EHR-based Health Literacy Strategy to Promote Medication Therapy Management

Principal Investigator: Stephen Persell
Address: 750 North Lake Shore Drive, 10th floor, Chicago, IL 60611
Site(s) where study will be performed: Northwestern University and ACCESS Community Health Centers
Protocol Version Date: March 29, 2016

Background/Rationale/Literature Review:

There is a well-documented need for feasible, effective and sustainable approaches to help patients safely execute complicated outpatient medical regimens. The overall objective of this study is to rigorously evaluate two related approaches to improving patients' medication self-management in primary care settings.

Medication Complexity, Non-Adherence and Medication Errors in Ambulatory Care

Patients with chronic conditions are asked to use increasingly complex medical regimens.\(^1\), \(^2\) For example, in 2000, 44% of U.S. adults with diabetes had 4 or more medications prescribed.\(^1\) Long-term proper adherence is essential to reap the health benefits demonstrated in clinical trials, however, non-adherence is widespread. For major chronic illnesses, all forms of non-adherence—failure to fill new prescriptions,\(^3\) incomplete adherence to medications being used,\(^4\), \(^5\) and premature discontinuation\(^6\)-\(^8\)—are all extremely common. Non-adherence has been clearly linked to increased morbidity and mortality from chronic conditions.\(^9\)-\(^12\)

Complex drug regimens raise the risk for errors and adverse drug events. Outpatient adverse drug events are prevalent and many are either preventable or ameliorable.\(^13\)-\(^18\) A recent Institute of Medicine report, *Preventing Medication Error*, suggests 1.5 million preventable adverse drug events occur annually, with a third occurring in outpatient settings at an estimated cost of $1 billion.\(^19\) Individuals with chronic illness and the elderly are at greatest risk for unintentional medication errors, failing to properly administer medication as intended.\(^13\), \(^14\), \(^20\)-\(^23\)

Steps in Successful Execution of Medication Care Plans for Chronic Conditions.

For outpatient care, patients (or their surrogates) are primarily responsible for the execution of medication care plans. The expectations for medication management placed on patients by the health care system are considerable. Multiple steps need to occur for patients to gain the benefits of chronic drug therapy while minimizing the risks of adverse drug events. Ideally this would begin with an exchange of information between prescriber and patient followed by reaching agreement on an appropriate medication plan. As a result of these interactions, or due to information obtained from other sources, patients acquire the information they will use to administer medications on an ongoing basis. Information about prescription medication may come from sources directly involved in the prescribing and dispensing process (prescriber/other healthcare team member, prescription, pharmacist, medication guides, Rx label or auxiliary labels) or from other sources (references, internet, family, friends, advertising).\(^24\) Patients and their healthcare providers must also recognize safety problems or adverse events when they occur and modify the medication care plan when necessary. Patients and providers must also monitor the efficacy and tolerability of prescribed medications. Changes to the medication plan are common in response to changing disease conditions, adverse effects, cost considerations or lack of efficacy. When changes are made, patients are the ones who must successfully execute these changes. New medicines may be added, others are discontinued, and dosages may be altered. Errors in any of these steps or could lead to adverse drug events or reduced efficacy of treatment.

Deficits in Provider Communication about Medications.

A basic understanding of one’s medication (the indication, how to administer, adverse effects to be aware of) is an essential prerequisite for patients’ safe, successful execution of their medication plan. Unfortunately, there is evidence that this important information is delivered to patients in a haphazard way.
Multiple studies show that physicians frequently do not adequately counsel patients on safe and appropriate drug use.\textsuperscript{25-29} Furthermore, physicians rarely assess patient comprehension,\textsuperscript{30} or discuss medication affordability even though out-of-pocket cost directly influences adherence.\textsuperscript{31,32} In routine outpatient practice, pharmacists seldom provide medication counseling.\textsuperscript{25,27,28}

**Patient Difficulty with Cognitive Tasks Surrounding Medications.**

The information patients do receive about their medications may often not be provided in an accessible manner to support use. Studies indicate that written medication information that accompanies prescription drugs is difficult to understand for many patients.\textsuperscript{33} Recent studies have repeatedly shown that a large proportion of patients have difficulty performing routine medication management tasks, such as correctly interpreting dosing instructions\textsuperscript{20,34-35} and warning labels on prescribed medications,\textsuperscript{21,36} accurately and completely self-report currently used medications, and possess knowledge of basic indications for prescribed medicine.\textsuperscript{37-39} In several studies, limited literacy was associated with an increased risk for these medication related problems.

**Discrepancies between Patient and Provider Medication Lists and the Importance of Reconciliation.**

Discrepancies between the medications patients are taking and the medications health care providers believe they are taking may indicate the presence of one or more important problems. (1) Patients may unknowingly be out of agreement with the medication care plan intended by their providers (e.g., they may have inadvertently not started a medication, or failed to realize that their clinician intended them to stop using one). (2) Patients may be deliberately not adhering. (3) The healthcare team may have made errors (e.g., errors in documentation or actual errors in care). (4) The healthcare team may be unaware of medications a patient obtained elsewhere. Without systems in place to regularly encourage medication reconciliation, these important problems may go unnoticed.

