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PROTOCOL TITLE: Testing a medication risk communication and surveillance strategy: The EMC2 Trial

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CONTENTS

1. OBJECTIVES

1.1 Specific Aims

Aim 1: Test the effectiveness of an EHR-based Medication Complete Communication (EMC2) strategy to improve patient understanding of medication risks, patients' demonstrated safe use, and the detection of patients' adverse drug events.
Aim 2: Assess whether the EMC2 Strategy can reduce disparities in understanding and demonstrated safe use by patient literacy level, English proficiency, and age compared to usual care.
Aim 3: Evaluate the effectiveness and fidelity of the EMC2 Strategy to promote provider counseling, deliver patient Rx information, monitor use, and inform providers of potential harms.
Aim 4: Explore patient, provider, and health system barriers to implementation and effectiveness.
Aim 5: Determine the cost of delivering the EMC2 strategy from a health system perspective.

1.2 Hypotheses

Related to Aim 1, we hypothesize that:
H1: Patients receiving the EMC2 intervention will have better understanding of medication risks than those in the control arm.
H2: Patients receiving the EMC2 intervention will demonstrate safer use of their medication than those in the control arm.

H3: Adverse drug events will have a higher rate of detection for patients in the EMC2 intervention arm than in the control arm.

Related to Aim 3, we hypothesize that compared to usual care, patients receiving the EMC2 strategies will:
H4: Report higher rates of provider Rx counseling
H5: Report higher rates of receipt of print Rx information.
H6: Be more likely to communicate Rx questions.
H7: Report a greater frequency of clinic follow-up.

2. BACKGROUND

2.1 Relevant prior experience and gaps in current knowledge

Research has repeatedly demonstrated that individuals lack essential information on how to take prescribed (Rx) medications safely. Knowledge deficits are greatest for information pertaining to risks and warnings. Inadequate patient knowledge has been cited as a root cause of unintentional misuse, which can lead to serious adverse drug events. This is not surprising, as neither prescribing clinicians nor pharmacists routinely counsel patients on medication risks and safe use. Instead, patients heavily depend on product labeling, such as package inserts, container labels, leaflets, and Medication Guides – all of which are limited in their clarity and effectiveness. Our team has found that even when evidence-based, health literacy best practices are employed to these written tools, the elderly and those with low literacy continue to be inadequately informed and are therefore at greater risk for medication errors and/or suboptimal treatment.

Medication errors refer to any mistake made by a provider or patient that occurs during the process of medication use. Adverse drug events (ADEs) are defined as "any injuries resulting from medication use, including physical harm, mental harm, or loss of function." Medication errors do not necessarily always result in an ADE, but often impact treatment effectiveness. While the exact prevalence of medication errors in ambulatory care is difficult to estimate, nearly 10 million outpatient physician visits and 4 million emergency department admissions are attributed to ADEs or side effects annually. These are more likely to occur in primary vs. specialty care settings, among older patients or those with multi-morbidity. Among adults seen in outpatient practices who take a medication, 16 to 25% experience an ADE over the course of a year. Occurrence of ADEs depends on patient factors and drug class; regardless, most are detected late - if at all. Thus, patients remain at risk for further harm and less effective treatment. From a public health/pharmacovigilance perspective, early detection of ADEs could provide new information on a medication's safety and inform the care of others taking it.

Root Cause: Patients Lack Sufficient Information to Ensure Safe Use. Poor patient awareness and/or misunderstanding of medication risks and instructions are often cited as an underlying, root cause of medication errors and ADEs. This is not surprising, as patients often lack sufficient information to help support medication use in ambulatory care. Although most patients prefer to receive medication counseling from their physician, doctors often fail to review even basic drug information with patients. Yet patients who receive medication counseling are more likely to be adherent to their regimen. While there are guidelines promoting counseling, physicians receive limited guidance on what specifically to tell patients about drugs. At the point of dispensing, pharmacists also frequently fail to counsel patients on safe medication use, despite federal and state mandates to do so. Pharmacists may not be fully aware of why a patient was prescribed a medication (i.e. indication for use) or what spoken instructions were provided by the physician. With limited spoken counseling or instruction, patients must instead rely on written communication, such as package inserts, container

labels, auxiliary warnings, and leaflets to support safe medication use. Our team and others have found all to be too complex, particularly for patients with limited literacy and/or English proficiency. Literacy, Age, and English Proficiency are Risk Factors. Many studies have found limited literacy skills to be significantly associated with patients' poorer recall of medication names and indications, inadequate understanding of Rx instructions and precautions, and demonstrated Rx misuse. Deficits are often greatest for information pertaining to risks and warnings. Older patients also may be more likely to lack sufficient knowledge to use prescribed medications safely, as they are disproportionately affected by limited literacy, cognitive impairment, and comorbidity. Limited English proficiency (LEP) also presents a formidable challenge to healthcare. Interpreters are rarely available to aid physicians and pharmacists in counseling LEP patients, instructions often are unavailable in non-English languages, and multilingual materials may be poorly translated and inaccurate. The result is higher misuse and non-adherence rates among LEP patients.

FDA Actions: Risk Evaluation and Mitigation Strategies and Medication Guides. The 2007 FDA Amendments Act (FDAAA) expanded the FDA's authority to require drug manufacturers to submit Risk Evaluation and Mitigation Strategies (REMS) for medications deemed to possess serious public health concerns in order to ensure product benefits outweigh known risks. REMS include: 1) Medication Guides (a.k.a. Med Guides) - print patient materials that highlight a drug's safety information and are required to be distributed to all patients receiving the medication; 2) Communication Plans - strategies to educate providers on safe, appropriate use, and how to counsel patients; 3) Elements to Assure Safe Use - other assurances for proper prescribing (i.e. physician certifications, patient registries), and 4) Evaluations of REMS Performance - periodic reporting to FDA on whether REMS components have achieved goals. To date, over 400 drug products have been required to include a Med Guide or Communication Plan as part of REMS.

Med Guides are the only mandated assurance that patients receive tangible safety information for a prescribed medication prior to use, potentially preventing ADEs and allowing patients to remain vigilant during use. A prior study by Shrank and colleagues found that Med Guides were rarely distributed to patients by pharmacies as required with prescriptions. This is understandable, as many pharmacies cannot embed Med Guides within their electronic record, therefore dissemination depends on the pharmacist remembering that a drug requires a Med Guide and physically retrieving the Guide for the patient. In another study by our team, only 1 in 4 patients reported ever reviewing Med Guides dispensed with Rx drugs. We also found that patient comprehension of existing Med Guides was extremely poor. While older adults and those with lower literacy were less able to understand Med Guides supporting safe use, all patients had considerable difficulty.

Yet the REMS requirement under Communication Plans (to educate and prepare providers on medication risks and patient counseling) is equally flawed. The current practice for drug manufacturers is to identify their 'prescriber pool' through provider ID numbers and collect a mailing list from state licensure boards. Physicians and other clinicians therefore receive letters in the mail from the manufacturer, which rarely are attended to by the recipient. The result is that neither prescribers nor patients are adequately informed about medication risks.

Inadequate provider counseling and print information explains why many patients are unaware and inattentive to drug risks. Poor knowledge and insufficient vigilance is likely to increase the risk of errors and ADEs. This is of greatest concern for older patients and those with limited literacy or LEP.

