinic for two weeks as an apprenticeship to gain insight into pharmacists' roles and activities (see letter of support from Jessica Tilton, Pharm.D., MTM Director).

Patient Encounters: The HP will communicate with each patient every week for the first three months, then every 2-4 weeks. HP encounters will include home visits and telephone contact. By performing home visits, the HP may evaluate home issues related to lifestyle changes (e.g., food inventory), medication adherence (e.g., medication storage), and technique in injecting insulin and testing blood sugar. In addition, the HP will check blood pressure and blood sugar to share with the pharmacist. The HP will follow six stages during encounters including: *social* (identify new changes or challenges), *assessment* (acknowledge beliefs and recall prior information), *education* (teaching and skill building), *review/reinforcement* (elicit understanding and competence), *goal setting* (identify short-term goal and review options and choices), and *referral* (access community or health care resources). These stages are based on the Mexican American Trial of Community Health Workers (NCT01067092) conducted with health promoters in Chicago.

Medication and Lifestyle Adherence Support: HPs will attend to both lifestyle and medication adherence related issues by identifying barriers, solving problems, and providing autonomy support (Table 2). For example, HPs will address language barriers with providers, limited health literacy, transportation barriers, and cultural barriers (e.g., alternative therapy use that may interfere or replace the use of conventional medicines). HPs will attempt to elicit and address concerns, beliefs, and social norms that may threaten acceptance and adherence to conventional therapies. The HPs will parallel pharmacist activities by evaluating adherence, assisting in medication reconciliation, reviewing home glucose and/or blood pressure monitoring data, and providing reinforcement of proper medication use. They will assist in the implementation of pillbox use and other adherence aids as needed. Also, HPs will have a touch tablet personal computer for participant use of multimedia for education, skill building, and motivation (*"Living Well with Diabetes"*).[52]

HPs will also provide education and support that reinforce lifestyle adherence in conjunction with medication adherence. HPs are trained on the diabetic and DASH diet along with basic physical activity recommendations so that they can work with patients to set individual goals. Education will address realistic and achievable food choices, portion sizes, cooking preparation, relationships between medications-meals-glucose levels, integration of physical activity into lifestyle, and local community resources for grocery shopping and regular exercise. Our pilot study found that lifestyle modifications complement patient incorporation of medication use (e.g., avoidance of sweetened beverages taken with oral medication, or timing of hypoglycemic medication with eating multiple small meals).

Communication with Pharmacists: The HP-pharmacist team will meet weekly to discuss each participant. Under certain circumstances (e.g., frequent participant hospitalizations), a meeting will be arranged

that includes the PCP. These meetings will provide a forum to share strategies and address common barriers to medication adherence. Based on our pilot study, frequent communication and meetings are necessary to reconcile medications, address barriers, and intensify therapy given patient complexity.

C.7. Crossover Transition: One year after enrollment, the 150 participants receiving *Pharm+HP* support will have the HP component phased out to assess maintenance (**Aim 2**). The 150 participants in the pharmacist only group during year 1 will receive HP support for the subsequent year to assess intensification (**Aim 3**). Prior to this transition, HPs will enlist social support and other community resources for long-term assistance with medications. HPs will remind participants and PCPs of the changes well in advance of impending disengagement to create a smooth transition. However, even though HPs becomes less *actively* involved in participant support, they remain a natural, *passive* form of assistance. HPs may periodically be contacted by their clients with questions or concerns. HPs will log this form of communication as well.

C.8. Participant Retention: Attrition is a challenge for follow up data collection, particularly in underserved populations. We plan to utilize several strategies including: (1) monetary reimbursement for each data collection; (2) periodic phone calls to verify address and phone data; (3) use of secondary alternative contact information (e.g., family abroad in Mexico); and 4) mailing birthday/holiday cards. Using similar strategies, our research group has demonstrated success in participant retention (follow up rates at 8-24 months between 75-93%).[52, 73] When individuals are lost, we will aggressively search for them using a comprehensive standardized web-based search protocol. The protocol includes five people locators, major social networking sites including those with more minority involvement, and the department of corrections database. Searches are conducted on the target individual as well as secondary contacts. This time-intensive procedure has been successful in locating individuals for retention in longitudinal studies when other methods have failed.