Multiple recent studies have shown that medication discrepancies are highly prevalent. Physicians rarely perform comprehensive review of chronic medications,\textsuperscript{40} and therefore may be unaware when patients are not taking essential medications or using medications that were discontinued. Problems result in either scenario, as patients become at risk for potentially dangerous use of medications that were stopped for medical reasons or duplication of medications when a substitution from one medication to the next was intended. Medications listed in patients' medical records are frequently discordant with the medications patients report taking.\textsuperscript{37,38,41-46}

Medication discrepancies are particularly common among patients using multiple medications who have been recently hospitalized.\textsuperscript{47-51} Among adults receiving care at community health centers, patients with low literacy are more likely to have medication discrepancies for their hypertension medications than were patients with adequate literacy,\textsuperscript{38} and reconciliation errors have been associated with worse blood pressure control in one study.\textsuperscript{37} Medication reconciliation is also necessary to reap the full safety benefits available through the use of EHRs. Safety features such as the detection of drug-drug interactions or allergies are not effective if medications are not recorded within a patient's EHR.

**Improving Medication Use through Medication Therapy Management**

**Definition and Rational for Medication Therapy Management.**

Medication therapy management (MTM) has evolved as a systematic approach to assist patients with many of the medication-related problems described above. Formally introduced with the implementation of Medicare Part D, MTM now serves as a mandate to Part D insurers to provide qualifying patients with medication assistance.\textsuperscript{52} As defined by the American Pharmacists Association, MTM includes medication review, assembly of a personal medication record, development of patient medication-related action plans, clinical interventions when necessary, and follow-up.\textsuperscript{53} The rationale for this program is to provide Medicare beneficiaries who have high drug complexity and high drug cost with additional education and support in order to improve medication adherence, improve the detection of medication misuse, and reduce adverse drug events.\textsuperscript{54}

**Evidence Base for MTM and Its Limitations.**

Published outcomes from MTM are scant and subject to important methodological limitations. In the Iowa State Medicaid Pharmaceutical Case Management program, MTM reduced the number of potentially inappropriate medications used, but the comparison group was not randomly assigned. In this study,
healthcare utilization did not change and important clinical outcomes were not examined.\textsuperscript{55, 56} Another report indicated that an MTM intervention increased medication knowledge but not adherence though there was no control group.\textsuperscript{57} A Minnesota BCBS study done within medical practices compared to historical controls suggested that the MTM program improved the achievement of therapeutic goals and significantly reduced healthcare costs.\textsuperscript{58, 59} To date, well controlled trials have not been performed to examine the impact of MTM on clinical outcomes. Rigorously testing viable MTM approaches, particularly among high risk groups such as those with limited literacy, is clearly warranted.

In contrast to the limited evidence base for general MTM interventions, multiple disease specific interventions that have employed some features of MTM have shown beneficial effects. In the case of hypertension, controlled trials employing pharmacists to perform several different hypertension-related tasks have, for the most part, shown beneficial effects on blood pressure. A meta-analysis of 13 controlled trials revealed greater reductions in systolic blood pressure in intervention groups compared to controls (6.9 mm Hg difference). Interpretation of these studies is somewhat limited because their quality, and publication bias may also have been present.\textsuperscript{60} Other recent trials employing pharmacists have also shown beneficial effects in hypertension.\textsuperscript{61-64} Studies employing nurses have been mixed with studies showing both positive effects,\textsuperscript{65-69} or no effect.\textsuperscript{70, 71} Similar to hypertension, the findings in interventions aimed at improving diabetes control using pharmacists or nurses are generally favorable but are similarly heterogeneous.\textsuperscript{72, 73} These disease-specific studies generally support the notion that the addition of a pharmacist or nurse to the larger care delivery team can produce favorable results. A recent meta-analysis of interventions to improve adherence among patients with cardiovascular disease or diabetes also supports this conclusion.\textsuperscript{74} However, it is impossible to apply conclusions from disease specific studies (which targeted disease-specific care processes) to general MTM approaches. Whether or not non-disease-focused MTM interventions change important indicators of chronic disease control is essentially unknown.

**Hypothesis/Key Questions:**

**Study Overview.**

Many patients have difficulty performing routine medication management tasks. Individuals with limited literacy are at high risk for these problems. The overall study objective is to rigorously evaluate two primary care-based medication therapy management strategies that leverage an electronic health record (EHR) to promote patient understanding, medication reconciliation, medication adherence and disease control among hypertensive patients at safety net clinics.

Medication therapy management (MTM) has been described as a set of procedures that include: medication review, assembly of a personal medication record, development of action plans, intervention when necessary, and follow-up. However, evidence showing the effectiveness of general MTM interventions is scant. MTM has often been performed separately from patients’ usual sources of care (i.e., at pharmacies). This could limit its effectiveness since medication-related concerns would be discussed by clinicians who are not aware of the regimen intended by patients’ prescribers. Cost is another barrier to widespread use of MTM.

Health information technology in primary care could be leveraged to assist with MTM tasks. We have field tested low literacy MTM tools embedded within an EHR to 1) activate patients to review medications, 2) automate the provision of plain language, medication information, and 3) provide print tools to help patients engage providers, and consolidate their regime. These tools were developed with patient, physician, and pharmacist feedback.

For this study, we combine tools to address the range of MTM tasks. In aggregate, we refer to this as an Electronic health record-based Health literacy Medication therapy management Intervention, or ‘EHMI’. We will evaluate the effects of this approach among patients with uncontrolled hypertension treated in federally qualified health centers (FQHCs). This may be a relatively low-cost strategy ideal for safety net practices that use EHRs and whose patients may be at greater risk for limited literacy. It is also possible that the EHMI strategy may not result in a significant change. Therefore, we will also evaluate using a nurse educator to help patients utilize EHMI tools, provide brief counseling, and track progress.

