INVESTIGATOR STUDY PLAN

1. TITLE
Improving Safety After Hospitalization in Older Persons on High-Risk Medications

2. EXTERNAL IRB REVIEW HISTORY*
None.

3. PRIOR APPROVALS:
Reliant Medical Group has approved this study (See Appendix A – Reliant Medical Group Letter of Support).

4. OBJECTIVES*
The overarching objective of our project is to pursue a large randomized controlled trial (RCT) focused on older patients recently discharged from the hospital who have been prescribed medications within one of three high-priority, high-risk drug classes in order to reduce the risk of clinically important medication errors. The National Action Plan for Adverse Drug Event (ADE) Prevention identified three high-priority drug classes as key targets for reducing the risk of drug-related injuries: anticoagulants; diabetes agents (insulin and oral agents); and opioids. These medication classes were chosen because they account for the greatest number of measurable drug-related harms to patients, and a substantial proportion of ADEs associated with these medications is considered preventable. The clinical trial will determine the value of a multifaceted medication error and ADE reduction intervention with a special focus on in-home assessment.

Components of the intervention will include: (1) in-home assessment of high-risk patients by a clinical pharmacist; (2) best-practice, evidence-based medication safety tools and resources targeted to high-risk patients and their caregivers; (3) communication with the primary care team via the electronic health record (EHR) regarding concerns relevant to the use of high-risk medications as well as other medication safety concerns; and (4) a follow-up phone call by the pharmacist to the patient and/or caregiver within 14 days of the home visit. The primary outcome of interest will be clinically important medication errors, a composite outcome comprised of preventable or ameliorable ADEs and potential ADEs due to medication discrepancies or non-adherence. Secondary outcomes will include: (1) preventable or ameliorable ADEs; (2) potential ADEs due to discrepancies or non-adherence; and (3) preventable or ameliorable ADEs judged to be serious, life-threatening, or fatal.

The specific aims for our study which we are seeking approval from the IRB at this time are as follows:

Aim 1 (no human subjects): To adapt and integrate existing “best-practice,” evidence-based medication safety tools, resources, and approaches into a cohesive, multifaceted intervention to reduce the occurrence of clinically important medication errors in older adults recently discharged from the hospital using one or more of the three high-priority, high-risk drug classes (anticoagulants, diabetes agents, and opioids).

Aim 2: To assess the impact of the multifaceted intervention on the incidence of clinically important medication errors employing a randomized controlled trial (RCT) design.

5. BACKGROUND*

Transition from Hospital to Home: Extraordinarily High-Risk for Older Patients

Up to one fifth of older patients suffers an adverse event within weeks of leaving the hospital, and many of these events may be preventable.[1,2] The risk for ADEs, defined as injury due to a medication, is especially high for older patients as they transition from the inpatient to the outpatient setting.[3,4] Our research team has recently reported that nearly one in five older adults newly discharged from the hospital experience an ADE and that medication prescribing and monitoring errors are particularly common during this high-risk, post-hospital discharge period.[5] In addition, we have reported that many patient-related medication errors in older adults involve certain high-risk medication categories, including diabetes agents and anticoagulants, and that the majority of these errors leading to ADEs relate to administering the medication, modifying the medication regimen, or not following clinical advice provided to the patient about use of the medication.[6] Patients that may be at special risk for medication errors and ADEs include those taking greater numbers of different medications and those with a higher burden of comorbidity.[7] Patients with impaired cognitive function and low health literacy may also be at especially increased risk.[8]

The National Action Plan for Adverse Drug Event Prevention: Targeting High-Risk Drug Classes

Insulins, opioid-containing analgesics, and warfarin are among the most common medications implicated in emergency department visits for outpatient adverse drug events,[9] especially among patients aged 65 or older.[10] These are also the most common medications implicated in emergency hospitalizations for ADEs in older adults.[11] Budnitz, Shehab, and colleagues have suggested that improved management of medications in these categories has the potential to reduce hospitalizations for ADEs in older adults.[11] Recent research findings have highlighted that adverse events related to diabetes agents are a growing concern among older patients. Lipska et al. have reported that hospital admissions for hypoglycemia now exceed those for hyperglycemia in Medicare beneficiaries.[12] Redberg and others have commented that older patients are now more likely to experience adverse events related to overtreatment of diabetes mellitus.[13,14] Geller, Budnitz, and Shehab have reported that rates of emergency department visits and subsequent hospitalizations for insulin-related adverse events are particularly common among those aged 80 or older,[15] and this should be considered in decisions to prescribe and intensify insulin therapy.[16] Insulin product mix-ups are suggested as important targets for hypoglycemia prevention efforts.

Clinically Important Medication Errors

As defined in PA-14-002 (Advancing Patient Safety Implementation through Safe Medication Use Research), “an ADE is an injury resulting from medical care involving medication use. Identifying something as an ADE does not imply error, negligence, or poor quality care. It simply indicates that an undesirable clinical outcome resulted from some aspect of diagnosis or therapy, and not an underlying disease process.” A “preventable” ADE is a drug-related injury relating to a medication error. While some ADEs are not entirely preventable, their duration or severity could be reduced; such events have been characterized as “ameliorable” ADEs. Other types of medication-related problems, referred to as “potential” ADEs, may present during the post-hospital discharge period. While these situations may not yet have caused any injury to the patient, they have the potential to cause future harm if not addressed. These potential ADEs include discrepancies in the patient’s medication regimen,[17,18] or episodes of non-adherence with a high likelihood of potential harm. Taken together, preventable or ameliorable ADEs and potential ADEs comprise “clinically important medication errors,” an important and meaningful target for patient safety interventions, as over 50% of patients discharged from the hospital experience one or more clinically important medication errors within weeks after hospital

discharge.[19] Clinically important medication errors are the primary outcome of interest in the proposed project.

Improving Medication Safety: Pharmacist-Based Interventions

Few high quality studies have rigorously examined the impact of pharmacist-based interventions on medication safety in older adults in the ambulatory setting. Lee and colleagues conducted a systematic review of U.S. pharmacist interventions on older adults and resulting patient-oriented outcomes.[20] To be included, studies had to compare outcomes of a patient-level pharmacist intervention in older adults with those of alternative care. The pharmacist intervention needed to have the intention of improving therapeutic outcomes, increasing medication adherence, reducing hospitalizations, or improving medication safety. Of 20 studies ultimately included in the systematic review, only six were RCTs, and only one focused on ADEs and medication safety. While inappropriate prescribing was reduced, there was no statistically significant difference in the percentage of patients experiencing an ADE in the intervention compared with the control group.[21]

Among studies not limited to older patients, some have suggested medication safety benefits from inpatient pharmacist-based interventions at the time of hospital discharge,[22,23] while others have not. In a randomized trial of adults hospitalized with acute coronary syndromes or acute decompensated heart failure, a multicomponent intervention comprised of pharmacist-assisted medication reconciliation at the time of discharge (including inpatient pharmacist counseling, low literacy adherence aids including a pill box and illustrated daily medication schedule, and individualized telephone follow-up after discharge) failed to demonstrate a significant reduction in clinically important medication errors.[19] The investigators emphasized that their findings "highlighted the difficulty of improving medication safety during the transition from hospital to home," reporting that clinically important medication errors affected over 50% of study subjects during the first 30 days after hospital discharge. The failure of this intervention has been attributed to a number of factors including inadequate communication and collaboration with the primary care team of the patient during this vulnerable transition period.[24] The lack of targeting of vulnerable, high-risk groups most likely to benefit, such as persons with cognitive deficits or poor health literacy, has also been highlighted. Kaboli and Frenandes have convincingly argued that providing the same intensity of a medication safety intervention "to every patient is neither efficient nor cost-effective." It is essential "to optimally channel the patients who need the most attention and can get the greatest benefit [from such interventions]."[25]

The knowledge to be gained from this study is substantial. As stated in PA-14-002, "Reduction of adverse drug events (ADEs) is a top priority for the Department of Health and Human Services (DHHS), and a comprehensive strategy is required to significantly reduce ADEs within the three classes which account for a significant proportion of all ADEs: anticoagulants, diabetes agents, and opioids." The ultimate goal of the proposed research is to mitigate the public health burden related to ADEs among high-risk elderly patients by demonstrating an effective intervention strategy to reduce this risk.

6. Inclusion and Exclusion Criteria*

Study Population

The study population will be derived from patients age 50 years or older who are cared for by Reliant Medical Group. The age and gender characteristics of this population are similar to those of the general population of the United States age 65 or older (Table 1).