A Health Literacy Approach to Patient Medication Information. The FDA has acknowledged the complexity of Med Guides and is actively investigating ways to improve them and other tangible sources of patient medication information. In July 2014, the FDA sponsored a Brookings Institution public workshop to consolidate health literacy research in this area and identify future directions. Guidance from a number of fields of study (communication, education, human factors, cognitive

psychology) helped set forth best practices for developing health information to optimize comprehension. In particular, our team developed and evaluated an evidence-based, 'low literacy', 1-page Med Guide Summary to accompany the longer, FDA-required Med Guide, to promote patient understanding of risk information. We conducted a clinical trial among 1003 primary care patients to test the effectiveness of this summary sheet. We found that that our Med Guide Summary (see Preliminary Studies) significantly improved patients' ability to retrieve and apply medication information. This was uniformly seen among patients across all literacy levels and ages. Despite this success, our results underscored the limitations of using only a print modality to convey important health information. More than a third of individuals with marginal literacy and over half with low literacy still struggled to understand information contained in the Med Guide Summary; none of the prototypes achieved >80% comprehension rates (a target threshold for patient education materials). More aggressive strategies beyond written materials are warranted to ensure all patients are adequately informed in support of safe medication use.

The Need for a Primary Care-Based Response. In primary care, many of the medications commonly prescribed have REMS and Med Guide requirements. Few if any mechanisms, however, exist to ensure and confirm patients receive easy-to-understand risk information. The ability to routinely monitor patients' actual use of these higher-risk medications is also not presently possible. Instead, physicians often rely heavily upon patients, both to learn independently about their prescribed medication and to inform their provider of any errors, ADEs, or adherence concerns. Frequently, clinicians do not learn of any medication problems, or only hear of such issues later at the next follow-up encounter. This is problematic, as many patients, especially those with limited literacy or taking multiple medications, have difficulty linking side effects to signs of a potential ADE and may be unaware of the need to contact their physician. In one study, 37% of ameliorable ADEs were attributed to patients not informing their provider of signs and symptoms.

To date, most initiatives to reduce ADEs have focused exclusively on physician prescribing practices. Yet most ADEs do not result from poor prescribing decisions, but from side effects experienced from an appropriately prescribed drug. As many as half of ADEs can be detected and mitigated at an early stage, making opportunities for amelioration up to 2.5 times as likely as opportunities to prevent ADEs through better prescribing. We will address current shortcomings by promoting: 1) provider counseling, 2) dissemination of understandable, actionable medication risk information, and 3) routine surveillance of medication use in primary care by using available health technologies to 'hardwire' medication communication and surveillance of higher risk medications.

2.2 Relevant preliminary data

A risk communication and surveillance strategy is needed in primary care to ensure that patients are adequately informed about medication risks and are taking prescribed regimens safely. This is most salient for Rx medications the Food & Drug Administration (FDA) has deemed to possess serious public health concerns, warranting a Medication Guide and/or Risk Evaluation and Mitigation Strategy (REMS). To our knowledge, no such strategy exists to support and monitor outpatient medication use in a cost-sustainable manner.

We devised an Electronic health record-based Medication Complete Communication (EMC2) strategy that leverages electronic health record (EHR) and interactive voice response (IVR) technologies to: 1) prompt and guide provider counseling; 2) automate the delivery of Medication Guides at prescribing; 3) engage patients post-visit via IVR to confirm they have sufficient information and are using Rx properly; and 4) activate the clinical team to help patients overcome any barriers to safe Rx use.

Collectively, our team has previously designed and field tested each of the core functions of the EMC2 Strategy components, and is now integrating these tools for this project at our sites:

• Health Literacy, 1-Page Med Guide Summary. Drs. Wolf and Bailey recently completed a series of investigations, culminating in a randomized trial comparing the effectiveness of 3 different print versions of an improved Med Guide, 1-Page Summary sheet to supplement the longer, FDA-approved document. All versions included plain language (<8th grade level) and varying formats modified to promote information accessibility. 1003 adults were recruited from two outpatient primary care practices. One specific format, referred to as the Health Literacy format consistently demonstrated the highest comprehension scores, and in multivariable analyses, outperformed all others and receipt of the FDA Med Guide alone. The 1-page summary form concept to include with longer Med Guides was recently reviewed and supported at the July 2014 Brookings Institution advisory panel. As part of a recent AHRQ-funded study, we created English and Spanish Med Guide Summaries using the Health Literacy format for 33 medications [R18HS17220].

• EHR Tools to Deliver Patient Medication Information. Drs. Wolf and Bailey continue to work together on several pilot projects that leverage EHR platforms (EpicCare, Cerner Powerchart, GE Centricity) to standardize prescribing, provide Spanish translations, prompt medication reconciliation before and during clinical encounters, and to automatically generate Med Guide Summaries (Epic, Cerner, Centricity). Med Guide Summaries are embedded in the EHR as PDF documents, linked to medications, and automatically cued to print with the after-visit summary once a prescriber places the order. As each Med Guide Summary was written in active voice, it also serves as a counseling support tool. In prior field tests [R18HS17220; R21CA132771], each PDF Summary had a 'dot phrase' function so a provider could manually access and share content on screen by simply typing the name of the drug and hitting return (i.e. ".REGLAN <ENTER>"). While >85% of the time patients received Med Guide Summaries, the dot phrase commands were too passive as a method for providers to use for counseling. Guided by Alliance clinical staff feedback, the EMC2 now will use a prescriber alert to prompt clinicians and automate a view of the Med Guide Summary, with an option to 'ignore' if desired.

• Training Clinicians on Health Literacy Spoken Counseling Best Practices. Collectively, Drs. Wolf, Bailey and Paasche-Orlow have extensive experience developing and implementing provider and nurse training sessions for brief counseling to support preventive screening, disease management, hospital discharge instructions, and medication education.

• IVR System Linked to EHR. Drs. Paasche-Orlow and Adams have 10+ years' experience developing and evaluating IVR systems in urban populations. They have led the development and evaluation of IVR systems designed to improve health for people with asthma, obesity, spinal cord injury, and primary care for children. Most recently, they have developed and evaluated an integrated, patient-centered health information system - the Personal Health Partner (PHP). The PHP is a fully automated conversational system that uses synthetic speech (TTS), automatic speech recognition (ASR), and a data-driven multimodal conversational system to gather personal health data and counsel parents before scheduled visits. Patient-reported data is then shared with the provider via the EHR (GE Centricity) and combined with decision support and recommendations. Their work with patient-facing IT system development has focused on usability for patients with limited literacy by integrating plain language principles and key informant feedback into the design, testing, and refinement of their systems. As a result, studies have shown that PHP patient use patterns did not vary by literacy level.

• User-Centered Design of Primary Care-based Interventions. The EMC2 Strategy involves clinical staff at performance sites to 'on-board' the intervention at practices. In field tests, our team included clinicians in the design of EHR and IVR tools. Providers reported high (>90%) satisfaction rates; time-motion studies found no differences in time spent in clinical encounters once tools were activated. Drs. Paasche-Orlow and Adams have also been mindful of the manner in which IVR

systems fit into clinical workflow to improve efficiency. As primary care physicians themselves, they are aware of the time pressures and competing demands, and as such, IVR tools are designed with this in mind. For IVR tools, 100% of physicians reported it improved patient care.

2.3 Scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how it will add to existing knowledge.

The FDA has acknowledged the complexity of Med Guides and is actively investigating ways to improve them and other tangible sources of patient medication information. In July 2014, the FDA sponsored a Brookings Institution public workshop to consolidate health literacy research in this area and identify future directions.

Technological solutions can be leveraged to prompt provider behavior, help patients explicitly learn how to safely take prescribed medications, and monitor medication use at a cost that is not prohibitive to clinics. Our EMC2 Strategy will impart these activities using technologies that are increasingly prevalent per federal mandates (Health Information Technology for Economic and Clinical Health (HITECH) Act), particularly among community health centers. With the EMC2 Strategy, we respond to the Office of the National Coordinator (ONC) 'Meaningful Use' criteria by leveraging an EHR to deliver standard, patient-centered information supporting safe use. In this model of care, we merge the benefits of our research on improving counseling at the point of prescribing (Wolf, Bailey) with our research to monitor and support patients in the most effective, available, and patient-centered manner using an interactive voice response (IVR) system (Paasche-Orlow, Adams). This multi-faceted, primary care approach will promote and monitor the use of high risk medications and activate the clinical team to respond to any concerns relating to medication acquisition, proper use, and safety.