This three-arm, clinic-randomized, controlled trial at 12 FQHCs will evaluate the EHMI and EHMI + Nurse Educator interventions compared to usual care. Recruited patients will be followed for 12 months. We will test the impact of these two strategies on blood pressure levels, , powered to detect a 4 mm Hg difference.
in systolic blood pressure as the primary outcome. We will also assess the impact on HbA1c and LDL cholesterol control in the subgroup with diabetes. We will determine the interventions’ effects on: 1) medication understanding, 2) discrepancies, and 3) adherence. We will specifically examine intervention effects among groups with different literacy levels. We will also assess the fidelity and cost of the interventions to guide future dissemination efforts.

Our primary aims and hypotheses are to:

**Aim 1** Test the effectiveness of the EHMI strategy, with and without a nurse educator, to improve patient understanding, medication reconciliation, adherence, and health outcomes compared to usual care.  
*Compared to usual care, patients receiving MTM interventions will have:*

- **H1** better functional understanding of medications  
- **H2** fewer discrepancies in their medication lists  
- **H3** greater medication adherence  
- **H4** better intermediate chronic disease outcomes (systolic blood pressure, LDL cholesterol, HbA1c)

**Aim 2** Determine if the effects of these strategies vary by patients’ literacy skills.  
**H5** The intervention effects will be greater among individuals with limited literacy.

**Aim 3** Evaluate the fidelity of the two strategies and explore patient, staff, physician, and health system factors influencing the intervention.

**Aim 4** Assess the costs required to deliver this intervention, exclusive of system design.

**Research Methods:**

**Methods Overview**

We will conduct a three-arm, clinic-randomized trial at 12 community health centers in Chicago, IL to evaluate the EHMI and EHMI + Nurse Educator interventions compared to usual care (N=1680 patients; 140 per clinic; 560 per study arm). Patients with uncontrolled hypertension will be recruited and assessed in-person at baseline, 3, 6, and 12 months. We will also assess the fidelity and economic impact of the interventions to identify any necessary modifications to guide future dissemination efforts. All study procedures performed at ACCESS sites or requiring the collection of ACCESS patients’ data will be reviewed by the appropriate ACCESS personnel for approval. If changes are deemed necessary, a revision to the study protocol will be submitted to the IRB for review and approval prior to implementing these changes.

**Endpoints**

The primary endpoint is systolic blood pressure measured approximately one year after the baseline interview is conducted.

**Clinic Randomization**

**First Randomization Block:**

To optimize the likelihood of obtaining similar populations in each intervention arm, clinics will be enrolled and randomized in blocks of 3. The blocks will be comparable based on their number of patients potentially eligible for the study. Dr. Persell and Ms. Friesema will randomly assign each clinic to an intervention arm in a blinded fashion and without knowledge of which number corresponds to which clinic. We will reveal clinics identities after randomization is completed.

**Randomization Blocks 2 and 3:**

To optimize the likelihood of obtaining similar recruitment numbers and populations in each intervention arm, clinics will continue to be enrolled and randomized in blocks of 3. Dr. Alfred Rademaker, the study’s statistician, will take over the randomization procedure. He will look at the current accrual rate in the 3 study arms to date and the anticipated accrual in the 3 arms over this next wave. Next he will take all the random
permutations of the 3 anticipated accruals (there will be 6) and look at the possibilities of where to allocate each permutation to the existing accrual numbers to come up with a total number randomized to each arm at the end of this period. Weights of the permutations will then be based on the inverse of the standard deviation of the resulting sample sizes in an effort to produce the most equal sample sizes. Finally, a pure randomization occurs where a permutation will be chosen at random and applied to the 3 clinic sites. We will reveal the clinic identities after the randomization is completed.

Remaining Randomization Blocks:
To optimize the likelihood of obtaining similar recruitment numbers and populations in each intervention arm, clinics will continue to be enrolled and randomized in blocks of 3. Dr. Alfred Rademaker, the study’s statistician, will continue to conduct the randomization procedure. He will look at the current accrual rate in the 3 study arms to date and the anticipated accrual in the 3 arms over this next wave. In order to address current size imbalances in the study arms, he will remove the 2 permutations that would allow for the smallest site to be randomized to the EHMI intervention only arm. Next he will take all the random permutations of the 3 anticipated accruals (there will be 4 remaining) and look at the possibilities of where to allocate each permutation to the existing accrual numbers to come up with a total number randomized to each arm at the end of this period. Weights of the permutations will then be based on the inverse of the standard deviation of the resulting sample sizes in an effort to produce the most equal sample sizes. Finally, a pure randomization occurs where a permutation will be chosen at random and applied to the 3 clinic sites. We will reveal the clinic identities after the randomization is completed.

Staggered Recruitment and Roll Out.
We seek to avoid exposure of study patients to the EHMI intervention tools prior to their enrollment in the study. To accomplish this, we will conduct enrollment and activation of EHMI tools (intervention group clinics only) in a staggered fashion at one clinic from each arm at a time. Recruitment and intervention commencement will occur over the first 30 months of the Intervention phase.

Study Interventions

We will collect data from in-depth, structured interviews that include literacy and mental status assessments, and medication use and review of medical records (demographics, comorbidities, hemoglobin A1c and cholesterol levels, and medication lists). At each study visit, standardized blood pressure measurement will be obtained and surveys will be conducted. A description of key measures is provided below.

Patient Characteristics and Other Variables of Interest.
Baseline assessment will include a socio-demographic and health questionnaire (10 minutes), number of current prescription medications used (total and by key categories: cardiovascular, diabetes, lipid lowering) and the Mini-Cog Exam. These will capture important covariates that may be related to study outcomes and be unequally distributed among the randomized clinics.