Table 1. Age and Gender Characteristics of Study Population vs. U.S. Population Aged 65 and Older

	Study Population (n=35,972)			United States (n=40,267,984)[26]		
Age Group	Male	Female	Total	Male	Female	Total
65–74	22%	24%	47%	25%	29%	54%
75–84	14%	19%	34%	14%	19%	32%
85+	7%	12%	19%	4%	9%	14%
Total	**44%**	**56%**	**100%**	**43%**	**57%**	**100%**

Inclusion Criteria:
≥50 years of age, discharged from a hospital and having been prescribed at least one medication in one of three high-risk drug categories (anticoagulants, diabetes agents, and opioids) during the 3-month period prior to hospital admission or at the time of hospital discharge, *and must meet one or more of the following screening items*:

1. Prescribed ≥2 high-risk medications.
2. Low health literacy (response of "Somewhat," "A Little Bit," or "Not at all" to the question "How confident are you in filling out medical forms?"[27])
3. Low adherence
4. Caregiver (an affirmative response to "Have you received assistance from one or more caregivers over the past 4 weeks?").
5. Using ≥7 different medications[28].

Exclusion Criteria:

1. Plans to enroll in hospice upon discharge.
2. Discharged following hospitalization for a psychiatric condition.
3. Discharged to a skilled nursing facility, rehabilitation hospital, or nursing home.
4. Patient is not capable of providing informed consent, and a proxy is not available.
5. Patient is non-English speaking.
6. Patient is pregnant.

Vulnerable Populations

Children
Children will not be included in this study.

Prisoners
Prisoners will not be included in this study.

Pregnant Women
Pregnant women will not be included in this study.

Adults Unable to Consent
We anticipate the identification and inclusion of patients with some cognitive impairment. We will implement consent procedures consistent with those recommended for patients with cognitive impairment. See also #18, *Vulnerable Populations* and #30, *Consent Process*.

7. STUDY-WIDE NUMBER OF SUBJECTS*
NA; this is not a multi-site study.

8. STUDY-WIDE RECRUITMENT METHODS*
NA; this is not a multi-site study.

9. STUDY TIMELINES*
The overall project timeline is described in the table below (Table 2):

Table 2. Project Timeline

	Study Quarter											
Activity	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12
Intervention materials finalized (Aim 1)	■	■										
Screening and enrollment procedures finalized and implemented		■	■									
Training of clinical pharmacists			■	■								
Randomized Controlled Trial (Aim 2)				■	■	■	■					
Data collection						■	■	■	■			
Analysis including Process Evaluation (Aim 3)				■	■	■	■	■	■			
Dissemination plan (Aim 4)										■	■	■
Manuscript development and submission										■	■	■

This study is planned to take place over the course of three years, but will be extended if need be until all of the tasks and deliverables are completed.

All study subjects are anticipated to be enrolled over a one-year period.

Duration of an Individual Subject's Participation
Individual patient subjects will be assessed for up to a 45-day period following hospital discharge. All Patient Subjects: All potential patient participants will be called by study staff for the purposes of study introduction, screening procedures, cognitive assessment, and to obtain verbal consent to participate in the study. This initial phone call should take approximately five to ten minutes to complete.

All subjects who are enrolled will then be randomized into one of the two study arms, intervention and control. Details on the differences in participation between these two groups follow.

Medical record data will be reviewed for all study subjects for the duration of 45 days post-hospital discharge.

All patient participants will be invited to take part in an interview 5 to 6 weeks post-hospital discharge to collect additional outcome measures. This interview will take place via telephone. The outcomes assessment interview script will be submitted to the IRB for review and approval prior to the initiation of the interviews. Please see #11, *Procedures Involved*, Aim 2,

Determination of Clinically Important Medication Errors, Overview, for a description of the type of content that will be included in the outcomes assessment interview.

Individuals who chose to participate in the focus group sessions will be expected to participate in one focus group session, to be scheduled up to 10 weeks post-hospitalization. This focus group session will last approximately 90 minutes.

Intervention Subjects: Subjects in the intervention group will receive one home visit from a clinical intervention pharmacist within four days of hospital discharge. We anticipate that this visit could take between one and one and one-half hours to complete. During the home visit, the pharmacist will complete the following:

(1) medication review;
(2) observation of medication organization and administration, when applicable;
(3) in-depth patient (and caregiver if applicable) discussions about challenges to safe medication use;
(4) distribution of targeted educational materials related to medication safety.

If medication safety concerns are identified during the home visit the pharmacist will communicate with the patient's Reliant Medical Group provider via the electronic health record or for time sensitive safety concerns via telephone.

The clinical pharmacist will also conduct a follow-up telephone call with the patient (and caregiver/proxy if appropriate) 2 weeks after the home visit is completed. This phone call, which will serve to reinforce medication safety principles and issues, should take approximately a half-hour to complete. The telephone call script has been submitted to and approved by the IRB.

Control Subjects: Subjects in the control group will be provided educational materials related to medication safety via mail.

Educational Materials: A sample of the educational materials to be distributed to study subjects were submitted to and approved by the IRB. Please see #11, *Procedures Involved*, Aim 1, Component 2 – Use of Educational Tools Specifically Targeted to High-Risk Patients and Caregivers, for a description of the type of content that will be included in the educational materials.

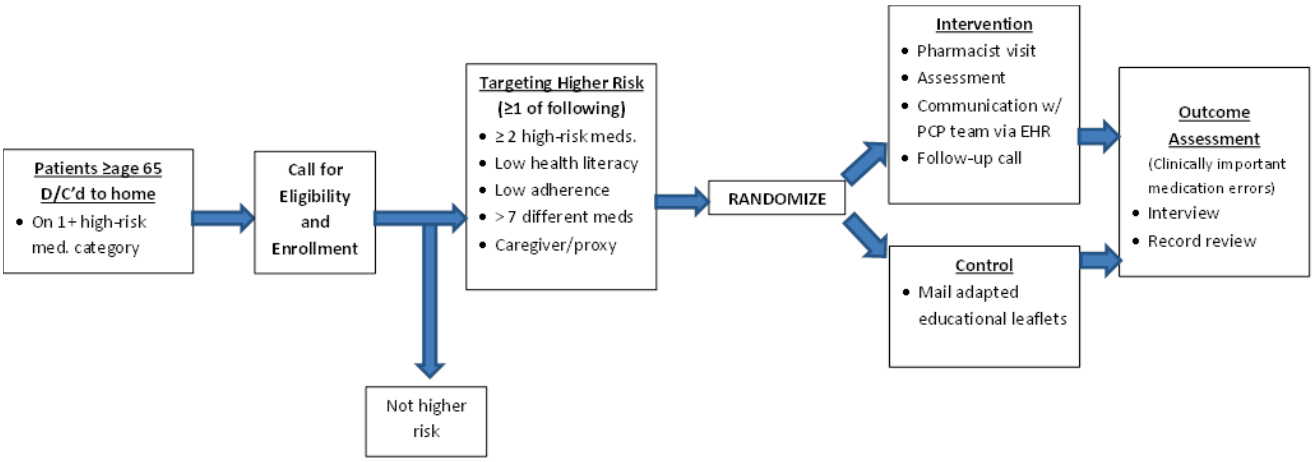
10. Study Endpoints*

The primary outcome of interest will be clinically important medication errors, a composite outcome comprised of preventable or ameliorable adverse drug events (ADEs) and potential ADEs due to medication discrepancies or non-adherence. Secondary outcomes will include: (1) preventable or ameliorable ADEs; (2) potential ADEs due to discrepancies or non-adherence; and (3) preventable or ameliorable ADEs judged to be serious, life-threatening, or fatal.

11. Procedures Involved*

The randomization process will occur after subjects are screened-in to the study (Figure 1).

Figure 1. Trial Design



The research plan and procedures involved are:

Aim 1 (no human subjects): To adapt and integrate existing best-practice, evidence-based medication safety tools, resources, and approaches into a cohesive multifaceted intervention to reduce the occurrence of clinically important medication errors in older adults recently discharged from the hospital using one or more of the three high-priority, high-risk drug classes (anticoagulants, diabetes agents, and opioids).

Overview

The intervention will be comprised of four key components. These include: (1) in-home assessment of high-risk patients by a clinical pharmacist; (2) best-practice, evidence-based medication safety tools and resources targeted to high-risk patients and their caregivers; (3) communication with the primary care team via the electronic health record regarding concerns relevant to the use of high-risk medications as well as other medication safety concerns; and (4) a follow-up phone call by the pharmacist to the patient and/or caregiver within 14 days of the home visit.