IVR vs. Other Technology Outreach Platforms. The longstanding criticism of IVR systems has been the frustration it may cause consumers. In recent years, however, dramatic improvements have been made with the technology, and studies repeatedly demonstrate high accuracy, patient satisfaction, cooperation rates, and patient engagement with IVR tools. In fact, Lyles et. al. found no differences by literacy, race/ethnicity, or language for pattern of use of their IVR system. Other options for monitoring patients post-visit were considered for the EMC2 Strategy (i.e. text messaging, smartphone applications, web-based EHR portal), however, we found these had serious limitations. In a recent study by our team examining health technology use among primary care patients (N=1,077), we found those with low literacy skills were significantly less likely to own a cell or smart phone or have access to high speed internet compared to those with adequate literacy. Among those that did, lower literate patients were less likely to send/receive texts or use the internet to communicate with healthcare providers (in press, Health Expectations). Similar differences were found by patient age, leading us to believe that older patients and those with limited literacy would be marginalized if our strategy utilized mobile or web portal platforms. In contrast, IVR works with landlines and mobile phones, capturing >90% of low literate and elderly audiences. It offers a simple interface that is usable by a broad range of patients including patients with low literacy and the elderly, and can now connect to an EHR to share results with providers. It was therefore a clear choice for our primary care-based EMC2 strategy, which will: 1) increase provider counseling at the time of ordering a higher-risk drug, 2) increase the frequency of patients receiving easy-to-understand, actionable information describing safe drug use, risks and warnings, 3) improve patients' understanding and demonstrated proper use of their medication, and 4) increase the rate of timely detection of an ADE or other medication-related concern.

3. INCLUSION AND EXCLUSION CRITERIA

3.1 Methods of screening for eligibility

Patients will be initially screened for eligibility by Alliance's data pull and further screened over the phone by Northwestern Research Assistants (RAs).

Screening by Alliance. Alliance will send information to Northwestern on patients who meet the following conditions: (1) newly prescribed (i.e. had not been prescribed at Alliance within the previous two years) one of our study medications, (2) preferred language listed as English or Spanish, (3) age as of clinic visit > 21 years, (4) clinic visit occurred at a participating health center location (7 clinics associated with Near North Health Services Corporation).

Screening by Northwestern. Northwestern Research Assistants (RAs) will call those patients identified by Alliance and further screen them by asking eligibility questions and screening for cognitive impairment, in alignment with the inclusion and exclusion criteria (3.2).

We will receive patient information from Alliance in one of two ways:
Method 1- Each morning, Research Assistants (RAs) at Northwestern University will be able to access an SSRS report on a secure platform (Alliance SharePoint) showing a list of patients triggered as potentially eligible during a clinic visit on the day prior. The report will show the patient's contact information necessary for outreach for the purpose of screening (record id, first and last name, date of birth, clinic name, phone number, preferred language, and date of index clinic visit), but will not include the patient's medication information necessary for conducting the baseline interview. The RA will then call each patient, ask the few remaining eligibility questions to complete the screening process, invite the patient to participate, and obtain informed consent over the phone. The RA will then schedule a time to call the patient back for the baseline interview the next day (or as soon as possible thereafter). At the end of each day, the RA will upload a list of newly consented patients to Alliance Sharepoint, prompting Alliance to send medication information for those patients the following morning.

Method 2- Each morning, Research Assistants (RAs) at Northwestern University will receive, via file sent to a secure ftp site, a list of patients triggered as eligible during a clinic visit on the day prior. The report will show the information needed to contact the patient and conduct the baseline interview (same data as listed in method 1, plus the name(s) of any study medications prescribed during the visit, the associated sig(s), prescriber name, and regular physician name). With this method, RAs will be able to conduct the baseline interview during the same phone call, immediately after screening and consenting the patient. This method would also allow the RA to explain to the potential participant which of their prescribed medicines would be the subject of the interviews and to confirm that the medication was actually prescribed, eliminating any confusion.

Automatic exposure to part of intervention. Clinics will be randomized either to the intervention arm or to usual care. All patients who see a prescriber at a clinic site randomized to the intervention arm and who receive a prescription for one of the study medications (Table 1) will automatically receive some components of the intervention during their clinic visit (provider counseling, Med Guide Summary), regardless of whether or not they meet further screening criteria. This randomization and recruitment process will ensure that recruited patients may receive all in-clinic EMC2 components on the day they receive a prescription for a study drug. It will also result in a trickle down of some components of the EMC2 Strategy being given to patients seen at the intervention clinic site, but not enrolled in the study for follow-up purposes (EHR tools, but not IVR or nurse follow-up). This specific strategy of "turning on" an EHR intervention with provider or clinic level randomization has been previously approved by the IRB at Northwestern University for three other AHRQ funded grants [P01HS021141-01, 1U19HS021093-01 & 1R18HS017220-01]. Prescribers at these intervention sites will be made aware that the EHR tools have been activated, with the understanding that the tools themselves are educational in nature and will have minimal, if no effect on patient care and clinic workflow.

3.2 Inclusion and exclusion criteria

Inclusion Criteria (Patients). To be eligible to enroll in the study, patients must attend one of the seven randomized clinics associated with the Alliance-affiliated health center Near North Health Service Corporation. They must also meet all of the following criteria: 1) age 21 and older; 2) English or Spanish speaking; 3) have received a new or changed prescription (i.e. had not been prescribed at Alliance within the previous two years) for one or more of our study medications (Table 1); 4) have a personal phone line (land or mobile).

Inclusion Criteria (Providers). To be eligible to complete the provider survey, providers must see patients at one of the three Near North clinics randomized to the intervention arm (Louise Landau, Komed Holman, Sunnyside).

Study medications. To select these drugs, we reviewed the top prescriptions ordered in 2013 by providers at Alliance FQHCs and selected those that have a Med Guide/REMS requirement. These drugs were reviewed by clinicians and pharmacists to ensure the list was comprehensive and appropriately reflects prescribing behaviors in the clinics. These drugs are diverse by class, indication, duration, side effects, route of administration, and potential for harm. Each has an FDA risk communication goal that presently is not being achieved.

Table 1.

testosterone	escitalopram	sitagliptin and metformin
amiodarone	fluoxetine	exenatide
carbamazepine	paroxetine	liraglutide
divalproex	sertraline	pioglitazone
gabapentin	doxepin	rivaroxaban
lacosamide	imipramine	ciprofloxacin
lamotrigine	mirtazapine	levofloxacin
levetiracetam	colchicine	moxifloxacin
oxcarbazepine	emtricitabine and tenofovir	salmeterol
phenytoin	nevirapine	budesonide and formoterol
pregabalin	fenofibrate	fluticasone and salmeterol
topiramate	clopidogrel	celecoxib
valproic acid	alendronate	diclofenac
aripiprazole	risedronate	indomethacin
quetiapine	pimecrolimus	meloxicam
clonazepam	tacrolimus	sulindac
bupropion	amphetamine	dexlansoprazole
trazodone	methylphenidate	pantoprazole
desvenlafaxine	linagliptin	metoclopramide
duloxetine	saxagliptin	tamoxifen
venlafaxine	saxagliptin and metformin	varenicline
citalopram	sitagliptin	propylthiouracil

alprazolam	ibandronate	mometasone-formoterol
apixaban	lisdexamphetamine	nortriptyline
dexmethylphenidate	lorazepam	olanzapine
diazepam	lurasidone	tramadol
fluticasone-vilanterol		

Table 1 – part 2.