C.9. Intervention Fidelity: To continuously evaluate the fidelity of the pharmacist and HP components of the intervention, investigators will review medical records of 20% of participants randomly selected to identify pharmacist encounters with participants, monitoring results, and changes in medication therapy. In addition, we will monitor HP activities through worksheets that include participant interactions and duration of time spent on activities. We will capture specific information on the type of support being provided by HPs, such as telephone reminder calls, travel vouchers, contact with others in the patient's support system, and discussion on traditional therapies. Drs. Castillo and Sharp will work together to help maintain a consistent level of involvement across HPs and incorporate retraining as necessary. They will evaluate HP competency following training/retraining using the Behavior Change Counseling Index (BECCI).[72]

C.10. Physiological and Survey Measures: The UIC Center for Clinical Translational Science (CCTS) and Clinical Interface Core (CIC) are located at the main UIMC campus and will provide data collection services for all physiologic measures (see letter of support from Dr. Jay Goldstein, CIC Director). Additional survey data collection will also occur in the CIC during the same visit. Data collectors will have a Bachelor's degree, at least two years of research experience with minority populations, and be bilingual. They will receive formal standardized training on survey administration. The survey requires an average duration of 50 minutes. Data collectors will be blinded to subject group assignment. Subjects will receive $40 as compensation for travel and time at each collection point. Public transit cards will also be available to patients when needed.

We incorporated survey measures based on Spanish language availability, reliability, validity, and prior experience (see Appendix VI). We also included measures from the *Peers for Progress Shared Evaluation Database*, developed by the grantees of that program (including consultants Drs. Bodenheimer and Heisler). These will allow for comparison with other research studies incorporating peer support in diabetes management (see letter of support from consultant, Dr. Fisher). Survey instruments not available in Spanish (e.g., autonomous self-regulation and perceived competence) will be translated by a certified translator with intent to establish cross-language equivalence.

Control Variables: Control variables will be completed at baseline only. *Socio-demographic Data* will include age, gender, self-reported race and ethnicity, country of origin (if other than U.S.), income, highest level of education, current employment status, global health status,[74] and insurance (see Appendix VI). If the participant is Latino, data will also include acculturation (Short Acculturation Scale for Hispanics).[75] *Diabetes and Medical History* will include time since diabetes diagnosis, receipt of diabetes education, current therapy, diabetes complications, and other co-morbidities from medical records. *Health Literacy* will be assessed using the 66-item Rapid Estimate of Adult Literacy in Medicine (REALM)[76] word recognition test in English speakers or the Short Assessment of Health Literacy for Spanish-speaking Adults (SAHLSA).[77]

Intermediate Variables: Intermediate variables will be collected at four time points (0, 6-, 12-, and 24-months; see Appendix VI). *Diabetes Knowledge* will be assessed using the SKILL-D questionnaire (reliability

of.72).[78] Health Beliefs toward medication use will be assessed through the *Benefits of Therapy* subscale (internal consistency .90).[79] Five items include beliefs towards medication controlling diabetes, preventing diabetes complications, and helping people with diabetes feel better, as well as beliefs that medications should be taken no matter how hard it is or if one is not feeling better. *Depression* will be measured using the eight item Patient Health Questionnaire (PHQ-8, reliability 0.86-0.89).[80, 81] *Social Support* will be measured using an assessment of amount of total support received and satisfaction of support from family, friends and healthcare team.[82] *Autonomous Self-Regulation* will be measured using six item Treatment Self-Regulation Questionnaire (TSRQ, reliability 0.85-0.93).[83, 84] The items begin with the stem, "The reason I would take my diabetes and cholesterol medications exactly as prescribed is…" Responses include ratings of reasons for taking medications, such as, "…because I feel personally satisfied when I keep my diabetes and cholesterol within strict guidelines." *Perceived Competence* will be measured using the four-item Perceived Competence Scale (PSC) to assess patients' experiences of feeling able to manage their diabetes successfully (reliability 0.80-0.94).[57, 83, 85] Scores are associated with quality of life, medication adherence, and A1c.[83, 85]