Component 1 – Pharmacist In-Home Visit

Within four days of hospital discharge, for patients randomized to the intervention arm of the study, the pharmacist will perform an in-home visit. The visit will involve a comprehensive medication audit including medication reconciliation and an assessment of self-medication management, as well as other intervention components described below.

For home visits, we will use an approach adapted from our prior efforts using home visits to understand medication errors in children with chronic conditions.[29,30] The home visits will have three components: (1) medication review; (2) observation of medication organization and administration, when applicable; and (3) in-depth patient and caregiver discussions about challenges to safe medication use. Similar to our previous efforts, methods used for direct observation to identify medication administration errors will be modeled on approaches used across various clinical settings by Flynn and colleagues.[31,32] In performing the home visits and intervention, the clinical pharmacist will have access to the EHR of the patient, including the hospital discharge summary and the discharge medication list.

Home visits will be performed in a nonintrusive and nonjudgmental manner. The clinical pharmacist will observe the organization and administration of medications. The person who

normally administers the medications will be asked to administer medications exactly as he or she normally would, and as if the clinical pharmacist were not present. Interviews will be used to identify patients' and caregivers' perceptions of barriers to safe home use of medications, with particular relevance to high-risk medications (anticoagulants, diabetes agents, and opioids), and to identify possible prior medication errors occurring in the home. Knowledge gaps and misconceptions that may contribute to medication errors, perceptions of barriers to using medications as prescribed, and recommendations for changes that would enhance medication safety will be carefully explored.

For medication reconciliation, the clinical pharmacist will have access to the EHR of the patient, the hospital discharge medication list, and the discharge summary for each patient. In order to assess for medication discrepancies, the pharmacist may use the Medication Discrepancy Tool.[33,34] The Medication Discrepancy Tool permits the pharmacist to identify the discrepancy, document the patient and system-level contributors to the error, and plan for resolving the error. The revised Medication Discrepancy Tool will be submitted to the IRB for review and approval prior to use in this study.

The clinical pharmacist will first determine who is responsible for the tasks related to medication management (the patient, a caregiver, or both). In the medication management assessment, proficiency will need to be demonstrated in multiple tasks. Table 3 below specifies various components of the assessment. The clinical pharmacist will review each of these tasks and remediate as needed. The patient, caregiver, or both will need to demonstrate appropriate storage and organization of medications. This is important, as our prior work has suggested that even using pill organizers can lead to the medication errors that, in turn, lead to ADEs.[6] In addition, the patient/caregiver will read and interpret labels of medications and show how medications are organized in a pill organizer, which the study will provide at no cost to the patient (if patient is not already using one). For medications such as warfarin, which might require varying doses on different days of the week, the patient will also need to describe management over a full week, and this will be compared with instructions provided at the time of discharge and also reconciled with any new instructions provided by the anticoagulation service. It will also be confirmed that the patient has connected or re-connected with the anticoagulation service subsequent to hospital discharge. The pharmacist will also query the patient/caregiver about special situations such as handling missed doses and overdoses.

Table 3. Pharmacist In-Home Visit

Patient/Caregiver Tasks	Pharmacist Assessment
Demonstrates safe medication storage and organization	• Observes for mix-ups in patient's medication storage and organization • Observes for unsafe access to medications for patients with cognitive, physical, and/or visual impairment
Reads and interprets labels of all OTC and prescription medications	Medication literacy
Organizes all oral medications into pillbox accurately	Notes accuracy in number of pills and timing; assesses for duplicate or missing medications
Cuts pills as required	Observes for skill / accuracy
Describes 24-hour medication administration of pills	• Assesses for potential for missed doses or overuse of medications • Assesses use of tools (timers, routines) to facilitate timing

Patient/Caregiver Tasks	Pharmacist Assessment
	• Assesses use of documentation if multiple caregivers are involved in medication administration • Assesses for interactions affecting bioavailability
Describes approach for missed doses	Assesses for inappropriate doubling-up
Use of "as needed" medications	Assesses knowledge of scheduled vs "as needed" medications and how much can/should be taken in a 24-hour period of time
Describes weeklong medication management for warfarin and other medications with varying daily dosage	Assesses for accurate medication management
Administers injectable medications (insulin)	Notes storage /refrigeration of insulin, and ability to draw up and inject
Describes refill process	Assesses for barriers to filling prescriptions (multiple pharmacies, cost barriers, and waiting too long to obtain refills)

In the case that a home visit cannot be conducted within the 4-day period (e.g. patient is out of town, has too many competing appointments, does not want someone in the home, etc.), the clinical pharmacist may conduct portions of the intervention that are feasible by telephone. We will also mail the patient educational materials (see Component 2 for details on educational materials). In these instances, the home-visit by the Clinical Pharmacist will not be conducted at a later time. Some subjects may only receive a portion of the research intervention.

Component 2 – Use of Educational Tools Specifically Targeted to High-Risk Patients and Caregivers

The clinical pharmacist will use "health literacy universal precautions" in providing instruction relating to all medication safety issues and concerns identified during the observation and interview.[35] For example, to ensure patient/caregiver comprehension and recall, the pharmacist will employ the "teach-back" method (also known as "show-me" or "closing the loop"). Teach-back is a way to confirm that a healthcare provider has explained to patients what they need to know in a manner that the patient understands, and is an important strategy for ensuring effective communication with patients at all literacy levels.[36,37,38] The clinical pharmacists will also actively encourage question-asking throughout the home visit.

Print educational materials can help to reinforce key messages, and well-designed print materials are recommended as an additional health literacy universal precaution.[35] During the in-home visit, the clinical pharmacist will distribute medication safety educational materials relevant to "high-alert" medications of relevance to our study, which have been adapted from those developed by the Institute for Safe Medication Practices (ISMP).[39] A variety of additional educational resources and tools are available on the ISMP website (ConsumerMedSafety.org). From among these resources, the clinical pharmacist will select the set of patient-specific educational materials which have been targeted to each of the three high-risk medications. The handouts feature medication instructions including timing of dose, dietary precautions, situational guidance (what to do when you miss a dose), recommendations for when to contact your doctor, etc. The clinical pharmacist will review materials with the patient/caregiver, using teach-back and encouraging questions. If the literacy level of the materials is found to be problematic, we will provide low literacy versions, following guidelines from the universal

precautions toolkit and other resources.[40,41] Samples of patient educational materials to be used in the study have been submitted to and approved by the IRB.

One of the Co-Investigators with expertise in health literacy and clinician-patient communication and will train the clinical pharmacists in effective methods of communicating with low literacy patients prior to the first home visit, drawing on a variety of resources (e.g., the universal precautions toolkit and the American Medical Association sponsored video "Health literacy and patient safety: Help patients understand").[42]

Component 3 – Communication with the Primary Care Team via the Electronic Health Record (EHR)

Key findings of the in-home visit by the clinical pharmacist will be communicated to the primary care team via the EHR immediately following the visit. These messages will alert the primary care physician and the care coordinator to safety issues particularly relevant to the high-risk medication categories (anticoagulants, diabetes agents, and opioids). The research team has extensive experience in employing electronic alerts in prior AHRQ-funded work performed in the same setting as this study and in other settings.[43,44] Messages will highlight problems relating to medication administration and monitoring, list specific errors that were uncovered, and provide recommendations. It is the standard for the medical group that these messages be reviewed within four hours of receipt. For any urgent medication-related problems, including serious medication interactions, side effects, or dosage outside of the usual range, the clinical pharmacist will directly call the primary care provider.

Component 4 – Follow-Up Phone Call to Patient/Caregiver by Pharmacist

The clinical pharmacist assigned to each patient will make a follow-up phone call within 14 days of the home visit. The nature of the phone call will be to discuss any interim problems and review and reinforce instructions provided during the in-home visit. The pharmacist will again communicate with the primary care team for any urgent medication-related problems. A follow-up phone call script has been submitted to and approved by the IRB.

Aim 2: To assess the impact of the multifaceted intervention on the incidence of clinically important medication errors employing a randomized controlled trial design.