Exclusion criteria. Subjects will be excluded from the study if any of the following conditions are met: 1) Aged <21 years, 2) non-English or -Spanish speaking, 3) any severe, uncorrectable vision, hearing or cognitive impairments (measured by the six-item screener) that would impede study interviews, 4) unable to complete follow up interviews.

4. STUDY-WIDE NUMBER OF PARTICIPANTS

See 23. Local Number of Subjects

5. STUDY-WIDE RECRUITMENT METHODS

See 22. Recruitment Methods

6. MULTI-SITE RESEARCH

Data will only be collected over the phone by Northwestern research staff. The provider survey, will have an email and pen and paper version available.

UNC will be home to key research collaborators who will be involved in the study design, intervention development, and interpretation of results, but will not interact with patients and will not have access to data.

Boston Medical Center (BMC) will facilitate the IVR component of the intervention. A data use agreement has been established between NU and BMC to this effect, and the Office of the Institutional Review Board at BMC has approved the transfer process proposed (described in 11.3).

Weekly meetings with all sites (Northwestern, BMC, Alliance, UNC, UIC) will be held throughout the study. This time will be used to discuss progress of the study and any changes to the protocol or study battery. The project manager will email any modifications to the IRB protocol to the team within one day of receiving approval. The project manager will hold weekly meetings with project staff to ensure that the protocol is being followed.

7. STUDY TIMELINES

An individual patient subject will be involved in the study for a total of up to 3 months. They will complete a screener enrollment interview, a baseline interview as soon as possible following the screener, a possible follow-up interview at 4 weeks, and a possible final interview at 3 months. The need for follow-up interviews will be determined by a patient's medication fill and take behavior (if they do not plan to fill or take the medicine or have already stopped taking the medicine, we will not need to continue with follow-up interviews). All interviews will be conducted over the phone.

We anticipate that patient enrollment will actively take place over 2 years. The date by which we expect to complete primary analyses is August 31, 2019.

Our proposed/anticipated study timeline is below:

Table 2. Study Timeline

TASKS	Y1				Y2				Y3				Y4	
	1	2	3	4	1	2	3	4	1	2	3	4	1	2
PREPARATION PHASE:														
Organize research team, convene DSMB	■	■												
Translate study materials	■	■												
Protocol development	■	■												
Prepare and refine EHR tools	■	■												
Prepare and refine IVR tools	■	■												
Site orientation, training, logistics planning			■											
Prescriber randomization			■											
Integrate, pilot, debug EMC²			■											
IMPLEMENTATION PHASE:														
Implement EMC² Strategy				■										
Recruit, consent participants				■	■	■	■	■	■	■	■	■		
Conduct baseline interviews				■	■	■	■	■	■	■	■	■		
Conduct 2 week and 3 month interviews				■	■	■	■	■	■	■	■	■		
Seek process feedback from clinical staff				■				■					■	
EVALUATION PHASE:														
Clean & analyze data						■	■	■	■	■	■	■	■	■
Summarize and interpret findings									■	■	■	■	■	■
Provide feedback to sites, review scalability									■				■	■
Submit manuscripts for publication									■				■	■
Present findings at national venues									■		■		■	■

8. STUDY ENDPOINTS

8.1 Primary and secondary <u>study</u> endpoints.

The study's primary endpoints are medication knowledge and medication behavior (fill, proper use, and actual use).

8.2 Primary or secondary <u>safety</u> endpoints.

The study's safety endpoints include assessment of any Adverse Drug Events (ADE).

9. PROCEDURES INVOLVED

9.1 Study design

We will conduct a 2-arm, randomized trial at one Alliance-affiliated federally qualified health center (FQHC) in Chicago, Near North Health Services Corporation, to evaluate the EMC2 intervention strategy compared to usual care.

We will assess patients' Rx knowledge and behavior at baseline, 4 weeks, and 3 months. Prevalence of ADEs and rate of their detection will be determined at 3 months or at an earlier interview if they state having already completed the course of medication. The fidelity and economic impact of the intervention will also be investigated via process and cost measures, in addition to patient and provider feedback. Results will determine effectiveness and identify any necessary modifications, guiding future dissemination efforts.

Study Arms:

Usual Care. Current usual care includes 1) variable physician and/or nurse counseling without any EHR notifications or counseling support; 2) no distribution of print medication information materials in Alliance clinics, and variable, limited distribution likely in pharmacies; 3) no active surveillance of medication use post-visits.

Intervention Arm: EMC2 Strategy. Following a patient's movement through a provider visit at one of the Near North clinics randomized to the intervention, the following five activities (described in more detail in 9.2) will occur:

- Provider counseling (prompted by provider medication alert)*
- Automated delivery of med guide summary*
- IVR follow-up phone assessment
- IVR lab report to clinic via EHR
- Nurse counseling (if warranted by lab report)

**Because the first two activities must occur at the time of the clinic visit, which is before we will have the opportunity to invite the participant to enroll in the study, those activities will occur for all patients prescribed a study medication at an intervention clinic, regardless of whether or not they subsequently enroll. (see last paragraph of 3.1)*

9.2 Description of the intervention

1. Provider Medication Alert: If a prescribing clinician attempts to place a new order or change an existing prescription for one of the study medications (Table 1), an EHR-generated alert will notify the provider that the medication requires patient counseling. This alert will contain a brief description of the top risks or side effects that patients may experience while taking this medication; this information is directly derived from the FDA-approved Medication Guide for the drug. The pop-up will also include an html link to the 1-page Med Sheet, which they can use to further inform their counseling.

2. Automated Delivery of Med Guide Summary: When the patient leaves an encounter and checks out, the medication order in Centricity will automatically cue printing of the 1-page Med Guide Summary.

3. IVR Follow-Up Phone Assessment: One day after a patient's baseline interview (which will occur within 1-30 days post-visit), the patient will be prompted to call into the automated IVR system. The goal of the IVR call is to confirm patients' understanding and safe use of the prescribed high-risk medication they are taking, and to screen for any adverse drug events that may arise from having taken the medicine.

The call will investigate content areas that will be standard across all medications under study: 1) medication recognition, 2) medication fill (and fill barriers, if applicable), medication adherence (and adherence barriers, if applicable), perceived effectiveness, and side effects experienced. The IVR content was derived from the Med Guide Summaries. Patients are able to speak their responses as "yes", "no", or "do not know" or use their keypad.

To facilitate the call, patients will be sent (via text or phone call) a call-in number for the IVR system so that they are able to make the call at their convenience. The text with the call-in number will be sent on the day following the patient's baseline interview. (The day lag is needed so that the participant's medication data can first be uploaded to the IVR system in preparation for the call).

If subjects have not used the system after one day, a reminder text message, again including the call-in number, will be sent by the RA at Northwestern. If subjects have not used the system after two days, the RA at Northwestern will call the patient to remind them to call into the system and to ensure they have the call-in details.

4. Clinician Lab Reports. When a patient is flagged as having a medication-related concern based on the responses they give to the IVR system, the system will send an HL7 message to Alliance, which will appear as a 'lab report' in the patient's chart and sent to a centralized desktop at the clinic. The lab report will indicate the specific nature of the medication concern (e.g. fill concern, adherence concern, or safety concern), allowing the clinic staff to respond appropriately. Each clinic will be able to detail a reasonable response based on the type of concern reported. The default plan is that this role will be undertaken by nurses involved with care management responsibilities.