Medication Reconciliation.
Patients will be asked to bring their prescription medications with them to the 3, 6 and 12 month study visits. Patients will be asked to report how many different prescription medications they are taking and can consult their pill bottles or other aids that they use to keep track of their prescriptions. Patients can identify additional medications prescribed that they may not have currently in their possession. Interviewers will have the most current medication list from the EHR in their possession at the time of the interviews. Interviewers will ask patients if unnamed medications are were ever filled or if they are currently taken. We will classify patients into three primary categories (1) Reconciled—patients name the same medications as recorded in the medical record, (2) Reconciliation Discrepancies—patients could name one or more medication but the list was not in full agreement with the medical record, and (3) Unable to Name Any Medication: patients provided no recognizable names of prescription medications listed in their medical record. We have already used this classification in two recent studies. We will apply binary classifications (reconciled vs. not reconciled) to five groups of medications for each patient: 1) all not-as-needed prescription medications, 2) antihypertensive
medications, 3) diabetes medications, 4) lipid lowering medications, and 5) all prescription medications including as-needed.

Medication Understanding.

Understanding of medication instructions and dosing will be assessed through a structured questionnaire that has been developed and used extensively by Dr. Wolf and colleagues in multiple studies and current NIH-funded grants. Patients will demonstrate how they take each medication by dose and frequency. We will apply binary classifications (full understanding vs. not) to the same five groups of medications for each patient. Patients’ knowledge of medication indication will be assessed by a physician, nurse, or pharmacist who is blinded to the patient’s study assignment in a fashion to what we have done previously.

Medication Adherence.

Adherence will be measured for each prescription medication using 1) a 4-day assessment of pills taken/pills prescribed based upon patient self-report, 2) a 24-item Patient Medication Adherence Questionnaire that will assess individual barriers (e.g. cost, adverse effects, salience, stigma, beliefs), and 3) in-person pill count using established guidelines employed by our team’s current IRB approved study [R01HS00167; PI Wolf]. The questionnaire developed by Morisky will also be used as a general measure of adherence.95 Pill count will be used for antihypertensive, diabetes, and lipid lowering medications. Adherence will be treated both continuously (pills taken/pill prescribed) and dichotomously (yes/no - ≥80% of expected pills absent from pill bottle).

Disease Control.

The primary study outcome is systolic blood pressure. Research assistants will perform standardized measurements of blood pressures and pulse at baseline, 3, 6 and 12 months using an automated device (validated Omron HEM-907XL or a device with comparable accuracy). Patients will be seated quietly with their feet and back supported for 5 minutes before blood pressure is obtained. Three recordings will be performed at each visit and the mean of the second and third readings will be used to indicate the blood pressure for that visit. Patient positioning, arm selection, cuff size selection and other techniques will follow the procedures for blood pressure measurement of the National Health Examination and Nutrition Survey.96 Measures of disease control for HbA1c, and low-density lipoprotein cholesterol will be obtained from patients’ electronic health records. We will use quality measures that can be scored even when repeat laboratory measurement is not obtained. For diabetes control, the quality measures we will examine are: 1) A HbA1c test was performed and the most recent measurement recorded within the EHR in the preceding 365 days was >9.0% (poor diabetes control). 2) An alternative measure will use the threshold of < 8.0% (HbA1c < 8.0). 3) LDL-cholesterol was obtained in the preceding 365 days and was <100 mg/dl.

Health Related Quality of Life (SF-12).

We will measure whether the interventions influence health related quality of life using the SF-12.

The Newest Vital Sign (NVS)

The NVS is a reliable (Cronbach’s alpha in 3 studies ranges from = 0.74-0.81) screening tool used to determine risk for limited health literacy.103, 104 Patients are given a copy of a nutrition label and asked 6 questions about how they would interpret and act on the information contained on the label. The interviewer records patients’ responses on a score sheet that contains the correct answers. The number of correct responses is summed to produce a health literacy score ranging from 0-6. Zero or 1 correct answers indicates a high likelihood of limited literacy, 2-3 correct answers indicates the possibility of limited literacy, and 4 or more correct responses indicates that low literacy is unlikely. While less studied, it has been found to demonstrate high sensitivity for predicting limited literacy skills (AUROC = 0.76, sensitivity >0.95 in 2 studies), and in a study led by Dr. Wolf, was found to show a strong correlation with the short form of the TOFHLA (S-TOFHLA, r=0.61), while less with the REALM (r=0.41).103

**Intervention 1: Electronic Health Record-based Health Literacy Medication Therapy Management Intervention (EHMI)**

The EHMI strategy consists of multiple components, all leveraged by the Epic EHR platform (Verona, WI) and field tested previously among patients with varying literacy skills. As described in our Specific Aims,
the EHMI intervention 1) activates patients at check-in to review their medication list and identify any adherence-related concerns, 2) automates a process for providing plain language, patient-centered print medication information for new and refilled prescriptions, and 3) provides additional print tools to help patients more effectively engage their providers, consolidate their regimen, and generally promote safe use and adherence. Descriptions of these EHMI components are detailed below in the order of their administration to patients in a primary care practice.

Medication List Review. Funded by the Agency for Healthcare Research and Quality (AHRQ; R18HS17220, PI: Wolf), our team developed a clinic protocol and EHR-based strategy to promote medication reconciliation. As patients arrive, electronic check in at the front desk triggers the printing of their current medication list, accompanied by plain language instructions for patients to 1) review medicines, 2) strike out medicines they are not taking, 3) identify if they are taking remaining medicines as described by the listed instruction (yes, no, only as needed), 3) identify any concerns for each medicine they would like to discuss with their doctor (none, need refill, side effects, cost, other), and 4) add any medicine (prescription, over-the-counter, vitamin or other supplement) that the patient takes regularly.