Under Aim 2, we will evaluate the impact of the multifaceted intervention on the occurrence of clinically important medication errors employing a randomized controlled trial (RCT) design. The RCT approach was chosen because this allows for the minimization of potential selection bias and confounding that might limit the interpretation of the study findings. We anticipate that over 3,000 subjects will meet the age criteria and be available for screening over a one-year enrollment period. Identification of the “at risk” population to be recruited into the trial will be accomplished through a formal screening process designed to: maximize the likelihood that procedures developed through this study can be generalized and scaled to affect the occurrence of clinically important medication errors across a broad range of healthcare systems; to maximize efficiency and effectiveness of the intervention; and to minimize selection bias.

Patients age 50 years or older will be identified at the time of hospital discharge as having been prescribed a high-risk medication of interest at the time of discharge from the primary hospital utilized by the medical group in an automated fashion via the medical group’s EHR. This approach has been used by the study team in a previous study to promptly identify patients newly discharged from the hospital.[44] Under Stage 2 CMS EHR “Meaningful Use” criteria, hospitals are required to send electronic summary documents containing discharge medications as discrete data. Upon receipt of these data at the time of hospital discharge, the medical

group's EHR will be configured to identify if the patient's discharge medications include one or more medications in one of three high-risk drug categories (anticoagulants, diabetes agents, or opioids). If the automated "screen" for high-risk drug categories is positive, a message will be sent to study staff, who will contact the potentially eligible patients by telephone within 48 hours for screening to identify those at increased risk for clinically important medication errors based on the items listed in inclusion criteria summarized in #6 *Inclusion and Exclusion Criteria*. The trained study staff responsible for contacting potentially eligible patients will be calling from within the medical group (Reliant Medical Group). Patients will not be cold-called by staff from an unfamiliar, outside organization; patients are already familiar with receiving calls from Reliant Medical Group personnel.

We wish to ensure even distribution of subjects into the treatment and comparison groups across two important factors: (1) number of high risk medications the subjects are taking (one vs. two or more); and (2) month within the year of the study in which the subject is recruited and enrolled. A block randomization design, stratified on presence/absence of caregiver to ensure balance across arms, will be constructed for management within REDCap through the REDCap randomization module (Institute for Clinical & Translational Science at the University of Iowa). This will include information derived from the eligibility interview with randomization of each eligible subject into the treatment or comparison group within the block design.

Determination of Clinically Important Medication Errors

To assess for the occurrence of clinically important medication errors, we will employ methods that we have developed and tested in previous investigations relating to drug-related incidents in various settings and populations. We have assessed and published on the reliability and validity of the approaches that will be employed.[5,29,45,46]

Overview: Two dedicated and highly experienced pharmacist-investigators will be responsible for reviewing the EHR for each patient following hospital discharge; these two pharmacists will not participate as clinical pharmacists in the intervention. They will review computerized records, including outpatient encounters, discharge summaries, emergency department visits, and laboratory results. A 45-day period post-hospitalization will be reviewed. In addition, the pharmacist-investigators will review information derived from a semi-structured telephone interview conducted with the patient and/or caregiver between 5 and 6 weeks following hospital discharge. The telephone interview will follow the approach used by Forster and colleagues,[1] and will assess the patient's condition since hospital discharge by using a full review of organ systems, with special attention given to symptoms that may be relevant to high-risk medications that the patient has been receiving (anticoagulants, diabetes agents, and opioids). The patient will be asked about symptom severity, timing in relation to hospitalization and treatments, and resolution. The interview will also assess the patient's use of home care services, physician services, laboratory services, and hospital readmissions.

Each review will follow a standardized procedure searching for signals we have previously identified as possibly indicating a clinically important medication error. If a clinically important medication error is suspected, an Event Identification Form will be completed, and then reviewed by two blinded physician investigators for final event determination. The Event Identification Form will be submitted to the IRB for review and approval prior to use in this study.

Definitions: The primary outcome of interest will be "clinically important medication errors," a composite outcome comprised of preventable or ameliorable ADEs and potential ADEs due to medication discrepancies or non-adherence. Secondary outcomes will include: (1) preventable or ameliorable ADEs; (2) potential ADEs due to discrepancies or non-adherence; and (3)

preventable or ameliorable ADEs judged to be serious, life-threatening, or fatal. A "preventable" ADE is a drug-related injury relating to a medication error. While some ADEs are not entirely preventable, their duration or severity could be reduced; such events have been characterized as "ameliorable" ADEs. Other types of medication-related problems, referred to as "potential" ADEs (PADEs), may present during the post-hospital discharge period. While these situations may not yet have caused any injury to the patient, they have the potential to cause future harm if not addressed.

Step 1 – Medical Record Review: The pharmacist-investigators, who will not be involved in the intervention, will screen for signals of possible clinically important medication errors in the EHR and the structured telephone interview. We will make every effort to blind the pharmacist-investigators to the status of the patient with regard to randomization to the intervention or control arm. Signals will include new use of drugs that might be employed as antidotes to treat an ADE, laboratory abnormalities, the entering of a new drug allergy, short-term use of medications that are commonly prescribed for extended periods of time but which are not refilled after a first prescription, and specific diagnoses of adverse drug effects. Access to comprehensive drug utilization, laboratory data, and medical records for all study patients makes this a practical approach for surveillance.

Step 2 – Event Identification: Each signal identified will lead to a more thorough investigation and, if confirmed, completion of an Event Identification Form. Data elements that will be gathered for each event include: patient age, sex, active medical conditions; time and date of incident; name, dose, and category of drug involved; documented indication for the use of the drug; other concurrent scheduled and *P.R.N.* medications; type and category of injury and source of information signaling the event; a narrative description of the event; and physician visits, emergency room presentations, and hospitalizations relating to the event. Duration of drug therapy and history of prior use will also be determined.

Step 3 – Physician Adjudication, Independent Review: Two of the physician investigators will independently review each Event Identification Form and classify the event, as well as its severity and preventability. If there is disagreement, the two reviewers will discuss the case in an attempt to come to consensus. For continued disagreement, a third physician investigator will rate the event. The physicians will be blinded to the randomization status of the subject.

Aim 3: To conduct a process evaluation assessing intervention fidelity, adaptation, mechanisms of impact, essential components, and the influence of contextual factors.

As part of the process evaluation for this study, we will conduct up to eight focus groups of 5-8 patients and/or their caregivers. The purpose of the focus groups is to:

a. Gather information from patients/caregivers on their views about medications and medication safety.
b. Gather ideas from patients/caregivers about the best way to improve the study's intervention.
c. Understand the reasons that patients/caregivers decided to participate or not participate in the ISAH study, and identify possible approaches to improving recruitment going forward.

The target population for the ISAH Study focus groups will be patients who either:

a. Declined to participate in the ISAH RCT.
b. Enrolled in the ISAH RCT.

We will not be reaching out to general population; see ISAH RCT study inclusion criteria for more details on the characteristics of patients invited to join the ISAH RCT.

We will recruit patients for the focus groups in two ways,

a. If a patient declines participation in the ISAH RCT:
    i. The screener will mention at the end of the RCT screening call that we would like to offer the patient another opportunity to participate in a different way, and will be mailing them an invitation letter in a few weeks. The revised screening script is included with this IRB submission for review and approval prior to use in the study.
    ii. If the patient agrees to the mailing, the screener will then mail the patient a focus group invitation letter 3-6 weeks after hospitalization. We will include a focus group fact sheet with the invitation letter. The invitation letter and fact sheet are included with this IRB submission for review and approval prior to use in the study.
    iii. The patient can then call a number listed on the invitation letter for more information about the focus groups and enroll in a focus group session. The script for enrolling patients in the focus groups is included with this IRB submission for review and approval prior to use in the study.
    iv. If the patient does not want to participate in a focus group s/he does not need to call the number and we will not contact the patient again.
b. If a patient enrolls in the ISAH RCT:
    i. The patient will be invited to join a focus group session at the end of the outcomes assessment call (this call takes place 5-6 weeks after RCT enrollment). The revised outcomes assessment call script is included with this IRB submission for review and approval prior to use in the study.
    ii. If the patient does not want to participate in a focus group, s/he can decline and we will not contact the patient again.

Each focus group will last approximately 90 minutes and will take place at the Meyers Primary Care Institute. A brief (5-8 questions) anonymous survey will be administered to patients and/or their caregivers during the focus group session to collect focus group participants' demographic information, as well as some brief information about their medications and caregiver(s). Each focus group participant will be paid $75 at the end of the focus group session.

The entire focus group session will be audio recorded, using a portable digital device. We will transcribe the focus group discussions, being mindful of protecting participant confidentiality by use of first names only.