5. Nurse Counseling: Depending on the nature of the concern flagged, the IVR lab report will trigger the expectation for a clinic nurse to respond. Each FQHC can tailor their proper protocol for responding. During the IVR call, patients are told that issues will be reported to their clinic but that if they have concerns, they should call the clinic directly. The IVR system provides their clinic phone number before ending the call. This is done so that a patient is not left waiting for a response from the clinic when the clinic doesn't feel that the lab report warrantedfollow-up.

9.3 Research procedures

Research activities will include a baseline interview and follow-up interviews at 4 weeks and 3 months; all interviews will be conducted over the phone. Patients in the intervention arm will receive a prompt to call into an interactive voice response (IVR) system one day after their baseline interview (so 2-45 days after their index clinic visit) to confirm understanding and safe use of their medicine (described in 9.2 Description of the Intervention).

Pilot Testing. We will pilot-test the study battery, protocol and patient materials among English and Spanish-speaking patients at Alliance sites. Cognitive interviews will be conducted among a convenience sample of 30 patients (n=15 per language) that meet full eligibility criteria. We will obtain average interview completion times, elicit patient comprehension, and acceptability of the interview and patient materials. Any identified problems will be analyzed and modifications made as appropriate. Pilot patient data will be used if no significant changes are made to the study.

Initial Interview. After confirming patient eligibility, obtaining verbal consent, and receiving patient prescription information, the RA will administer the baseline interview via phone. As long as the patient is still taking or planning to take the prescribed medicine, the patient will then be eligible for follow-up interviews and, if in the intervention arm, to receive the remaining EMC2 components (IVR, nurse follow-up).

Follow-up Interview #1. The first follow-up interview will be scheduled at the time of the baseline interview for 4 weeks later.

Follow-up Interview #2. The second follow-up interview will be scheduled at the time of the 4-week interview for 8 weeks later.

Spanish Language Materials. All study materials (screener script, consent form, battery, IVR call) have been or will be translated into Spanish to accommodate Spanish speakers. Several of the measures in the battery already have validated Spanish versions; everything else has been translated by Research Support Services, led by Dr. Alisú Schoua-Glusberg, using a modified committee approach. In this translation approach, three bilingual, bicultural translators independently translate one-third of each document into Spanish, then discuss the resulting texts and reach an agreement on best words/phrases for the final product. The strength of this approach has been recognized by the Census Bureau Guidelines for Survey Translation.

Provider Survey: We will send brief surveys to providers via email from the intervention clinics toward the end of the study to collect data about their experience with the tools. We will also have the provider survey available in a pen and paper version in the event that the Northwestern research team can attend an in-person provider meeting.

9.4 Data Sources

Data sources for this study will include phone interviews with participants, data from participant responses to the IVR call, and survey responses from providers.

Data collected. The following measures, including covariates, effectiveness and fidelity outcomes, are described below.

Patient Covariates. Baseline assessment will include socio-demographics, social support, English proficiency, country of origin, health status, including number of comorbidities, and cognitive function (assessed by the Mini-Mental Status Exam). We will also probe for medication concerns (i.e. about costs, side effects, risks) for patients who do not fill or are not taking their medicine.
We will assess health literacy via the Newest Vital Sign (NVS). Patients are given a copy of a nutrition label and asked 6 questions about how they would interpret and act on the information. Scores are classified as high likelihood of limited literacy (0-1), possibility of limited literacy (2-3), and adequate literacy (4-6). The NVS has a high correlation with the Test of Functional Health Literacy in Adults (TOFHLA) takes less time to administer, is validated in Spanish and includes numeracy items.

Patient Motivation. The Consumer Health Activation Index (CHAI) assesses participants' 'activation' or motivation to participate in healthcare decisions and actions.

Effectiveness Outcomes: Medication Knowledge. Medication-specific knowledge measures will be created per high-risk medication. Similar items will be made standard across drugs, related to 1) decision making prior to use, 2) risks and benefits, and 3) side effects. Correct answers will be

tailored to the available content included in each Med Guide Summary, as done previously by our team. Total scores range from 0-100, calculated reflecting the % correct of total possible points for each medication.

Medication Behavior. We will assess medication behavior by three domains: fill, proper use, and actual use.

- Fill will be assessed by patient self-report (yes/no) of having attained the medication from the pharmacy.
- Proper Use, measured as yes/no per medication, will be assessed by requiring patients to properly indicate the correct indication, dose (# pills each time), frequency (times per day), and total pills per day.
- Adherence will be measured via the ASK-12 that includes 12 items assessing general medication attitudes and beliefs as well as, specific behaviors within the past 3 months.

Adverse Drug Events (ADE). ADEs will first be assessed using a validated questionnaire administered by the RA during the 3-month follow-up phone call. If the patient reports that their medication is finished at the 1-month interview, the ADEs will be assessed using the same approach at the 1-month interview. Dr. Oramasionwu will review all self-reported ADEs to determine whether these symptoms could reasonably be linked to one of the prescribed high-risk medications. We will then determine whether confirmed ADEs were reported to the clinic via the IVR system by reviewing IVR data. Drs. McCarthy and Paasche-Orlow will oversee this process.

Fidelity Outcomes:

- Provider Counseling. We will ask patients (yes/no) whether their prescriber/nurse/pharmacist counseled them. We will also ask the Health Literacy supplemental items of the Consumer Assessment of Health Providers Survey (CAHPS) to evaluate the extent and quality of provider verbal counseling on Rx medications. Prescriber/nurse counseling will be assessed immediately following the appointment (during the baseline interview);pharmacist counseling will be assessed at baseline if the prescription has been filled by that time, otherwise on the 4-week call.
- Receipt of Med Guide Summaries. We will ask patients in both arms whether they received any written information from their provider.
- Receipt of IVR Calls and Nurse Counseling. We will collect data from the IVR to determine whether interviews were completed and whether responses warranted nurse counseling.
- Frequency of Clinic Follow-Up. We will ask patients (yes/no) whether someone from the clinic contacted them following any concerns reported to the IVR system.
- Helpfulness of EMC2 components. Intervention patients will be asked (yes/no) whether they received Med Guide Summaries, IVR calls, and follow-up nurse calls and how helpful they were. “On a scale of 1 to 10, 1 being not helpful at all and 10 being extremely helpful, how helpful was…?”
- Provider experience. We will ask providers at intervention clinics about their use of the BPA pop-ups (if they saw them and if so, how they used them), med sheets (if they noticed patients receiving them), and IVR (if they received any feedback from the patients about the call and if they saw any of the IVR reports).

10. DATA AND SPECIMEN BANKING

10.1 Data storage

Patient interview data and provider survey data. Data from patient interviews will be collected in REDCap. The provider survey data via email will be collected in REDCap. Any provider survey filled out by pen and paper will be transferred into REDCap by the project manager.

Upon completion of all study activities, a final de-identified dataset will be created. This dataset will be stored indefinitely on the GIM server for secondary analyses. Only authorized personnel will have access to the dataset.

IVR data. Patients' responses to the questions on the IVR call will be captured in BMC's REDCap. The responses and record ID will be kept in REDCap until the completion of the study and analyses. The identifiable data will be deleted from REDCap within a week. Data for patients whose responses suggest a medication issue are sent to BMC's Mirth system to create the HL7 message that is then sent to the Alliance. Data is stored in Mirth for 7 days before deletion.

10.2 Data description

Interview data noted above will be stored.

10.3 Release of data

Data will not be released.

11. DATA AND SPECIMEN MANAGEMENT

11.1 Data analysis plan

Aim 1 Analysis Plan. The proposed trial uses a cluster-randomized design where the practice location is the unit of randomization. We will randomize 12 locations to two arms (usual care, EMC2) resulting in 6 per arm. Locations will be matched by total number of patients eligible for the study as well as proportion of Spanish speaking patients, with one location from each pair randomized to each arm. We will accrue ~100 patients per location, on average, and conservatively anticipate ≥80% retention at 3-month follow-up. These estimates result in 1200 participants recruited with an anticipated 960 patients (480 per arm, 80 per location) available for primary data analysis.