We conducted a field test among 150 patients at the Northwestern Medical Faculty Foundation (NMFF) General Medicine clinic, with their physicians randomized to have this function turned on for their patients or usual care. Nearly all of (91%) patients in the intervention arm receive their medicine list at check in, 85% of those receiving lists review it with their physician, and >90% had discrepancies identified and removed, with an updated list printed and given to patients at discharge. Feedback from the 20 physicians randomized to the intervention arm offered unanimous positive feedback on the value of this process, and it is expected to become the new standard of care at this clinic.

Med Sheets. As an additional measure funded by the same grant (R18HS17220), we created single-page, plain language medication information sheets with content appropriately sequenced from a patient’s perspective (drug name, indication, purpose/benefit, how to take, for how long, when to call your doctor, when to stop taking and call your doctor, important information) and following other health literacy best practices. These sheets have been embedded within the Epic EHR at NMFF and are automatically generated and distributed to patients at check out for any prescription medicines that are new or have been changed. Lexile analyses were performed on a total of 300 sheets, confirming each to meet a < 8th grade readability standard. The content was initially developed by two pharmacists, supported by an environmental scan of existing tools. Patients, physicians, and health literacy experts reviewed the material and guided revision.

‘My Meds’ Tools. Other tangible, supplementary tools have been developed for patients to support their ability to 1) effectively communicate with health care providers (both physicians and pharmacists) about their medicine regimen, and 2) consolidate how they take their entire regimen to reduce medication taking behavior to the fewest times per day. This includes an educational folder that details to patients what they should do before, during and after a medical encounter.

Intervention 2: Nurse Educator + EHMI

The training and intervention protocol for using a nurse educator to support medication therapy management is based on an existing model our team is currently implementing in a clinic-randomized trial evaluating the American College of Physicians Foundation ‘Everyday Guide to Diabetes’ intervention (funded, Missouri Foundation for Health; PI: Wolf). A nurse will serve as the ‘MTM champion’, responsible for the following: 1) identifying eligible patients, 2) contacting patients and scheduling post-medical encounter, brief counseling sessions at their next appointment, 3) meeting with patients after their doctor visit in person or by phone to educate them on new prescriptions or medication changes, help them safely organize their daily regimen, and discuss any adherence concerns, 4) follow-up with patients 4 to 7 days after their visit to confirm they have filled all prescriptions, and can accurately teach back their medicine regimen, 5) communicate with prescribing physician when problems are identified.

Expected Duration for Subject Participation

The initial study visit will be conducted at the time of patient enrollment or will be rescheduled if necessary to accommodate patients’ schedules. RAs will schedule three follow-up data collection visits with
patients that will be conducted at approximately 3, 6 and 12 months. Study participation will conclude after the completion of the 12 month interview.

Data Abstraction from the Electronic Health Record.

The programmer analysis (TBD) working under the supervision of Dr. Eder and Ms. Bonello will write Structured Query Language (SQL) programs to extract the required data from the Access Epic EHR database and perform periodic data extraction. Data sets containing study identification numbers only (no other unique patient identifiers) will be prepared for sharing with the Northwestern University team.

Selection and Withdrawal of Subjects:

Eligibility Criteria.

Patients are eligible if: 1) age is 18 years or older, 2) at least 3 medications are prescribed by their physician, 3) 3) standardized mean blood pressure measurement ≥130 mm Hg systolic or ≥80 mm Hg diastolic if they are diabetic or mean blood pressure measurement ≥140 mm Hg systolic or ≥90 mm Hg diastolic if they are not, 4) a Mini-Cog Exam score of ≥ 3, 5) the patient is the person primarily responsible for administering medication, and 6) the patient does not intend to move or change their usual source of medical care during the next year.

Exclusion Criteria.

Based on additional eligibility criteria, exclusion criteria include if the patient 1)is non-English language speaking 2) does not meet mean blood pressure criteria, 3) has a Mini-Cog Exam score of <3, 4) is not the person primarily responsible for administering medication, 5) intends to move or change their usual source of medical care during the next year.

Withdrawal of Subject:

Subjects may withdrawal from the study at any time by notifying the Principle Investigator in writing at:

Dr. Stephen Persell
Northwestern University – General Internal Medicine
750 N. Lake Shore Dr. 10th Floor
Chicago, IL 60611

All data that was obtained about prior to withdrawal from the study will be included in analysis.

Recruitment Strategies:

Strategy 1: Recruitment flyers and posters

Dr. Eder, Dr. Persell, and Ms. Friesema will describe the research study to primary care physicians at each participating clinic. IRB approved flyers and posters will be placed in the clinic to direct potential participants to the research assistant currently there or provide them with a telephone number and email address where they can receive more information. Primary care physicians and Access clinic staff will also hand flyers out to potential participants they feel may qualify for the study, directing them to speak with the research assistant that will be located in the waiting room of each clinic or call the telephone number listed on the flyer for more information.

The research assistant will also randomly approach potential participants as they are waiting to receive care at the clinic to see if they are interested in hearing more about the study. She will answer any questions for the potential participants. If the patient is interested in participating or in learning more about the study, the research assistant will bring them to a private room and obtain verbal consent to ask the patient a brief series of questions to determine eligibility (determine age, determine if the patient is the person primarily responsible for administering medication, determine if they are prescribed 3 or more medications, determine if the patient can communicate in English, and determine if there is cognitive impairment) and take 3 blood pressure readings.

If the patient is determined to be eligible, a written consent form will be discussed.