The focus group script and survey are included with this IRB submission for review and approval prior to use in the study. Written informed consent will be obtained from focus group participants or their proxy (see also #31, *Process to Document Consent in Writing*).

12. DATA AND SPECIMEN BANKING*

No specimens are being collected as part of the research. A limited data set will be securely stored for potential future use by the Principal Investigator.

See also #13, *Data Analysis and Management* and #14, *Provisions to Monitor the Data to Ensure the Safety of Subject*s for details on data security and storage.

13. DATA ANALYSIS AND MANAGEMENT*

Data Analysis

To evaluate the impact of the multifaceted intervention on the incidence of clinically important medication errors, we will estimate the average incidence rates of this composite outcome within each treatment group. Time denominators for the incidence rates will take into account the number of days subjects are available for medical record review and the telephone interview during the 45 days post-discharge, excluding days after a subject was re-hospitalized, died, or dis-enrolled as a patient cared for by the medical group. Possible differences between the randomized intervention and comparison groups across patient characteristics including demographic factors, comorbidity, prescribed medications, and aspects of the index hospitalization will be investigated using t-tests for continuous variables and chi-square tests for dichotomous and categorical variables. All analyses of outcomes will be intention-to-treat. Analysis of the primary outcome will be a direct comparison of the incidence rate ratios between the intervention and comparison groups. We will also calculate the distribution of levels of severity and source of errors. Given the sample size, we anticipate satisfactory balance of patient characteristics across arms. If there are substantial differences between the two groups on any of the assessed patient characteristics, we will perform multivariable analyses using Poisson or negative binomial regression (after considering the distribution), taking into account the number of days each subject was followed. Analyses also will adjust for key characteristics of interest, including visits by a home health care nurse, as well as variables related to the outcome in order to reduce unexplained variability.[47] A sensitivity analysis will be limited to those subjects with whom the telephone interview was conducted (estimated at 85% within each arm). In exploratory analyses, we will examine possible effect modification by factors such as presence/absence of caregiver, visits by a home health care nurse (yes/no), use of anticoagulation clinic services, and whether the prescription of the high-risk medication(s) is new since hospital discharge or pre-existing.

Power and Sample Size

A prior study using a similar process for identifying clinically important medication errors during 30 days post hospital discharge found a rate of 0.95 in the comparison group.[18] We estimate the same baseline rate and provide two power estimates. With tracking over 45 days post-hospital discharge, we will have 0.80 power to detect a reduction of 19% (Rate ratio=0.81), as summarized in Table 4.

Table 4. Power Size Calculation

Power	Sample Size* (N)	Rate Ratio	Baseline Rate Exp (B0)	Two-Sided Alpha	Beta
0.95908	500	0.7500	0.9500	0.05000	0.04092
0.94322	500	0.7600	0.9500	0.05000	0.05678
0.92300	500	0.7700	0.9500	0.05000	0.07700
0.89787	500	0.7800	0.9500	0.05000	0.10213
0.86743	500	0.7900	0.9500	0.05000	0.13257
0.83146	500	0.8000	0.9500	0.05000	0.16854
0.79000	500	0.8100	0.9500	0.05000	0.21000

**Total sample size including both arms.*

Some subjects will not be followed for the full 45 days due to re-hospitalizations, deaths, and disenrollment, or inability to be re-contacted for the interview. Therefore, we calculated a parallel

estimate based on a worst case scenario of an average of only 30 days of follow-up, which provides us with 0.80 power to detect a reduction of 23% (IRR-0.77).

Data Security
All persons collecting or handling data will be trained in human subjects' procedures, confidentiality, and privacy protection. All investigators and project staff are required to receive, and complete Human Subjects and HIPAA training.

All computerized data will be kept on secured computers or network servers, beyond University of Massachusetts firewalls. These data will be accessible only to research staff with approved access, using confidential usernames and passwords. Any paper data will be kept in locked cabinets or a locked file room accessible only by research staff.

Study participants will be assigned a numerical code (Study ID) for identification in study files. Names and other direct identifiers will not be included in study datasets (other than age and dates). A data file containing a link between the Study ID to the patient's medical record number (MRN) will be kept separate from the research dataset. This linkage data is necessary to implement the intervention and conduct the medical record reviews. The linkage data file will be destroyed at the earliest possible time, once data collection is complete and data accuracy are verified. The research dataset used for study analysis will be a limited dataset (containing only date and age identifiers). No data will be accessed from RMG without explicit authorization from RMG.

Analyses will be performed using only limited datasets and only aggregate data will be reported. All data will be used for research purposes only; published data will not contain any individual identifiers and will be reported in the aggregate.

See also #14, *Provisions to Monitor the Data to Ensure the Safety of Subjects*, #26, *Confidentiality* and #27, *Provisions to Protect the Privacy Interests of Subjects.*

14. PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS*

The proposed study involves no more than minimal risk to participants. However, we believe that a data and safety monitoring plan is appropriate.

Data and Safety Monitoring Plan
1. Membership: We propose that the Data Safety Monitoring Board (DSMB) be comprised of two members with expertise in the areas of medicine, epidemiology, and patient safety. Members will not be involved in the study in any way, have no vested interest in its outcome, and have no substantive ties to the investigators.

2. Responsibilities: The DSMB will be responsible for assuring study participants are not exposed to unnecessary, unreasonable, or unexpected risk. Further, the DSMB is charged with ensuring that the study is conducted according to the highest scientific and ethical standards. Specific tasks include: (a) review and approval of the proposed monitoring plans prior to study initiation; (b) assessment of trial performance with respect to recruitment, follow-up, protocol adherence/deviation, and data quality; (c) monitoring of interim safety data; (d) review and recommendation for considered protocol modifications or ancillary studies proposed after the main trial has begun to ensure that ancillary studies do not impact the major trial outcome; and (e) advising the principal investigator whether the protocol should continue as scheduled, be

paused, or modified.

3. Meeting Frequency and Format: The DSMB will hold conference calls or meet in-person at least every six months during the three years of the project to discuss study progress and procedures and the findings of interim analyses. Prior to study initiation, the DSMB will meet with the Principal Investigator and other key investigators to review the study protocol. Specific attention will be focused on the main study outcomes and their clear definition, the analysis plan, procedures for recording and reporting serious adverse events, the monitoring protocol, informed consent documents, and responsibilities of the group. At the initial meeting, the DSMB may recommend modifications or request clarifications of the protocol. Also, it will formulate operating procedures for the group including: meeting schedules; expectations for reporting prior to each meeting; protocol-directed study stopping procedures; and interim data releases that will be allowed to the Principal Investigator. At the conclusion of each DSMB meeting, the DSMB will provide a verbal report to the Principal Investigator noting any areas of concern in study performance and/or safety. Care will be exercised to ensure no information will be conveyed that could compromise the study or its outcome. Within two weeks of each meeting, the DSMB Chair will provide a written report to the Principal Investigator which includes the DSMB assessment and recommendations. The report will cover data reviewed, recommendations, and date of the next scheduled review.

The identification and confirmation of clinically important medication errors will be done in the context of medical record review by the research pharmacists and subsequent review of abstracted information by physician reviewers. Because these reviews and determination of a clinically important medication error will likely happen months after the error occurred, the information will not be actionable.

The clinical pharmacists performing the home visits are mandatory reporters; as such, they will report suspected elder and/or child abuse as required by law.

Audio recordings of the focus group sessions will have identifiers redacted during transcription, and all recordings will be destroyed after 1 year. Transcription will be done by study staff. Portable devices will be used for the recordings. All portable devices will be stored in a secure location (locked drawer that only study staff can access) and will be password protected. Recordings will be transferred via upload to a secure folder on the network drive as soon as possible after the recording takes place. The recordings will then be deleted from the portable device immediately after the transfer.

See also #26, *Confidentiality* and #27, *Provisions to Protect the Privacy Interests of Subjects.*

15. WITHDRAWAL OF SUBJECTS WITHOUT THEIR CONSENT*

Because our data collection from patients will occur over a brief period of time (45 days), we do not anticipate the need to withdraw patients unless it is at their request. Other than participation in study interviews, which are voluntary in nature, there are no expected actions the subject must take to continue enrollment. However, we will remove patients who appear unduly distressed during a research interview. Additionally, any subject who fails to provide written consent will be withdrawn from the study.

16. RISKS TO SUBJECTS*

The risks associated with participation in the study intervention itself are deemed to be minimal because the intervention: 1) is aimed at maximizing current standard of care; 2) is being implemented by trained professionals; and 3) none of the components of the intervention that will be provided is experimental care. Our assessment of minimal risk does not, however, absolutely preclude the possibility that serious adverse events could occur (see below).