Medication knowledge associated with high-risk medications is the first primary outcome of interest for Aim 1 (H1), and will be analyzed as a score ranging from 0-100 reflecting the percent of items correct for each medication. Medication use outcomes (proper use, adherence) and detection of ADEs are relevant to the other hypotheses of interest for Aim 1 (H2, H3). Associations between the outcomes and potential confounders at the patient (socio-demographic characteristics, comorbidities, # and type of medications taken, previous history with side effects, literacy, and primary language) and medication (drug type, route of administration) levels will be examined. We intend to use generalized linear mixed models (GLMM) to analyze the data, which can handle data that is missing at random (MAR). Additionally, we will examine rates of missing data, and determine if there are any discernible patterns using GLMMs with a logit link function to predict the presence of missing data. Should we find significant predictors, we will use multiple impute methods and present results as secondary analyses.

To account for the correlated nature of the data from participants at the same practice and multiple observations per patient, we will use GLMMs for analyses of all data, specifying identity link for continuous and the logit link for binary outcomes using PROC GLIMMIX in SAS (v.9.4). Treatment assignment by time will be the independent variable of primary interest and modeled as a fixed effect and practice location as a random effect, with additional subject statement to model correlations within patient. We will also include fixed effects for any potential confounding covariates noted in the descriptive studies. For all GLMM analyses we will report point estimates and 95% confidence

intervals, and the extent to which random effects suggest correlation of outcomes within practice location. Additionally, we will estimate the ICCs for all outcomes to be used in future studies.

Aim 2 Analysis Plan: We will repeat all GLMM analyses described in Aim 1, but with the inclusion of a fixed effect for participants' literacy defined as limited (inadequate or marginal literacy) vs. adequate. We will formally test for differences in intervention effects according to literacy by including a literacy-intervention interaction term. Statistically significant interaction terms ($p<0.05$) will indicate that the disparities in understanding between the intervention and usual care group vary by literacy level. Similar analyses will be used to test for interactions of intervention effects by age and English proficiency (using Census criteria of 'very well' vs. 'less than very well').

Aim 3 Analysis Plan: Following completion of enrollment, we will determine the extent to which the intervention was implemented as planned in the intervention arm. We will ask patients in the intervention arm if they were counseled, and whether they received the Med Guide Summaries and the post-visit IVR call. Bivariate analyses will be performed to compare relevant outcomes for H4-H7 between arms using t-tests, Wilcoxon Rank-Sum, or $\chi 2$ tests, as appropriate. Aim 3 findings will also directly inform follow-up qualitative investigations in Aim 4.

Aim 4 Analysis Plan: A combination of patient focus groups (N=3; 1 per FQHC site; ~ 6-7 per group) and individual interviews with prescribers and nurses (N=7 per site; 5 prescribers, 2 nurses) will be conducted to understand in detail any barriers to implementation of the EMC2 Strategy. Preliminary findings from Aim 3 highlighting process outcomes and possible 'voltage drops' in implementation will be explored further in Aim 4. In addition, we will contact via phone a convenience sample (n=30) of pharmacies exposed to e-prescribed counseling requests. Feedback will be sought as to whether the order influenced pharmacy behavior. Our conceptual framework will guide discussions and interviews, along with Normalization Process Theory (NPT). NPT follows sociological principles pertaining to the implementation of innovations into practice. It takes the worldview that multifaceted interventions are often needed, and that implementation and integration often depends on: the work (tasks to be completed), who is responsible, how it impacts current practice, and how it is understood by an organization. Suggestions for further improvement of the strategy will be solicited. Discussions will be audio-recorded and transcribed for thematic analyses. Responses will be organized and summarized by provider/patient and component.

Aim 5 Analysis Plan: We will directly measure and assess the provider perspective costs of developing and running the EMC2 Strategy. Specifically, we will estimate the incremental cost of the intervention relative to usual care from the perspective of the Alliance and each FQHC implementing this process and tools. The primary costs of running the EMC2 Strategy involves the limited expenses around printing (printer ink, paper, staff time) as a result of generating new medication information with after-visit summaries. However, we will include estimates for minimal programming maintenance, for both GE Centricity EHR and the IVR system, and will test the sensitivity of results to changes in the maintenance requirements in terms of programmer hours. We also will separately track development costs for software and other programming requirements based on programmer hours. Staff/programmer costs will be measured using tracked time spent on the intervention and wage estimates. We will test the sensitivity of operational costs to different assumptions about the potential use of variable staff using different salaries but assuming the same proficiency in terms of time required. Further, we will assess the sensitivity of estimates to different proficiency levels that could arise from learning by doing.

11.2 Power analysis

The sample size for this study was based on comparisons of the primary outcome of medication knowledge between the two arms (i.e., usual care vs EMC2) at the 3-month interview. We expect

participants in the usual care arm to score an average of 55.6 (SD=28.4) based on a previous study testing comprehension of the FDA standard Med Guides to those to be used in this study. Enrolling 1200 participants and estimating 80% retention at the follow-up interview (n=960, 480 per arm), we will have 80% to detect a minimum difference of 5.5 between the EMC2 and the usual care arm assuming a Type I error of 5%, assuming 100 patients per practice site enrolled at baseline and n=80 available at 3 month follow-up. This effect size was calculated based on an independent t-test with a variance inflation factor to account for the cluster-randomized design. An intra-class correlation coefficient (ICC) of 0.001 was used as we expect the clustering of practice site to have minimal influence on patient outcomes.

Usual care estimates for understanding of risks and demonstrated safe use outcomes were obtained from prior work. For subgroup analyses on these outcomes for Aim 2, we expect roughly 38% to have limited health literacy. Detectable differences at 3 months are based on estimates of 3 patients per provider with limited literacy and 5 with adequate literacy. Detection of ADEs is defined as the number of events recorded in the medical chart out of the total number reported by patients at the 3-month interview. In a study in which 20% of participants reported at least 1 adverse drug event, 35 of their 166 (21%) reported events were recorded in their medical chart. Therefore, the sample size calculation for this outcome was based on 21% of reported ADEs in 20% of our expected sample at 3 months (n=96 per arm, 3 patients per 32 providers, assuming an equal number of providers in each arm will have patients with no ADEs). We will be able to detect a minimum of 18.2 between the EMC2 and the usual care arm. For subgroup analyses by literacy, we assume 1 patient per provider with limited literacy and 2 with adequate literacy.

11.3 Confidentiality

Each subject will be tracked using an Access database. The database, containing identifiers and other related information for coordinating research activities (recruitment outcome, interview call log and interview visit schedule, etc.), will be password protected and kept on the secure Northwestern network drive. Only the PI, project manager, and RAs will have access this database.

Data will be collected via REDCap. REDCap is a secure online data collection tool, which can only be accessed by NU authorized personnel listed on the project's IRB.

To reduce the risk of breach of confidentiality, a study identification number will be assigned to each subject in the study. This study ID will be the only means of communicating about the patient outside of the secure REDCap or Access environments and will be the primary identifier in REDCap and Access as well. All identifiable information will be deleted upon completion of the study.