Process Measures: *HP Activity* will be collected on a standardized worksheet completed after every participant contact (by phone and in-person, see Appendix VII). Information will include mode, time, and content of contact, results of glucose or blood pressure self-monitoring, goals, and interventions. Drs. Sharp and Castillo will review HP worksheets for intervention fidelity and calculate cumulative contact time for cost analyses. *PCP and Pharmacist Activity/Medication Changes:* The pharmacist will reconcile medications as part of the intervention, and the reconciled list from the medical chart will be used as data to evaluate medication changes and overall complexity of therapy. Intensification of therapy will be defined as the number of increases in the dosage of antihypertensive, hypoglycemic agent, or insulin or the addition of a new agent since the baseline visit.[33] Chart review will define the number of PCP and pharmacist encounters as well as the number of pharmacist- or physician-initiated medication changes. *Drug Related Problems Identified:* Drug problems will be identified using the Pharmaceutical Care Network Europe (PCNE) classification system which uses a hierarchical system to classify drug related problems by problem, cause, intervention, and outcome (see Appendix VIII). We will track reported adverse drug events (e.g., allergic reaction, side effect/intolerance, etc.) and hypoglycemia frequency by medical record review. This will help determine how often adverse events arise during the intervention, especially in the context of medication intensification and reconciliation.

Clinical Outcomes: Clinical outcomes will be collected at four time points (0, 6-, 12-, and 24-months). Professional research staff from the Clinical Interface Core (CIC) will perform phlebotomy, blood pressure, weight and height recordings requiring 30 minutes on average. CIC staff will be blinded to subject group assignment. Hemoglobin A1c will be obtained via phlebotomy. The laboratory test has National Glycohemoglobin Standardization Program certification. Fasting lipid profiles will also be obtained via phlebotomy, including HDL, LDL, and triglyceride measurements. Height and weight measurements will be obtained to determine body mass index (BMI). A calibrated digital scale will measure weight. A height stadiometer will measure body height, with subjects removing their shoes. BMI is particularly important to measure, as intensification of certain therapies (e.g., insulin, sulfonylurea) results in weight gain. Blood pressure measurements will be recorded on subjects sitting down for at least five minutes, following standard procedure. Extreme blood pressures are reported to the principal investigator (Dr. Gerber) per CIC protocol.

Behavioral Outcomes and Adherence: Self-care behaviors related to diabetes self-management including diet/physical activity will be evaluated through the *Summary of Diabetes Self-Care Activities Measure (SDSCA)*.[86] This includes 11 core items on diet, exercise, blood sugar testing, foot care, and smoking. Adherence to medications will be quantified using self-report and objective measure on a portion of the sample. The 8-item Morisky scale (reliability 0.83) will assess medication adherence by self-report. This scale has been validated in patients with hypertension and correlates with blood pressure.[87] Also, adherence to one oral hypoglycemic or antihypertensive medication will be measured using the *Medication Electronic Monitoring System (MEMS)* for one month at each data collection time point. Due to cost and feasibility, only a subset of 50 randomly selected participants from each group will receive MEMS. The MEMS system includes a microcircuit is integrated into drug packages that records the time and date of use. The device is highly acceptable among low-income, minority populations[88] and can store up to 3800 medication related events. We will calculate medication adherence as the number of observed events per expected prescription events. Participants who use a pill box will keep the MEMS bottle beside their pill box and take the medicine from the MEMS bottle when other medications are taken from the pill box.

Quality of Life: *Health Related Quality of Life* will be measured using the EQ5-D (general)[89] and DDS4 (diabetes specific)[90] quality of life measures. The scores will be used to determine treatment effectiveness in the cost effectiveness analysis using Quality Adjusted Life Years (QALYs).

Cost and Healthcare Utilization Data*:* We will conduct a cost-utility analysis comparing *Pharm* with *Pharm+HP*, following the guidelines for conducting pharmacoeconomic analyses by the Panel on Cost-Effectiveness and Medicine and the International Society for Pharmacoeconomics and Outcomes Research.[91-93] We will conduct the analysis from the *health-system perspective*, taking into account *direct program costs and direct non-program costs.* Direct program costs will include personnel, educational materials, and any visit related costs. Direct non-program costs will include cost for all major health care utilization for hospital admissions, emergency room visits, outpatient visits and prescription medications during the intervention period. Participants will be followed throughout the course of the study to obtain data on their program and healthcare costs. A participant diary, provided upon enrollment, will be used by participants to collect self-reported data on healthcare use events outside of the UIMC. For health care use received at UIMC, we will collect information electronically from the hospital electronic records and billing data for enrolled subjects. These data sources will provide details of ambulatory and hospital use, professional and technical visit fees, emergency room visits, as well as laboratory and other ancillary services use. Cost estimates for the program costs (salaries for HPs, etc.) will be based on prevailing costs at the time. Cost estimations for healthcare use will be based on national Medicare reimbursement rates (average DRG rates) for hospitalization, Medicare fee schedules for physician and other professional services, and Medicare's Resource-Based Relative Value Scale (RBRVS) for outpatient procedures. Since our study will span a time period exceeding one year, costs will be adjusted to reflect societal rate of time preference and inflation (and all costs will be adjusted to a current year).