Monitoring for Serious Adverse Events
This trial is likely to confer minimal risk given that the protocol aims to implement standard of care medication safety practices. However, this assessment of minimal risk does not preclude the need to monitor the study and its impact on subject safety. We feel that it is not necessary to assign monitored serious adverse events as "related" or "unrelated" to the study protocol as there is inherent bias in this assessment, and attribution of "relatedness" would likely be unfeasible. Mechanisms for timely reporting after serious adverse event ascertainment are important, but collective totals of monitored serious adverse events at assigned intervals will meet "timeliness" for the purposes of this study. Furthermore, the study outcomes may not require additional serious adverse event reporting even though they are likely to result in the definition of a serious adverse event. While still ensuring the protection of participants from potential harm, our plan focuses on a limited set of serious adverse events for acquisition and monitoring – hospitalizations and deaths.

Authority for monitoring the safety of the protocol will reside in an independent Data Safety Monitoring Board (DSMB) responsible for holding the Principal Investigator accountable for data quality and completeness, and assessing the ongoing safety of the trial participants through periodic meetings/review. Ongoing participant safety monitoring is the responsibility of the Principal Investigator.

See details described in #14, *Provisions to Monitor the Data to Ensure the Safety of Subjects*.

Potential Loss of Confidentiality
There are potential risks associated with data collection and information management. These include inadvertent disclosure of personal health information or research variables collected. The risks also include the risk of mandatory reporting for the intervention group. Every effort will be made to inform the subject of this potential and minimize the risks.

There are potential risks associated with the focus group sessions. These include the risk that subject's personal information could be discussed outside of the closed focus group session, as it is possible that focus group participants may repeat information shared during the focus group session.

Protection Against Risks
Minimizing Risks: All efforts will be made to minimize risks and participant inconvenience. Risks will be minimized by: 1) adequate training of all staff with proficiency testing; 2) ensuring participants are verbally informed of the details of the intervention and/or focus group session as it is delivered; 3) frequently encouraging participant questions throughout the intervention and/or focus group session; 4) the ability of study personnel to immediately inform the patient's primary care team of any urgent safety issues uncovered in the context of home visits (as that is a component of the intervention); and 5) serious adverse event reporting and monitoring of overall study safety by a DSMB.

To protect against the risk that a subject's personal information could be discussed outside of the closed focus group session, the focus group leader will remind focus group participants at

the beginning of the focus group session that anything discussed in the focus group should remain confidential.

Additional protections for risks associated with potential loss of confidentiality are detailed further in sections #26, *Confidentiality* and #27, *Provisions to Protect the Privacy Interests of Subjects.*

17. Potential Direct Benefits to Subjects*

The potential benefits to the control group subjects from study participation include: 1) feedback to the primary care team regarding safety issues about patients on high-risk medications; and 2) provision to subjects of tailored information regarding high-risk medications they are receiving.

The potential benefits to the intervention group subjects from study participation include: 1) feedback to the primary care team regarding safety issues about patients on high-risk medications; 2) provision to subjects of tailored information regarding high-risk medications they are receiving; and 3) strategies to use medications more safely in the home setting.

18. Vulnerable Populations*

Children

Children will not be included in this study; inclusion/exclusion criterion excludes minors.

Pregnant Women

Pregnant women will not be included in this study; inclusion/exclusion criterion excludes pregnant women.

Prisoners

Prisoners will not be included in the study.

Adults Unable to Consent

We anticipate the identification and inclusion of patients with some cognitive impairment. We will implement consent procedures consistent with those recommended for patients with cognitive impairment (see also #30, *Consent Process*).

19. Multi-Site Research*

N/A; this is not a multi-site study.

20. Community-Based Participatory Research*

N/A.

21. Sharing of Research Results with Subjects*

There are no specific plans to share results with study subjects; study procedures do not include any type of diagnostic testing. All results shared in published research will be in aggregate or summary format, and will not include identifiable information about participants. Published results will be available to the greater community at large, including study subjects.

22. SETTING

The study will be conducted in the context of a large multi-specialty group practice (Reliant Medical Group) located in Central Massachusetts, which has proven to be an ideal setting for conducting a number of prior AHRQ-funded studies focused on improving medication safety and health outcomes in the elderly.

Reliant Medical Group employs 265 physicians and 80 mid-level providers, and provides care for over 180,000 patients at 23 office locations across Central Massachusetts; 35,972 patients cared for by Reliant Medical Group are age 65 or older. The vast majority of these patients are Medicare Advantage (over 80%) and the remainder is provided care under an Accountable Care Organization (ACO) model. The practice has used an EHR since 2006 (Epic Systems Corporation). Epic's EHR, EpicCare®, is ARRA certified by the Certification Commission for Health Information Technology (CCHIT). Reliant Medical Group recently received Patient-Centered Medical Home recertification from the National Committee for Quality Assurance achieving level 3 status. Reliant Medical Group has been the setting for many of our prior studies relating to medication safety in the ambulatory setting beginning more than a decade ago.[5,6,44,46,47,48,49]

Essentially, all patients cared for by Reliant Medical Group are hospitalized in a 321-bed general medical and surgical hospital in Central Massachusetts, with which the medical group is closely aligned. Hospital care is delivered only by Reliant Medical Group hospitalists. Only patients discharged from this hospital will be eligible to participate in the study.

Recruitment and consent will take place via telephone at Reliant Medical Group offices in Worcester, MA. The intervention will take place at study participants' homes; data collection/analysis will take place at Reliant Medical Group and Meyers Primary Care Institute offices in Worcester, MA.

23. RESOURCES AVAILABLE

All study personnel will read the study protocol, receive the appropriate supervision and possess the appropriate experience (both higher education and related work experience) needed to fulfill their roles and complete their responsibilities for this study. All investigators and project staff are required to receive and complete Human Subjects and HIPAA training. All research personnel will hold a current Human Subjects Training Certificate. All study staff have adequate time budgeted to fulfill their responsibilities in the study. The Principal Investigator (Dr. Gurwitz) will oversee all personnel and all research activities conducted within this study.

The Principal Investigator (Dr. Gurwitz) will also have responsibility for the overall conduct of the project at the study site. He will have primary oversight of all study personnel. He will participate in the design and the execution of the respective study analyses and will be responsible for the reporting of study results. The Principal Investigator has extensive experience and expertise in adverse event and patient safety research and has qualified as PI under NIH guidelines and served as PI on numerous other grants.

The Co-Investigators will assist the Principal Investigator in research design and intervention development as well as analytic aspects of the study.

The Pharmacist Investigators will be responsible for training the Intervention Pharmacists. They will also participate in study activities relating to the characterization of clinically important medication errors and the process evaluation. Additionally, they will participate in the evaluation of the study outcomes and development of study findings (e.g. presentations and publications).

The Intervention Pharmacists will be responsible for performing the in-home visits and related components of the intervention including: assessment, education and consultation.

The Biostatistician will assist in the design and performance of analyses relevant to the project and will assist in the development of study deliverables.

The Programmer/Analyst will perform a range of programming and data management activities essential to conduct of the project. S/he will develop study data bases, and perform analyses under the direction of the Principal Investigator. Programmers at the Meyers Primary Care Institute all hold graduate-level degrees and have vast experience working with administrative claims data for research purposes.

The Project Manager will assist the Principal Investigator and the Co-Investigators in implementing all aspects of the project. Under the direction of Principal Investigator, the Project Manager will be responsible for day-to-day coordination and oversight of the project, including: developing timelines, work allocation, workflow plans, monitoring project progress and task completion, monitoring spending and effort allocation, and managing correspondence and administrative tasks. S/he will monitor/manage ethics and regulatory approvals (IRB, HIPAA/DUA). The Project Manager will attend and plan for all project-related meetings as needed. S/he will work under the direction of the Principal Investigator to assist with all study activities, preparing IRB submissions and reports, and developing study materials, such as development of data collection instruments and intervention-related tools. S/he will be responsible for maintaining communications with all parties participating in the project. S/he will track and provide feedback and serve as liaison between the Data Safety Monitoring Board and the research team. S/he will maintain project documentation and will assist in developing and filing required project reports. Project Managers at the Meyers Primary Care Institute all hold graduate-level degrees and have vast experience working on healthcare services research projects.