IVR data. A subset of data from the baseline interview received by Northwestern will be sent to Boston Medical Center in order to inform the IVR call and facilitate the eventual relay of IVR data to the patient's electronic record for participants assigned to the intervention arm. This data includes: first and last name, date of birth, MRN (Centricity ID), phone number, language spoken, study medication(s) prescribed and date prescribed. This will be sent along with clinic information including: clinic name, clinic phone number, provider name, PCP and prescriber (NPI #). These data are used solely to inform the IVR call and to facilitate the eventual relay of information to the provider, by identifying the correct EHR. As part of the consent process, the patient is informed of this data transfer. Northwestern will export these data daily from Northwestern RedCap to a file stored on FSM department server and then upload directly to Boston's REDCap instance. This data is backed up daily on a secure BMC server and stored for a period of 3 days. After 3 days, the backup is deleted from the server. On a weekly basis, the programmer at Northwestern will identify participants who have completed the IVR call and subsequently delete their identifiable information from RedCap (keeping only the study ID and IVR call responses). Identifiable information for all

patients (regardless of having called into the IVR system) will be deleted from BMC's RedCap after a period of 6 weeks.

Results of any IVR call on which a concern is identified will be sent via secure HL7 message to Alliance clinics, appearing in Centricity as feedback to the providers in the form of a laboratory report. In order to create the HL7 message, the data passes through BMC's Mirth system, where it is stored for 7 days before deletion. In Centricity, the message will be routed to a centralized care coordinator desktop. In the event that a serious concern is identified, the issue (non-adherence, patient-reported side effects etc) will be detailed in this report. Clinic staff will monitor reports and respond to any identified concerns according to clinic protocol.

Provider data. Providers at the intervention clinics will be sent an email with a link to a consent form and, if they consent, to a survey in REDCap. They will be able to complete the survey anonymously; the most personal information that the survey will capture is "what type clinician are you? (nurse, doctor, physician's assistant, other).

11.4 Data collection quality control

Training will begin after surveys and interview protocols have been refined and standardized. The project manager will lead sessions to orient the research staff to the surveys and study protocols (e.g., interview process, use of laptop PCs, data security). Research staff will be trained together to ensure uniform administration of the study protocols and interviews. RAs will then practice interviews; each will be required to demonstrate competence in survey administration.

11.5 Study-wide data management

Data Access: Only authorized personnel listed on the IRB will have access to the data.

Data Storage: NU: Data will be stored on the Northwestern server for the length of the study. All identifiable information will be deleted upon completion of the study. BMC: Identifiable data will be stored in BMC's HIPAA-compliant REDCap database until the IVR call is completed or for a maximum period of 6 weeks. The REDCap database is backed up by a secure BMC server for a period of 3 days. After 3 days, data is deleted. HL7 text files will be stored (for IVR calls requiring a lab report) in the Mirth database for 7 days and then deleted.

12. PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

N/A (study does not involve more than minimal risk to subjects)

13. WITHDRAWAL OF PARTICIPANTS

13.1 Forced withdrawal

There are no anticipated circumstances when a participant would be withdrawn from the study without his or her consent.

13.2 Voluntary withdrawal

Participants can choose to withdraw from the study at any time. If a participant chooses to withdraw from the research, any data collected up until the point of withdrawal will still be utilized, as it will not include identifying information.

14. RISKS TO PARTICIPANTS

Participation in the study poses minimal risk of psychological, social *or* economic harm. Informing subjects in advance that they may decline to answer any questions asked during the interview will mitigate any risks associated with expressing their opinions (e.g., feeling uncomfortable). They will also be assured they can terminate their participation in the study at any time without penalty. The risk/benefit ratio is low. Minimal to no risk is expected for subjects in this study.

15. POTENTIAL BENEFITS TO PARTICIPANTS

We do not anticipate participants to receive direct benefit from participating in the study.

16. VULNERABLE POPULATIONS

N/A

17. COMMUNITY-BASED PARTICIPATORY RESEARCH

N/A

18. SHARING OF RESULTS WITH PARTICIPANTS

Study results will not be shared with participants or anyone else.

19. SETTING

19.1 Research sites.

Sites from which we will recruit participants (via phone) include clinics associated with The Alliance, an EHR user community composed of safety net health centers. The Alliance is an innovator and national leader in using health information technology (HIT) among FQHCs. The Alliance links 67 community health center practices in the metropolitan Chicago area; all are Public Health Service 330-funded FQHCs with federal mandates to care for medically underserved areas. Patients are mostly African American, Latino and low income. Alliance FQHC's share a common EHR (GE Centricity®). Drs. Wolf and Bailey have a long history collaborating with the Alliance and Dr. Rachman. We will work specifically with Near North Health Services Corporation, randomizing seven of their clinics.

20. RESOURCES AVAILABLE

20.1 Research team qualifications

The research team is comprised of 2 PhD level researchers with expertise in health literacy, 4 Physician-researchers (all of whom hold research masters degrees) also with expertise in health literacy, a research-pharmacist, a PhD economist, PhD statistician, software developers, and a group of research assistants and statistical analysts (who have 2-10 years of experience working on similar projects). We have significant experience in recruiting patients from the FQHCs (Alliance clinics specifically), conducting studies related to medications, consenting patients to follow-up, and conducting multi-part follow-up with both in-person and telephone interviews. Additionally, the

team has experience in managing data in accordance with the best practices of the IRB to protect patients' confidentiality.

20.2 Other resources

Recruitment pool. To reach our recruitment goal of 1200 patients over 24 months, we will recruit 50 patients per month, or about 12 per week. The clinics at which we will be recruiting have a combined patient population of 100,484 patients, any of which may be prescribed a high-risk medication and be likely eligible for the study.

Dedicated time. The investigators have a history of successful collaboration on several research projects. They have already established dedicated time each week to discuss this project. All persons assisting in the project will be adequately informed about the research protocol, the research procedures, and their duties and functions. We will ensure this by conducting weekly research meetings (already in-place) and by reviewing key concepts and conducting practice sessions for the consent process and interviews.

Facilities. All interviews will be conducted at a time of convenience for the patient and the RAs will have access to a closed offices wherein to conduct the calls and record data.

Training protocols.

Northwestern staff training. The Northwestern project manager and bilingual RA have completed Human Subjects Training (CITI) and have received intensive training, led by Drs. Wolf and Bailey, in interview protocols and safe data transfer. Any new research staff will go through the same rigorous training requirements.

Alliance clinical staff training. One week prior to the recruitment launch of the study, a WebEx conference will be held with all providers at Alliance participating FQHC clinics (randomized to the intervention arm. This is the standard communications platform Alliance uses to share updates to the EHR functionality with clinicians. This will be interactive, introducing them to the EMC2 strategy and trial and showing them where in Centricity these EHR tools reside, what patients will receive, and their role to counsel patients for these study drugs. They will be shown how the Provider Medication Alert will serve as an alert to notify the provider that the medication required counseling and that it will give a brief description of the key risks or side effects associated with this medicine. They will also be shown the Med Guide Summary and how it is cued at the time of order and automatically printed.

21. PRIOR APPROVALS

21.1 Approvals prior to beginning research.

Funding agency. This study was approved by the funding source, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Clinic site. The study will be presented to the clinical advisory board of all participating clinics for approval prior to commencing recruitment.

22. RECRUITMENT METHODS

22.1 Recruitment materials

None

22.2 Identification of potential participants

See 3.1 – Screening by Alliance

22.3 Recruitment procedure

Recruitment will be done over the phone by CITI-certified Northwestern Research Assistants (RAs). The RAs will receive contact information for suitable patients (see 3.1 Methods of screening for eligibility) and call them to determine eligibility, invite to participate, and obtain verbal consent (see 28.0 Consent Process). The patient will then be eligible to receive the remaining components of the intervention (depending on study arm), and participate in evaluation activities. While the majority of outreach to patients (to recruit or conduct interviews) will be done by phone, we will offer participants the option to receive a text or email reminder prior to their interview, if they so desire.