Strategy 2: Targeted Mailing
The research study will be described to primary care physicians at each participating clinic and their approval obtained to generate lists of their potentially eligible patients. Physicians will receive emails within the Epic EHR and will have the opportunity to indicate which potentially eligible patients should not be contacted. With the physician approval, a letter will be mailed to the patient notifying him or her that clinic staff will be telephoning to invite him or her to participate in a study and that they may opt out.

Ten days after the initial mailing, the interviewer or study coordinator will contact patients by telephone to ask whether they would be interested in participating in the study. If the patient is interested in participating or in learning more about the study, the study coordinator will obtain verbal consent to ask the patient a brief series of questions to determine eligibility (confirm age, determine if the patient is the person primarily responsible for administering medication, determine if the patient can communicate in English). If the patient is not ineligible, an appointment at the clinic for the baseline interview will be scheduled. Verbal consent will be obtained to contact the patient by telephone within a few days of the scheduled office visit to confirm, and to obtain consent for the interviewer or study coordinator to approach the patient in the waiting room.

Risk:

Individuals involved in any aspect of this study will be subject to minimal risk through their participation. It is possible that subjects may feel shame and/or some emotional discomfort when taking the literacy and medication use assessments, and performing medication related tasks. Patients from clinics randomized to the nurse intervention will receive additional medical care provided by these nurses. There is a possibility that increasing the medical attention paid to patients' medication use will have some unanticipated adverse effect. This study collects personal health information and information that identifies study subjects. While we work to keep this information confidential, there is a risk of loss of confidentiality. There is a risk that personal identifying information could be released.

Protection against Risks:

Subjects will be informed in all cases about their rights as research subjects. They may withdraw at any time during the study without penalty or loss of any healthcare benefit or service to which they are entitled. Subjects will be assigned a unique identification number; the research database will be password protected and accessible only to the research team and the Institutional Review Board. Information linking subjects’ names and contact information with their unique identifier will be kept in a separate password protected file on local hard drives of authorized study personnel in the offices of the Division of General Internal Medicine at 750 North Lake Shore Drive as well as 3 encrypted study laptops. The laptops are whole disk encrypted utilizing Symantec Endpoint Encryption. Whole Disk Encryption (WDE) provides protection for computers by preventing data loss with strong access control and powerful disk encryption. It is important that Northwestern University personnel storing sensitive information such as Protected Health Information (PHI), Personally Identifiable Information (PII) or research data, protect their machines and data with whole disk encryption software. We believe that in using these methods we will be compliant with the “Standards for Privacy of Individual Identifiable Health Information” under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule. Information obtained during the delivery of clinical care at the Access clinic sites (such as documentation of clinical encounters with the nurse) may be recorded in patients’ medical records and will be subject to the confidentiality protections for medical records under HIPAA. We will also attempt to reduce shame and performance anxiety as a result of interviews about compliance with screening and assessments through extensive training of the interviewers.

Benefit:

It is possible that subjects enrolled in either intervention arm of the study may directly benefit in that they may have, as a result of this study, fewer discrepancies in their medication lists, a better functional understanding of their medication regimen, greater adherence to their medication regimens, lower systolic blood pressure, and/or better chronic disease control (LDL cholesterol and HbA1c control). Subjects enrolled in the control arm of the study are not likely to directly benefit from the study, although it is possible that completing the medication reviews and additional standardized blood pressure measurements with the research assistants may positively influence their care. More broadly, the results of this study may provide
important information regarding how medication therapy management interventions can be effectively implemented.

All subjects recruited for this research study (N=1,680) will receive $25 in cash at the time of the baseline interview as compensation for their participation. Subjects who also participate in a 3-month follow-up visit will receive an additional $25, those who return again for a 6-month follow-up will receive yet another $25, and those returning for a one-year follow-up will be given an additional $50. Therefore, a patient who participates in all interviews will receive compensation of $125.

Safety Assessment:
Protection against Risks:

Subjects will be informed in all cases about their rights as research subjects. They may withdraw at any time during the study without penalty or loss of any healthcare benefit or service to which they are entitled. Subjects will be assigned a unique identification number; the research database will be password protected and accessible only to the research team and the Institutional Review Board. Information linking subjects' names and contact information with their unique identifier will be kept in a separate password protected file on local hard drives of authorized study personnel in the offices of the Division of General Internal Medicine at 750 North Lake Shore Drive as well as 3 encrypted study laptops. The laptops are whole disk encrypted utilizing Symantec Endpoint Encryption. Whole Disk Encryption (WDE) provides protection for computers by preventing data loss with strong access control and powerful disk encryption. It is important that Northwestern University personnel storing sensitive information such as Protected Health Information (PHI), Personally Identifiable Information (PII) or research data, protect their machines and data with whole disk encryption software. We believe that in using these methods we will be compliant with the "Standards for Privacy of Individually Identifiable Health Information" under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule. Information obtained during the delivery of clinical care at the Access clinic sites (such as documentation of clinical encounters with the nurse) may be recorded in patients' medical records and will be subject to the confidentiality protections for medical records under HIPAA.

We will also attempt to reduce shame and performance anxiety as a result of interviews about compliance with screening and assessments through extensive training of the interviewers.

Data Safety and Monitoring Plan:

Our program official, Joan Wasserman, at the NIH informed us that an external Data Safety and Monitoring Board is not required by the NIH and requested that we remove this from our budget. The data and safety monitoring plan proposed in the grant application will be conducted by the PI and co-investigators (Dr. Wolf, Dr. Rademaker, Dr. Eder, Dr. Mejia and Dr. Woodard). They will be organized for meetings once a year. At these meetings the study protocol, procedures, and any issues of concern related to research integrity will be discussed. E-mail correspondence, or teleconference meetings may be arranged for issues that require immediate attention.