The Site Principal Investigator (Dr. Garber) at Reliant Medical Group will work with the Principal Investigator and other members of the research team to design specifications, and create and test automated approaches to identifying eligible study subjects. He will also provide input relating to the in-home pharmacist-based intervention, and s/he will participate in study activities relating to the characterization of clinically important medication errors. The Site Principal Investigator will also be the liaison with Reliant Medical Group's clinical and IT departments, promoting the project and its workflows. He will work closely with the IT programmer in the design and implementation of the report and interface that will identify potential subjects newly discharged from the hospital and eligible for recruitment into the study, as well as build the documentation tools in Reliant Medical Group's EHR. The Site Principal Investigator will also participate in evaluation, data analysis and reporting of study findings.

The Reliant Medical Group Programmer will perform activities relevant to the development, testing, refinement, and implementation of an automated process for identifying, characterizing and notifying the study team of potential study subjects. During years one and three of the project, the Reliant Medical Group Programmer will also assist in development of study databases, and data cleaning and validation activities. The Reliant Medical Group Programmer

will also collect baseline and post-intervention metrics from the EHR and claims data as needed to support the project evaluation, data analysis, and reporting of study findings.

The Research Assistant will work under the direction of the Principal Investigator, Site Principal Investigator and Project Manager to assist with all study activities. S/he will assist the Principal Investigator and other study staff in managing the administrative activities of the study. S/he will prepare materials for team meetings, and will facilitate communication between all project staff through written correspondence, telephone, fax, and email. The Research Assistant will assist with data collection, screening, obtaining informed consent and HIPAA authorization, and interviewing of study subjects.

The REDCap Administrator will be the contact with UMass for all REDCap administrative needs throughout the study. As the appointed REDCap administrator for the Meyers Primary Care Institute site, s/he will have access to all study data collected within REDCap. S/he will advise the study team on the development of REDCap data collection tools and its use for data management.

24. Local Recruitment Methods

Screening and Recruitment

Reliant Medical Group patients age 50 years or older will be identified at the time of hospital discharge as having been prescribed a high risk medication of study interest. Identification will be made in an automated manner via EHR data sent to Reliant Medical Group at the time of hospital discharge. Identified patients will be contacted by telephone within 48 hours of hospital discharge by trained study staff for screening to identify those who meet study inclusion criteria. During the telephone interview, the study staff member/recruiter will review the purpose of the study, answer any questions, assess for competency to provide informed consent, obtain verbal consent (or proxy verbal consent as necessary) and collect data relevant to inclusion and exclusion criteria. No data will be accessed from RMG without explicit authorization from RMG.Scripts for the screening and informed consent process will be submitted to and approved by the IRB prior to use in the study.

Patients who screen-in and consent will be enrolled in the study and randomized into one of the two study arms. Patients who “screen-out” will be rescreened on subsequent hospital discharges, if applicable.

Patients will be invited via a letter or phone call to participate in one focus group session, to take place up to 10 weeks post-hospitalization. See also #11, *Procedures Involved.*

See also #30, *Consent Process.*

25. Local Number of Subjects

To enhance generalizability, essentially all screen-positive patients will be recruited using the inclusion/exclusion criteria until the minimum desired numbers have been enrolled (n=500; n=250 in intervention and control groups).

We plan to conduct up to eight focus groups of 5-8 patients each (n=64 maximum):

- Up to four focus groups will consist of patients who **declined** to participate in the ISAH RCT.
- Up to four focus groups will consist of patients who **enrolled** in the ISAH RCT.
    - Control and intervention patients will participate in the same focus group.

26. CONFIDENTIALITY

Only a limited dataset will be kept for analysis by the study team at University of Massachusetts Medical School. Results of the analyses will be presented in the aggregate.

Personal identifiers such as medical record numbers (MRN) will be kept in a separate data file from the research dataset. This linkage data file (containing a link between the Study ID and MRN) will only be accessed by authorized study personnel who require such information to implement the intervention and conduct the medical record reviews. This linkage data file will be destroyed at the earliest possible date, once data collection is complete and data accuracy are verified.

Surveys administered during the focus group session will be anonymous.

Focus group sessions will be audio recorded, which may pose a breach to confidentially. To minimize the risks associated with the potential loss of confidentiality, audio recordings of the focus group sessions will have identifiers redacted during transcription, and all recordings will be destroyed after 1 year. Portable devices will be used for the recordings. All portable devices will be stored in a secure location and will be password protected. Recordings will be transferred via upload to a secure folder on the network drive as soon as possible after the recording takes place. The recordings will then be deleted from the portable device immediately after the transfer. The focus group leader will remind participants at the beginning of the focus group session that sessions are being audio recorded and to use first names only during the focus group session. Participants will also be reminded that all information shared during the focus group session is confidential.

See also #13, *Data Analysis and Management*.

Protection for Risks Associated with Potential Loss of Confidentiality

The organizations proposing this study have systems, oversight, experienced personnel, and an organizational culture that supports the appropriate use, access and storage of confidential information. All persons collecting or handling data will be trained in human subjects' procedures, confidentiality and privacy protection. All investigators and project staff are required to receive and complete Human Subjects and HIPAA training. All research personnel will hold a current Human Subjects Training Certificate.

See also #13, *Data Analysis and Management*.

Data Collected via REDCap

Study data will be captured via REDCap (Research Electronic Data Capture). The REDCap Consortium is comprised of hundreds of active institutional partners from CTSA and other institutions, and it supports a secure web application (REDCap) designed exclusively to support data capture for research studies (http://www.project-redcap.org). University of Massachusetts Medical School is a REDCap Consortium site.

REDCap is used to build and manage online surveys and databases. The front end of REDCap is written in PHP, which is widely used, robust, open source scripting language. Web servers, database servers, and security of communication between servers occur locally at each Consortium site where data capture is stored. Thus, all study data is stored and hosted at the local institution, and no project data is ever transmitted at any time by REDCap from that institution to another institution or organization.

Some additional security features include: a) specification of "user access": by account, by project, or by User Access group; b) system Log-in: assigned username and user-identified password required, automatic inactivity logout, password specificity requirements, passwords must be changed every 30 days, restrictions on use of previous password; c) system lock-out: following succession of unsuccessful login attempts, or if no login to the system within 30 days.

27. Provisions to Protect the Privacy Interests of Subjects

HIPAA Waiver Request

We are requesting a HIPAA authorization waiver to access medical record (EHR) data; these data will be used for the purposes of recruitment as well as to assess study outcomes (see detailed information on the HIPAA Waiver Request (A) form).

We will provide a combined written consent and research authorization form with a signature block for PHI collected during the study to all study subjects. For subjects randomized to the control group, we will mail two copies of the consent and research authorization form and request that the subject (or their legally authorized representative) mail one copy back to us with a signature, and retain the second copy of the form for their records. For subjects randomized to the intervention group, the pharmacist will bring the consent and research authorization form with him/her to the home-visit. The pharmacist will review the consent and research authorization form with the study subject and obtain written documentation of authorization during the course of the home-visit.

Each signed consent/authorization from will be maintained for a minimum of six years after the completion of the research.

Protection for Risks Associated with Participating in Research Interviews

All participants will be told that participation is voluntary, that they are free to not respond or to terminate involvement at any time, with no adverse consequences. Participation in the study will have absolutely no bearing on participants' medical care. At the start of each study interview (telephone, in-home visit, and focus groups), participants will be told that they can decline to answer any questions they want and that they can discontinue participation at any time. Verbal consent will be obtained prior to enrollment in the RCT portion of the study.

If a participant appears to be distressed at any point during any of the study interviews, research staff will suggest that the participant take a break. The interviewer will recommence with the activity only when and if the participant reports the desire to do so.

The interviews during the course of the study involve no specific risk or discomfort beyond those of a standard clinical interview.

28. Compensation for Research-Related Injury

None; there are no resources available. We do not anticipate any research-related injuries. We believe the research poses no more than minimal risk to subjects.

29. Economic Burden to Subjects

N/A. There are no anticipated costs to participate in the study.