C.11. Sample Size Justification: Sample size calculations are powered to detect change in A1c. The ADA Technical Review of Diabetes Self-Management Education reported that successful education programs achieved reductions of 5-20% in A1c.[69] The UKPDS 35 demonstrated that each 1% absolute reduction in mean A1c is associated with a 21% decrease in risk for any diabetes-related endpoint, a 21% decrease in diabetes-related deaths, a 14% decrease in risk for myocardial infarctions, and a 37% decrease in risk for microvascular complications.[94] Based on our previous study, we estimated a mean baseline A1c level of 10.0% with standard deviation of 1.8 and an effect size of (1.0/1.8) 0.56 for **Aim 1**. The cross-time correlation was estimated to be 0.30. We adjusted for clustering, assuming an intraclass correlation coefficient (ICC) of 0.02 and cluster size of 30 which yields a design effect of 1.58. Two-sided alpha of 0.05 and 80% power are assumed requiring a minimum of 114 per group. Allowing for 10% drop-out during each of the two years, 150 patients will be required for enrollment for each group (300 total).[95]

Billing data from UIMC reveal that there were approximately 30,000 ambulatory encounters by adult African-Americans and Latinos with diabetes during fiscal year 2009 (representing over 8,000 unique patients). We estimate that approximately half of these patients have an A1c level above 8.0% based on prior study.[52] Therefore, at least 4,000 subjects are potentially eligible for recruitment. The proposed study requires enrollment of 7.5% (300/4,000) of potentially eligible UIMC patients. We are confident that we can meet our recruitment goals as we have successfully recruited a similar size of patients with type 2 diabetes.[52]

C.12. Data Management and Analyses: All data will be stored in a secure, locked location. Data will entered, cleaned, and analyzed in SPSS. Data will be analyzed for clinical effectiveness using intention-to-treat principles.[96-98] To represent dropouts in the analysis, missing data will be imputed using various schemes, such as "last value carried forward" (LVCF). The Little and Yau "return to baseline" imputation rule, in which any gains over baseline levels dissipate upon dropout, will be used for primary analyses.[96] Of note, patients in the *Pharm+HP* group who share a single PCP might exhibit similarities that are not shared with patients attended by other PCPs. To address this, we will include random effects in the model for clinic site, PCP, and HP (though the small numbers of HPs may call for a fixed effect approach, or "insufficient replication").[99] Rather than model idiosyncratic heterogeneity among providers we will include as predictors relevant care and treatment-related variability such as medication therapy intensifications and clinical encounter frequency.

Aim 1/H_1 (Effectiveness): We will test the hypothesis that A1c, blood pressure, and LDL-cholesterol levels will be lower and diabetes behaviors (including medication adherence) will be improved with patients receiving *Pharm+HP* compared with those receiving *Pharm* alone. Univariate comparisons between the two study groups with respect to outcome measures and covariates at baseline will be conducted using chi-square tests for categorical variables, Kruskal-Wallis tests for ordinal variables, and ANOVA for continuous variables. Non-normal continuous data will be transformed prior to analysis (e.g., natural logarithm). The baseline variables include demographic, medical, therapy complexity, and health literacy data. With randomization, imbalances between groups should be due to chance alone; moreover, statistical differences between groups may result from performing many univariate tests (i.e., Type I error). However, if we find any between-group differences, we will adjust for this in our primary multivariate analyses by including relevant covariates.