Thresholds have been established for blood pressure readings taken as part of the study. All study participants will receive a notification of their average blood pressure taken on that day.

Lower threshold: If the average systolic blood pressure is <80 or the average diastolic blood pressure is <50, study staff will alert the patient to speak with their clinician that day.

Upper threshold: If the average systolic blood pressure is >180 or the average diastolic blood pressure is >110, study staff will alert the patient to speak with their clinician that day.

Statistical Analysis:

We will perform analysis to address each primary and secondary aim using SAS v9.2 (SAS Institute, Carey, NC). Analyses for Aim 1.
The proposed trial uses a cluster-randomized design where clinic is the unit of randomization. We will randomize 12 clinics to 3 intervention arms (usual care, EHMI, and EHMI + nurse) resulting in 4 clinics per arm. We will accrue approximately 140 patients at each clinic, and conservatively anticipate at least 75 to 85% retention for follow-up at 12 months. This will result in 1680 total participants recruited to the study with an anticipated minimum of 1260 participants available after one year and therefore contributing to primary data analysis.

Before conducting formal analyses, we will perform descriptive studies to ensure adequate balance of potential confounding factors across the three treatment arms. At a minimum we will evaluate the following potential confounders: socio-demographic characteristics, comorbidities, number of medications used, health literacy level, and Mini-Cog Exam scores. For continuous variables, we will use ANOVA models with the potential confounder as the outcome and intervention arm as a three-level predictor to evaluate global differences in means. For categorical variables, we will use \( \chi^2 \) tests to evaluate differences in distributions across the three groups. Variables found to have significant differences (p < .05) across treatment groups will be entered as covariates in the generalized linear mixed models (GLMMs) used for formal analyses as described below. We note that detected differences may be clinic-specific, so if we observe differences across the treatment arms, we will explore whether the difference might be attributable to individual clinics. We will compare baseline systolic blood pressure (SBP) across treatment arms using an ANOVA model, and across clinics within treatment arm also using an ANOVA model. We will control for baseline SBP in formal analyses, and if we see systematic differences in SBP at baseline between clinics, this will be of particular importance.

SBP at 12 months is the primary outcome of interest for Aim 1 (H4), with binary and continuous variables measuring outcomes relevant to hypotheses of secondary interest for Aim 1 (H1, H2, H3, and H4). We will use generalized linear mixed models (GLMMs) for analyses of the data, specifying the identity link function for the continuous outcomes and the logit link function for binary outcomes. Analyses will be performed using PROC GLIMMIX in SAS (v. 9.2). The 3-category treatment group variable will be the independent variable of primary interest and will be modeled as a fixed effect with the usual care group specified as the reference group. We will also include fixed effects for any potential confounding covariates noted in the descriptive studies. Random effects will be included for each clinic to account for intra-clinic correlation among participants. Since participants within a clinic could see the same physician and could possibly have further correlated outcomes, we will also explore the use of a random effect in each GLMM for physician (nested within clinic). This random effect could account for many physician-specific differences, for example volume of patients seen.

The statistical tests of primary interest will pertain to the fixed main effects comparing EHMI to usual care and EHMI + nurse to usual care. The beta estimates from the GLMMs will be deemed ‘statistically significant’ for p<0.05. We will report point estimates and corresponding 95% confidence intervals for the analysis of the primary SBP outcome, as well as the secondary binary outcomes. We will also examine and report the extent to which the random effects suggest correlation of outcomes within clinic.

Analyses for Aim 2.

For Aim 2, we will repeat all GLMM analyses described for Aim 1, but for subgroups defined by participants’ literacy defined as inadequate (Newest Vital Signs score indicating inadequate health literacy vs. all others). We will report estimated effects and 95% confidence intervals of the EHMI and EHMI + nurse interventions compared to usual care for each subgroup. We will formally test for differences in intervention effects according to literacy by including a literacy-intervention interaction term. Statistical significance for the interaction term (p<0.05) will indicate that intervention group differences in SBP at 12 months, as well as the secondary outcomes, vary by literacy level. We do recognize, however, that we are not formally powered to detect such an interaction and so the analyses will be considered exploratory.

Power Considerations.

The sample size for this study was based on the primary outcome of SBP at 12 months. Table 2 shows participants per clinic needed to detect a 4 mm Hg difference in SBP for pair wise comparisons of treatment groups (e.g. EHMI + nurse vs. usual care). Required sample sizes are reported for a range of standard deviations, 80% power, 5% Type I error, and intra-class correlation (ICC) of 0.001. Based on our preliminary data and values reported in large trials, a standard deviation of 16 or less seems likely. Based on these
calculations, we plan to recruit 140 participants at each randomized clinic so that even with only 75-85% retention at 1 year, we will still have sufficient power to detect a meaningful effect size.