22.4 Payment for participation

Patients will be mailed a $20 money order after completion of the baseline interview and an additional $20 money order upon completion of the final interview. Depending on the patients' medication fill/take behavior, the final interview might be the 3-month (ideal), 1-month, or baseline time point. If an earlier interview is determined to be the final interview, it will include several additional measures moved up from later interviews.

Providers will not be paid for completing surveys.

23. NUMBER OF LOCAL PARTICIPANTS

1200 patients will be enrolled in the study from Alliance clinics, with the expectation of retaining at least 960 patients through study completion. We will recruit equal numbers of patients from control clinics as from intervention clinics (n=600 per arm; 1200 patients total).

There are approximately 40 providers at the Near North intervention clinics; all will be invited to complete the provider survey.

24. CONFIDENTIALITY

See 11.3 Confidentiality

25. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

25.1 Protection of subjects' privacy.

When inviting patients to participate in our study, we clearly tell them that participating in the research is voluntary and that they are free to decline or withdraw at any time. If they decline (or remain unresponsive to our phone calls for 4 weeks), we do not reach out to them again during the study. All enrolled participants will provide verbal consent, including verbal HIPAA authorization, for the collection of all data, including data transfer process with BMC. During the consent process and before each interview, we remind participants that they are free to skip any questions that make them feel uncomfortable or that they do not wish to answer.

Subjects will be informed that participation in any part of this research study may result in a loss of privacy, since persons other than the investigators at NU may view their study records if deemed necessary for oversight purposes. However; they will be identified by a unique identification number ("study id"), not by name, and any other identifying information (e.g. personal and/or contact information) will be kept separate from the other data; all information will be kept in secure, password-protected files. Personal information will be encrypted and linked to the study number. Further, subjects will be told that unless required by law, only the study investigators, members of the project staff, and representatives of the Northwestern University and local Institutional Review Boards will have the authority to review any study records. In such case, they too will be required to maintain confidentiality.

25.2 Making subjects feel at ease.

Participation in the study poses minimal risk of psychological, social and economic harm. Informing subjects in advance that they may decline to answer any questions asked during the interviews will mitigate any risks associated with expressing their opinions (e.g., feeling uncomfortable). RAs are trained to assure patients that some of the questions are meant to be difficult and that the research is to assess the health care system, not the patients themselves.

25.3 Access to patient information.

The way in which we access patient data is outlined in 3.1 Methods of Screening for Eligibility

If receiving data via method #1 (See 3.1), the research team will receive the minimal contact information necessary for phoning and inviting patients to participate in the research study.

If receiving data via method #2, the team will also receive, in addition to contact information, the name and sig of the patient's medication prescribed the day prior, and name of prescribing doctor, and patient's address. While this method involves sharing of additional information, it has the benefit of allowing the patient to proceed with the baseline interview immediately following consent rather than waiting a day or more and setting time aside for a second call. In addition, it allows the RA to more clearly explain the study by telling the patient which medicine the questions will be concerning.

The research team will not have access to patient medical records.

26. COMPENSATION FOR RESEARCH-RELATED INJURY

N/A (no more than minimal risk to subjects)

27. ECONOMIC BURDEN TO PARTICIPANTS

N/A

28. CONSENT PROCESS

28.1 Consent setting for patients.

Verbal consent process. Subjects will be informed about the nature of the study by a CITI certified RA and asked to provide verbal consent. Specifically, they will be told that they *might* be asked to call

into an automated phone system to inquire about any medication-related concerns and that they *will* be asked to complete up to three phone interviews over three months. They will be told who might have access to their PHI. Finally, they will be informed that they may withdraw from the study at any time, and will be given contact information for the PI and study coordinator.

If a patient agrees to participate after the research assistant (RA) reads the consent, the RA will record the patient's Record ID on the consent form and the RA will sign their own name on the form. These consent forms will be locked in a file cabinet only accessible to necessary research staff. Patients will be given the option to receive a blank consent form for reference via mail or email if they request it.

This specific strategy of verbal consent for participants has been previously approved by the IRB at Northwestern University (IRB #: STU00097744).

28.2 Consent setting for providers.

Providers will be sent an email describing the survey along with a link to an online consent form. They will be told that completing the survey is voluntary and that their responses will be kept confidential. Providers may also consent and complete the same survey approved as pen and paper at a provider meeting hosted by Near North Health Services Corporation.

28.2 Non-English Speaking Subjects

All study materials are available in both English and in Spanish and our RAs are bilingual. We have included Research Support Services as part of the grant to provide Spanish translations for materials that have yet to be created. Patients who do not speak either Spanish or English will be ineligible to participate. Patients will be asked their language of choice as they are consented. Research assistants will be able to conduct all interviews and schedule phone calls in either language. The IVR system prompts will also be available both in English and Spanish; the patient will self-select the language of choice at the beginning of the call.

29. PROCESS TO DOCUMENT CONSENT IN WRITING

A verbal consent, or a waiver of documentation of consent, is deemed appropriate because the nature of the study involves minimal risk and appropriate measures will be taken to protect PHI (see 12.3 Confidentiality). The RA will read the consent form to the patient over the phone and ask if the patient has any questions. If the patient would like additional time to think about it, the RA will offer to call the patient back at a time that would be convenient for the patient. If a patient agrees to participate after the research assistant reads the consent, the research assistant will record the patient's Record ID on the consent form and the RA will sign their own name on the form. These consent forms will be locked in a file cabinet only accessible to necessary research staff. Patients will be given the option to receive a blank consent form for reference, via mail or email, if they request it.

Waiver for alternative HIPAA authorization. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Due to the nature of the study, a waiver for alternative HIPAA authorization is required. The research could not practicably be conducted without the alteration to verbal HIPAA as any form of written consent or HIPAA authorization is not possible given the nature of the clinical trial. There are two major factors that do not allow for the collection of written informed consent from patients, and as such, written HIPAA authorization. We have set forth a rigorous process for adequately capturing verbal informed consent and HIPAA authorization in the

recruitment process (see 28.0 Consent Process). The specific barriers that prevent written HIPAA authorization include:

Time-sensitivity: Subjects become eligible at the time they are newly prescribed one of the study medications, with primary outcomes including their proper understanding and use of the medication, near to the time of fill and for the following 3 months. Therefore it is imperative that we are able to recruit them within the first week of their new prescription to launch the intervention. Receiving data from the EHR to identify and recruit eligible patients and consenting via phone is the only viable solution given the time constraints of the intervention. The IVR intervention call is triggered from completion of baseline (as early as 1 day after the baseline interview and within 4 weeks of the clinic visit), with the aim to reinforce learning and identify medication errors, including serious side effects. Given the range in duration of the medications included, including a number of short duration medications, it would not be possible to wait for a written HIPAA consent to be mailed by participants. It is imperative that the IVR functions while participants are currently taking the medications to accurately capture side effects and medication issues.

Resource limitations: While we did consider the possibility of on-site recruitment or leveraging clinic staff to support consent and/or data collection efforts, this is not possible. Working within the confines of the financial limits of the R01 mechanism, we cannot afford the resources to have staff in all of the 12 geographically diverse locations. Potentially eligible patients cannot be pre-identified, as patients only become eligible once they are prescribed a medication from the study list. It would also be too great a burden to ask clinic staff to remember to disperse a consent form and written HIPAA at the time of prescribing (this has been discussed with clinic sites), and an alert cannot also be included to that regard. Asking clinic staff to distribute consent forms would also require all staff at each clinic site to become research study personnel authorized to consent participants. Training each nurse and care coordinator who could potentially interface with patients once triggered would be an impossible task, especially given the shift-work nature of these positions. Any other efforts to have the patient provide written HIPAA consent would place undue burden on the patient for participating.

30. DRUGS OR DEVICES

N/A