In order to provide comprehensive analysis for $\mathbf{H_1}$, we will extend the usual analysis of crossover

designs[100] by including a longitudinal trend component in the first year. Thus, we can examine the time course (0, 6, and 12 months) as linear or quadratic over the first three measurements. This will allow us to investigate whether changes are made early, and at what rate they continue through the rest of the time period. This analysis permits the comparison of trends between *Pharm* and *Pharm+HP* conditions. In addition, we will regard subjects as a random effect and will use Gaussian mixed-model estimations (SPSS MIXED command). We can then substitute treatment by period interactions for the carry-over effects, and the model can be reduced in a recommended sequence (first omit carry-over, then omit treatment, finally omit period).[100]

The primary analysis of each outcome in the repeated measures design will be conducted in a general linear model framework. SPSS MANOVA (for repeated measures) will be used to explore the simultaneous impact of the treatment on multiple correlated dependent variables, including the use of Roy-Bargmann stepdown F-tests and discriminant function analysis as post hoc tests to identify subsets of outcome measures affected.[101] SPSS MIXED will be used to explore patterned structures such as compound symmetry and autoregression along with incorporating time-varying covariates, such as depression. MANOVA secondary analyses will explore the impact on results of inhomogeneous baseline variables. Exploratory subgroup analyses will determine which subjects in the intervention group had the greatest improvement in outcomes, based on demographic factors, health literacy, and medication regimen. Group by time-trend interaction contrasts also will be used to explore different group trajectories of change. In addition, we will investigate the potential consequences of medication intensification (e.g., initiation of insulin) by evaluating changes in BMI, identified drug related problems and adverse drug events.

If *Pharm+HP* is associated with improved outcomes, we will examine whether improvements in autonomous self-regulation and perceived competence serve as mediators for these outcomes according to our conceptual framework (SDT). In addition, we will explore diabetes-related behaviors (including eating habits, physical activity, and medication adherence) as well as medication treatment intensification as alternative mediators using MPlus.[102-105] Given the sample size, observed (rather than latent) variables will be used in the mediation models. To enhance the power of secondary (exploratory) mediation modeling, we will adopt an α=.10 Type I error criterion to improve the chances of finding promising mediators for future study.

Aim 2/H_2 (Maintenance): We will test the hypothesis that diabetes behaviors and clinical outcomes will be maintained one year after phase out of HP support. These analyses will be conducted similarly as for **H_1**, and will evaluate change in the initial *Pharm+HP* group after HP phase out at one year.

Aim 3/H_3 (Intensification): We will test the hypothesis that diabetes behaviors and clinical outcomes improved by adding *HP* support after one year of *Pharm* alone. These analyses will be conducted similarly as for **H_1** and **H_2**, and will evaluate change in the initial *Pharm* group after HP has been added at one year.

C.13. Costs and Cost Effectiveness Analysis (Aim 4): We will obtain program and healthcare use data for the study period to estimate cumulative costs for each group over 24 months. However, complete cost data will not be available for all subjects. Some subjects will drop out, and some may have missing data (i.e., data may be censored). To accommodate drop outs and censoring in the cost estimates, we will use a modification of survival analysis. To estimate average cumulative costs, we will divide the time interval following randomization into months, and then estimate cumulative costs to time *T* (i.e., 6, 12 and 24 months) as: $\overline{C}_{(T)} = \sum_{t=1}^{T} p_t \times c_t$, where p_t is the probability of participating at month *t* (the Kaplan-Meier estimator of the probability of participating to the start of month *t*), and c_t is the mean cost at month *t* given participating at *t*, (estimated using data from patients who participate to the beginning of month *t*).[106] The estimate is based on patients' costs during time period *t*, which includes costs of patients who participate to the start of time period *t* but who may dropout or may be censored during time period *t*.

To estimate cumulative costs, patients participating at the end of follow-up contribute cost information from the point of randomization up to the end of follow-up, while patients who dropped out before the end of follow-up contribute costs from randomization through their drop out date and zero costs from drop out to the end of subject follow-up.[107] To account for society's general preference for events in the present over events in the future, we will estimate the average present value of costs by discounting costs that occurred in the years following the intervention.[106] The issue of time preference is separate from cost inflation and would occur even in the absence of inflation.[106] If the discount rate is *r*, then the average present value of costs cumulative to time *T* (i.e., 6, 12, and 24 months) $\overline{C}_{(T)}$ is: $\sum_{t=1}^{T} \frac{\hat{S}_t \overline{C}(t)}{(1+r)^{t-1}}$

where $\hat{S}_t$ is the Kaplan-Meier estimator of the probability of participation to month *t*. Following the recommendation of the U.S. Public Health Service's Panel on Cost-Effectiveness, we will use a discount rate of 3% per year.[92] We will calculate the average cumulative cost at time *T* (i.e., $\overline{C}_{(T)}$ from above) for subjects in both groups. To conduct the cost-effectiveness analysis, we will calculate the incremental average costs

resulting from *Pharm+HP* relative to *Pharm*. A two-sample t-test for independent groups will be used to compare costs between the two groups. Costs may not be normally distributed; however, if the sample is sufficiently large, t-tests on untransformed costs are appropriate.[108, 109]