With sample size set by the primary outcome of SBP at 12 months, we also present detectable differences for the secondary outcomes and for the subgroup analyses according to health literacy. We expect roughly 30% to have inadequate health literacy.\textsuperscript{38} Table 3 show the detectable difference in SBP for pair wise comparisons of the intervention groups at 80% power, 5% Type I error and ICC=0.001 assuming 140 patients per clinic are enrolled at baseline, 75% (105) are available for follow-up at 12 months at each clinic, and of those roughly 73 and 32 have adequate/marginal and inadequate health literacy, respectively. This sample size will permit the detection of a difference of 0.43 standard deviations for secondary continuous outcomes. Appendix A, Supplemental Table 3 records detectable differences for the secondary continuous outcomes both for the entire group and for the health literacy subgroups, given estimated standard deviations. The secondary binary outcomes have a range of expected baseline rates for the usual care group. The detectable differences for the secondary binary outcomes range from a change in proportion of 0.08 to 0.12 both for the entire group for control group values ranging from 0.1 to 0.7. For the subgroup with adequate or marginal health literacy, detectable differences range from 0.10 to 0.14 and for the inadequate health literacy subgroup from 0.15 to 0.20. Appendix A, Supplemental Table 4 provides additional details. For the analyses of medication-specific understanding and reconciliation outcomes, not all patients may have medication(s) in the category of interest. Therefore, the detectable differences may be slightly larger than what is recorded above.

**Implementation Fidelity, Aim 3.**

We will determine the extent to which the interventions were implemented as planned (a process evaluation) in clinics randomized to the two intervention arms.\textsuperscript{101} 102 We will determine which patients received the plain language medication information sheets.

We will use direct observation performed during random samples of clinical sessions in each of the 3 study arms to determine the frequency with which 1) medication lists were provided to patients, 2) medication lists were used by a physician or another healthcare provider to address medication concerns, and 3) whether patients actually received the print materials from the EHMI intervention. The fidelity of the nurse intervention will be evaluated using these same techniques. Nurses will also log all in-person and telephone encounters with patients, and RAs will perform direct observation of nurses during random samples of clinical sessions. In an effort to further understand why the interventions were more easily adopted at some clinics than others, we will survey the providers from these sites to assess their general attitudes and beliefs about medication therapy management, medication reconciliation, and their opinions on the study interventions. Surveys will be collected via REDCap, a secure electronic web interface. Providers may complete the survey on paper if they prefer. These hard copy forms will be given to project staff who will manually enter these data into REDCap.

Explicit written consent will not be obtained for this study. We request a waiver of documentation of consent since we will not be meeting with the doctors or speaking to them unless they call us with questions. Therefore we have no way to complete a thorough consent process. Consent will be implied by taking the time to fill out and return the paper version of the survey. Participants who choose to complete the survey through the provided url link, rather than the paper version will see an online consent form to read through and accept prior to seeing the first question of the survey. For anyone who clicks “accept” the first question of the survey will appear. For those who choose to click “decline” a screen thanking them for their time will appear.

Data collection will take two forms, paper surveys and online surveys. All participants will be first notified of the study from the Access Site PI. They will be provided with a package containing an introductory letter/email, a $5 bill, the survey, and a prepaid envelope for returning the survey. The letter will invite them to participate, explain the survey, include a url link that they can type into their browsers if they prefer to complete the survey online (rather than returning the survey by mail), and explain that the $5 bill is theirs to keep regardless of whether they complete the survey or not. Over the next month we will follow up with potential participants via letter or email (2 weeks after the initial survey is sent out, then 2 weeks after that). Each letter/email that is sent will remind them of the invitation to participate, and the link to complete the survey online.
Cost Analysis, Aim 4.

We will perform a cost analysis of the educational interventions. We will estimate the incremental cost of the interventions from the perspective of the clinic implementing these systems in a fee-for-service environment. The primary costs of the nursing intervention will include the costs of the nurse time and estimates of additional office resources consumed. These costs will include annual maintenance costs for the system, but will not include development costs for software that will be available at no additional cost. We will test the sensitivity of results to changes in these and other assumptions.

The major cost will be that for the nurse intervention. The nurses will record on a daily basis in a study database (Microsoft Office Access, Microsoft Corp.) the number of face-to-face and telephone encounters for MTM they perform for study patients. During randomly selected weeks, research assistants will perform time motion studies of MTM nurses to determine the time spent performing the different MTM tasks and these estimates will be used to estimate the personnel time consumed for contacts during the entire study period. Combined with nursing salary (plus fringe), this will allow us obtain the direct cost of the nurse intervention. We will test the sensitivity of costs to different assumptions about indirect costs and to the use of less costly staff being substituted for nurse time assuming less costly staff could have the same impact.

We also will perform a limited cost-effectiveness analysis (CEA) of the nurse-led EHMI relative to each of the alternatives. The cost effectiveness analysis will be limited in that it will not provide a health-related utility measure for the outcome and the costs measured will not be all-inclusive. More specifically, the primary outcome measured, change in mean systolic blood pressure, will be compared to the measured intervention costs to obtain a cost per unit change in systolic blood pressure.

Limitations of this analysis are 1) that the change in systolic blood pressure is not a utility-based measure subject to easy comparison with the results of other studies, 2) we include only the costs of the intervention and do not measure medical care utilization as a part of our costs, and 3) costs do not include indirect measures such as patient time. We use the change in systolic blood pressure rather than a health-related quality of life utility measure because the primary outcome in this study, change in systolic blood pressure, is an intermediate outcome unlikely to have a major short-term effect on health-related quality of life – those outcomes are expected to occur outside the study timeframe. Thus, we make no attempt to measure the change in medical resource use resulting from improved health due to improving systolic blood pressure, because the substantial gains in reduced medical resource use and health-related quality of life will be, with few exceptions, outside the timeframe of this study. The measures we are collecting do not require costly patient questionnaires about detailed resource use (subject to substantial recall error and subject to large random variation unrelated to the intervention). Given the above concerns about recall accuracy and large medical care utilization unrelated to the intervention, we do not believe an attempt to obtain more inclusive medical care costs would be worth the large additional cost.

Scientific References/Bibliography:


64. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. *JAMA.* 2006; 296:2563-2571.