30. Consent Process

As noted previously in the screening and recruitment procedures (see #24 *Local Recruitment Methods*), subjects will be contacted by study staff via telephone. We will seek verbal consent during the initial screening phone call and written informed consent for all subjects who are enrolled in the study. For subjects randomized to the control group, two copies of a combined written consent and research authorization form will be sent via mail; we will request that the subjects send one copy of the completed, signed form back to us as soon as possible and retain one copy for their own records. For subjects randomized to the intervention group, a combined written consent and research authorization form will be brought to the scheduled home-visit with the pharmacist. The pharmacist will review the form with the study subject during the course of the home-visit and obtain written documentation of informed consent at this time. In the case that a home-visit cannot be conducted within the 4-day period and the clinical pharmacist instead conducts feasible portions of the intervention by telephone, we will obtain verbal consent to conduct the phone intervention, as outlined below, to conduct the phone intervention. We are requesting a waiver of written documentation of consent to conduct the phone intervention (see #31, *Process to Document Consent in Writing*). We will still mail the informed consent and research authorization form as soon as possible after enrollment.

The written informed consent and research authorization form will be submitted to the IRB for review and approval prior to use in the study. See also #31, *Process to Document Consent in Writing*.

During the initial screening phone call, a truncated verbal consent process, which does not include all of the components of consent and disclosure, will be conducted with all study subjects. We feel that an alteration of the complete consent process is reasonable, as the study:

1. Is minimal risk, as the research procedures are noninvasive and there are appropriate confidentiality protections.
2. The alteration will not adversely affect the rights and welfare of subjects as we will ultimately obtain written informed consent.
3. The study could not practicably be carried out without the alteration of complete consent, as including the complete verbal informed consent process in the initial screening phone call is more burdensome than beneficial to potential study subjects.

Given the short duration of the trial, we will not reassess consent with research participants. Study participants will generally have only three interactions – the home visit, the follow-up phone call at two weeks post-home-visit, and a semi-structured telephone interview conducted with the patient and/or caregiver between 5 and 6 weeks following hospital discharge. It would be impractical to conduct the research if we had to gauge each participant's ability to consent for him-or-herself at each of these interactions, as the first interaction for the intervention group will take place within days of the screening call. The other interactions are phone calls, and it

would be more burdensome than beneficial to subjects and/or their legally authorized proxies to repeat the formal initial consent process during these follow-up phone calls. While we will not formally reassess consent with study participants during these follow-up phone calls, in the event that the study subject was enrolled via a legally authorized proxy, we will ask the legally authorized proxy if we should speak to the subject instead of the proxy.

For Aim 3, Process Evaluation Focus Groups: The focus group leader will review informed consent with patients and/or their proxy prior to beginning the focus group discussion, and obtain a signature for written informed consent at this time. Informed consent will include consent for audio recording the session. The focus group consent form is included with this IRB submission for review and approval prior to use in the study.

For the consent process, we will follow *HRP-800 INVESTIGATOR GUIDANCE: Informed Consent*.

Proxy Consent (For Adults Unable to Consent)
It is recognized that potential participants with cognitive limitations need to be identified – not to exclude them from participation, but to identify those who require added processes to participate in an ethical manner. Therefore, at the time the potential patient subject is initially contacted, professional judgment will be used to determine the need for alternate consent. Study personnel responsible for recruitment, consent, and interviewing will be highly trained and experienced in determining decisional capacity in senior populations.

Patients will be assessed for competency to consent to the research. Patients will be asked a series of questions during the screening call that will evaluate their understanding of the study and their competency to consent to the research (three consent screening questions: “True or False: The project is about using medications safely,” “True or False: A pharmacist may come to your home,” and “True or False: As part of the project, we will look at your medical records”). Patients who fail the brief evaluation of competency to consent will be required to have a caregiver/proxy willing to: (1) provide consent and (2) participate in the in-home visit by the clinical pharmacist.

We will follow *HRP-021 POLICY: Legally Authorized Representatives, Children, and Guardians* to ensure that the person who provides proxy informed consent is a legally authorized representative. We will verify the individual identified as the legally authorized representative to ensure that they are, in fact, the subject’s legally authorized healthcare proxy by reviewing the subject’s electronic medical record during the screening. In the event that the subject does not have a legally authorized healthcare proxy recorded in their electronic medical record, we will verify during the proxy consent screening process that the person serving as proxy meets the criteria for legally authorized representative in accordance with the *HRP-021 POLICY*.

Additionally, we have defined a suitable (or designated) proxy as a person who is cognitively intact. We will assess the competency of the proxy to consent to the research. Proxies will be asked a series of questions during the screening call that will evaluate their understanding of the study and their competency to consent to the research (three consent screening questions: “True or False: The project is about using medications safely,” “True or False: A pharmacist may come to [Patient’s Name]’s home,” and “True or False: As part of the project, we will look at [Patient’s Name]’s medical records”). We will not record this data. For patients with cognitive impairment, the intervention will also involve participation by the caregiver (e.g., a family member, friend, or surrogate invested in the care of the patient).

In addition, specific assessment of decisional capacity will be part of study training. For example, potential participants will be considered impaired with regard to decisional capacity if they: 1) have an inability to express or communicate a preference/choice; 2) cannot understand the consequences of a potential situation – e.g. cannot understand the implications of releasing their PHI; 3) are unable to provide a logical rationale for participation/non-participation; or 4) have a legal guardian or have been identified legally as incompetent to make decisions for themselves.

If there is any uncertainty in the decisional capacity of a potential patient study subject, study personnel will be instructed to obtain proxy consent. When proxy consent is deemed necessary, the proxy will be contacted and informed consent will be obtained from the proxy; we will also obtain verbal assent from the study subject. In the event that a legally authorized representative is needed, we attest that the following criteria for a waiver of informed consent in this circumstance are true:

1. The study is minimal risk as the research procedures are noninvasive and there are appropriate confidentiality protections.
2. The waiver will not adversely affect the rights and welfare of subjects, as we will ultimately either obtain informed consent or otherwise discard or anonymize the collected data.
3. The screening could not practicably be carried out without the waiver, as it cannot always be known ahead of time who will decline or require an LAR.
4. In the event it becomes appropriate to provide individuals with additional pertinent information, we will seek the guidance of the IRB.

31. Process to Document Consent in Writing

We will request written consent from all subjects. The sequence of the process we propose to use to document consent in writing differs slightly from the sequence described in the grant application. Despite what was described in the grant application, we have concluded that it is impractical to conduct the study in a timely manner if we are required to obtain written documentation of consent prior to randomizing subjects to either control or intervention groups. It is crucial to the study design to implement the intervention as soon as possible post-hospital discharge, as many (likely the majority) of clinically important medication errors occur very soon after hospital discharge. Obtaining written consent by sending study staff into all subject's homes before randomization takes place would delay our ability to efficiently and effectively implement the intervention and have an opportunity to impact the outcome of interest (i.e., a reduction in clinically important medication errors).

We propose that we obtain verbal consent and randomize subjects during the initial screening call, and subsequently obtain written informed consent. A written consent form will be sent via mail to subjects who are randomized to the control group; we will request that the subjects send the completed, signed form back to us as soon as possible. For subjects randomized to the intervention group, a written informed consent form will be brought to the scheduled home-visit by the pharmacist. The pharmacist will review the form with the study subject during the home-visit and obtain a signature for written informed consent at this time.

In the case that a home-visit cannot be conducted within the 4-day period and the clinical pharmacist instead conducts feasible portions of the intervention by telephone, we will obtain verbal consent to conduct the phone intervention. As with the home-visit, the phone intervention will be conducted within 4 days of hospital discharge. It is not feasible to mail and receive the written consent form back from the subject prior to conducting the phone call. We are requesting

a waiver of documentation of written consent to conduct the phone intervention. We feel that the waiver of documentation of written consent is reasonable in this instance, as:

1. The research presents no more than minimal risk to subjects.
2. The research involves no procedures for which written consent is normally required outside of the research context.
3. The investigator will provide a written statement regarding the research that embodies the elements of consent.
4. The investigator will provide subjects with that written statement.

We will mail the combined written consent and research authorization form to the subject as soon as possible after enrollment. We will request that the subjects send one copy of the completed, signed form back to us as soon as possible and retain one copy for their own records.

If any subject does not return the written consent form, we will consider them withdrawn from the study. We will not retain any records on subjects who have not consented to the study, and will not conduct the medical record review unless we have the signed HIPAA authorization from the subject.

The combined written consent and research authorization form will be submitted to the IRB for review and approval prior to use in the study.

For Aim 3, Process Evaluation Focus Groups: The focus group leader will review informed consent with patients and/or their proxy prior to beginning the focus group discussion, and obtain a signature for written informed consent at this time. Informed consent will include consent for audio recording the session. The focus group consent form is included with this IRB submission for review and approval prior to use in the study.

See also #30 *Consent Process*.

32. Drugs or Devices

NA; this research does not involve testing drugs or device

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