Our effectiveness measures will include improvements in A1c, blood pressure, of cholesterol levels and projected quality-adjusted life-years (QALYs).[110] The incremental cost-effectiveness ratio (e.g., cost per change in A1c) of *Pharm+HP* vs. *Pharm* will be estimated at the end of 12 and 24 months. Cost per QALY will be determined from projections of continued *Pharm+HP* involvement and assumptions concerning the continued effects of *Pharm+HP* on outcomes over time. The QALY and utility estimates will be based on the Markov model developed by the Diabetes Cost-effectiveness Group at the CDC (using UKPDS data).[110] Sensitivity analyses will estimate the impact of changes in factors such as age, induced health-care visits, incidence of complications, HP costs, physician time, and discount rates.

We will follow standard cost-effectiveness methods and discount both QALYs and costs at 3% per year to maintain equivalent treatment of the measures of costs and effectiveness over time.[92] To compare discounted QALYs, we will integrate the area under the Kaplan-Meier quality-adjusted survival curves for each patient group to obtain mean QALYs and then take the difference between the two areas,[107] which will give the incremental effectiveness from receiving the *Pharm+HP* intervention rather than *Pharm* alone.

The ratio of net costs (Δ costs) and net utility (Δ utility) will yield the incremental cost utility ratio between the *Pharm+HP* and *Pharm* groups. One-way sensitivity analyses will be used to determine the impact of discount rate (between 0% and 10%) on the cost utility ratio. We will also examine variability associated with the cost-utility ratio using a bootstrapping technique which involves drawing 1,000 or more random samples with replacement from the data. After each resampling, we will recompute mean costs and QALYs.[107] The results of the bootstrapping will be presented using the acceptability curve approach. The acceptability curve shows the probability an intervention is considered cost-effective, given a range of maximum amounts that a decision maker is willing to pay for the outcome (e.g., $50,000/QALY). The ceiling ratio that has a probability of 0.5 on the acceptability curve is the point estimate of the ICER, and the ceiling ratios where the probabilities on the curve are 0.025 and 0.975 provide an estimate of the 95% confidence interval on being cost-effective.[111, 112]

C.14. Organization/Timeline: A project coordinator will lead weekly steering committee meetings at UIMC with all study investigators and staff. Drs. Gerber and Sharp will supervise all study procedures. Dr. Gerber is a UIMC staff physician who is well connected with UIMC ambulatory clinical sites; he will lead monthly phone conferences with participating pharmacists. Drs. Sharp and Castillo have extensive experience training and supervising HPs and will establish monthly individual or small group meetings in a community setting. Dr. Mihailescu, endocrinologist, will provide specialist support regarding diabetes care and algorithms. Jessica Tilton, Pharm.D. will assist HPs in learning about pharmacist medication management. Dr. Berbaum will lead data management and main analyses, and Dr. Touchette will conduct the cost-effectiveness analysis.

A Community Advisory Board (CAB) will be established to ensure that all recruitment and intervention procedures are sensitive to the needs of the communities. The board will include UIC research investigators, a pharmacist, a physician, and a nurse from the UIMC, the HPs, and up to three African-American or Latino community members with type 2 diabetes. The board will meet every quarter during the first year of recruitment and biannually thereafter to review recruitment measures, HP activities, and discuss means of maximizing retention and support for participants. The following is the proposed study timeline:

Year:	**1**				**2**				**3**				**4**				**5**			
Quarter:	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Stage 1: Preparation																				
Health Promoter Training	■	■	■	■				■				■				■				
Prepare Surveys	■	■																		
CAB Meetings		■		■		■		■		■		■		■		■		■		■
Stage 2: Implementation																				
Study Advertisement		■	■	■	■	■	■	■	■	■										
Recruitment		■	■	■	■	■	■	■	■	■										
Pharm+HP Delivery			■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■		
Data Collection			■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■		
Stage 3: Analysis																				
Data Entry/Management				■	■	■	■	■	■	■	■	■	■	■	■	■	■			
Chart/Worksheet Review					■		■		■		■		■		■		■	■		
Data Analyses								■				■						■	■	
Presentations/Manuscripts								■	■			■	■			■	■	■	■	■

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